Boehringer Ingelheim

Briefing Document

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Drug Substance:	Flibanserin (BIMT 17 BS)	
Dosage Form, Strength:	Film-coated tablets 100 mg	
Indication:	Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women	
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LIST OF ABBREVATIONS AND DEFINITION OF TERMS

Term	Definition/description
ADRs	Adverse drug reactions
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR(1)	Autoregressive first order covariance structure
ASEX®	Arizona Sexual Experiences scale
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{\tau,ss}$	Area under the plasma drug concentration-time curve over a uniform dosing interval at τ steady state
BI	Boehringer Ingelheim
b.i.d.	Twice daily dosing (once in the morning and once in the evening)
BMI	Body mass index
BSS	The Beck Scale for Suicide Ideation
CGI	Clinical Global Impression
CI	Confidence interval
$C_{max,ss}$	Maximim drug concentration in plasma after a single dose
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CS	Compound symmetry covariance structure
CTMF	Clinical Trial Master File
CTR	Clinical trial report
DHEA-S	Dehydroepiandrosterone (sulphate)

Term	Definition/description
DSDS	Decreased Sexual Desire Screener
DSM-IV-TR®	*Diagnostic and Statistical Manual,* Fourth Edition, Text Revision
ECG	Electrocardiogram
eCTR	Electronic clinical trial report
eDiary	Electronic diary
EU	European Union
FAS	Full analysis (population) set
FAS2	Full analysis (population) set during the second period (double-blind placebo-controlled period) of 511.74
FDA	Food and Drug Administration
FMRI	Functional magnetic resonance imaging
FOD	Female orgasmic disorder
FSAD	Female sexual arousal disorder
FSD	Female sexual dysfunction
FSDS	Female Sexual Distress Scale
FSDS-R	Female Sexual Distress Scale-Revised©
FSFI	Female Sexual Function Index©
FSFI-d	sexual desire items of the Female Sexual Function Index©
hCG	Human Chorionic Gonadotropin
h/mL	Hour(s)/millilitre
HSDD	Hypoactive sexual desire disorder
ISE	Integrated Summary of Efficacy
LOCF	Last observation carried forward
LOCFZERO	Last observation carried forward-zero

Term	Definition/description
LS means	Least square means
MCID	Minimal clinically important difference
MDD	Major depressive disorder
mg	Miligram
MMRM	Mixed model repeated measures
N/A	Not applicable
NDA	New drug application
NERI	New England Research Institutes
ng/mL	Nanogram per mililiter
NSAID	Non-steroidal anti-inflammatory drug
OC	Observed Cases
OL	Open label
PBE	Patient Benefit Evaluation
PET	Positron Emission Tomography
PGI	Patient Global Impression
PGI-I	Patient Global Impression of Improvement
PPS	Per protocol (population) set
PRO	Patient reported outcome
PT	Preferred term
q.h.s.	Once every evening
q.d.	Per day
ROC	Receiver operating characteristic
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy

Term	Definition/description
SCS	Summary of Clinical Safety
SD	Standard deviation
SDS	Sexual Desire Score
SE	Standard error
SF-12	A 12-item generic health status questionnaire derived from the longer and widely used SF-36
SF-36	A general health status measure with 8 domains that is commonly used to assess quality of life
SHBG	Sex hormone binding globulin
SIGH-D	Structured Interview Guide for the Hamilton Depression Scale
SNRI	selective noradrenergic reuptake inhibitors
SOC	System Organ Class
SSE	Satisfying sexual event
SSRI	Selective serotonin reuptake inhibitors
SNRI	Sective noradrenergic reuptake inhibitors
t.i.d.	Three times daily
TSAP	Trial statistical analysis plan
UN	Unstructured covariance structure

1. EXECUTIVE SUMMARY

This briefing document has been prepared for the Food and Drug Administration (FDA) Advisory Committee Meeting scheduled on June 18, 2010, in support of the New Drug Application (NDA) for flibanserin as a treatment for Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women (NDA 22-526). Flibanserin is a serotonin 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist developed by Boehringer Ingelheim to provide safe and effective therapy for pre-menopausal women with Hypoactive Sexual Desire Disorder (HSDD).

1.1 BACKGROUND

Clinicians and researchers have recognized for decades that the most common sexual dysfunction that women experience is a loss of sexual desire which causes them personal and/or interpersonal distress. Categorized in the DSM-IV-TR® as Hypoactive Sexual Desire Disorder (HSDD), this condition is characterized by a persistent or recurrent deficiency or absence of desire for sexual activity; it must cause marked distress or interpersonal difficulty, and it must not be better accounted for by the effects of another (non-sexual) disorder, other Axis I disorders, substance, or circumstance [R05-1015].

Premenopausal women with acquired HSDD, such as those who participated in the extensive flibanserin clinical program, are women who previously had a level of desire which was satisfactory to them, but who have lost their sexual desire in all situations and across significant intervals of time – that is, women for whom there has been a significant, noticeable, and distressing change in level of sexual desire. These women experience and express distress; they feel a sense of loss of their sexuality and of emotional closeness with their partners, they experience frequent frustration with their lack of desire and with their inability to restore it using strategies that used to spark their interest. A woman with HSDD expresses concern about how her partner feels and the potential effect that her low desire is having on her relationship.

As such, HSDD is not, as is sometimes assumed, an adaptive response to a poor relationship with an uncaring or unsupportive partner, nor simply a discrepancy between the level of desire a woman may feel compared to that of her partner. HSDD is not simply due to stress or the result of fatigue, or of being a working mother with small children. HSDD is not the result of taking medications such as SSRIs, known to affect sexual desire, nor is it a manifestation of depressive illness.

Unfortunately, this distressing condition is often ignored or marginalized as being a “normal part of life”, despite the fact that research has repeatedly shown that women who have HSDD experience significant quality of life burden, distress, marital dissatisfaction, and difficulties developing stable sexual relationships. Moreover, recent research has demonstrated that women with HSDD, compared to unaffected women, have differential attention to sexual cues in their environment as well as exhibiting differing patterns of brain activation and deactivation in response to visual sexual stimuli as assessed by both fMRI and PET neuroimaging techniques, supporting the role of central mechanisms in the condition.

The SF-36 Health Survey is a general health status measure with 8 domains that is commonly used to assess quality of life. It assesses: (1) physical functioning, (2) role limitations caused by physical problems, (3) bodily pain, (4) general health perceptions, (5) vitality, (6) social functioning, (7) role limitations caused by emotional health problems, and (8) mental health. Leiblum and colleagues noted that with the exception of bodily pain, women with HSDD had significantly worse scores for each of the domains compared to women with normal desire [R08-1427].

More recently, the negative effect of HSDD on quality of life was confirmed in a large study of postmenopausal women with HSDD. Using the SF-12 (a 12-item generic health status questionnaire derived from the longer and widely used SF-36), Biddle and colleagues found "Women with HSDD reported similar profiles of impairment when compared with the SF-12 norm scores for diabetes, hypertension, back pain, and arthritis" [R09-0761].

Current estimates indicate that between 6% and 10% of American women between the ages of 20 to 49 years (5.5 to 8.6 million) may suffer from the hallmarks of HSDD: lack of sexual desire accompanied by significant distress.

Currently, there is no approved treatment for women seeking help for this clinically relevant and consequential disorder. Sex therapy is neither widely available from accredited providers nor has been shown to be consistently effective. Moreover, there is no approved pharmacologic therapy for the treatment of HSDD, and in consequence many women are exposed to off-label treatments such as buproprion and testosterone, whose safety and efficacy have not been prospectively assessed in adequate and well controlled trials in women with HSDD and whose risks may not be well understood. Safe and effective treatment of HSDD represents a widespread and unmet medical need.

Flibanserin was originally developed to treat depression, based on anti-depressant-like effects in pre-clinical models. Phase IIa depression trials flibanserin failed to show efficacy on the primary endpoint, however a retrospective assessment noted virtually no occurance of sexual dysfunction. As negative sexual sequelae are common side effects of anti-depressants, in 4 subsequent Phase IIb depression studies a multi dimensional measure of sexual dysfunction, the Arizona Sexual Experiences Scale (ASEX), was included. These IIb studies compared flibanserin, standard antidepressants, and placebo and also failed to show efficacy of flibanserin, leading to termination of the development as an antidepressant. In one of these 4 trials, flibanserin was superior in women not only to the positive comparator, as expected, but also to placebo on the ASEX scale, mainly on the item "How strong is your sex drive?" This was the basis for pursuing the indication of HSDD in women.

Two identical 12-week proof-of-concept trials (511.68 and 511.69) have been completed in premenopausal women with HSDD. These were randomized, double-blind, placebo controlled trials that utilized 50 mg twice daily (b.i.d.) to 100 mg b.i.d. flibanserin vs. placebo (511.68 [U04-3099]; 511.69 [U04-3124]). Based on these studies, 50 mg and 100 mg daily as b.i.d. or q.h.s. were carried forward in an attempt to limit adverse events (AEs) and dropouts in Phase III trials.

In the End of Phase 2 meeting, the Division required the Sponsor to develop a validated, simple tool for practitioners to make an accurate diagnosis of HSDD, so flibanserin would be prescribed appropriately, and to include the tool in at least one Phase III clinical trial. This was accomplished and the results with this new instrument, the Decreased Sexual Desire Screener (DSDS), showed that in the hands of clinicians without specific training or expertise in female sexual dysfunction, this simple 5-item tool had a sensitivity of 83.6% and a specificity of 87.8% in comparison to an expert interview to diagnose HSDD correctly. These results led to the acceptance of the DSDS by the Agency.

Following the FDA draft guidance for a registration program in female sexual dysfunction (FSD) [R02-1030], the North American clinical development program consisted of 5 studies: Trial 511.74 [U08-3394-01] was designed as a randomized withdrawal study in which patients first completed a 24 week open-label (OL) flibanserin treatment period after which patients meeting the predefined enrichment criteria entered a 24 week double-blind (DB), placebo-controlled, randomized withdrawal period. As well, 3 adequate and well controlled efficacy trials (511.70 [U09-3115-01]; 511.71 [U09-3195-01]; and 511.75 [U09-3194-01,]) of 24 week duration were conducted using different dosage regimens. Finally, subjects who completed any one of these 4 trials were allowed to roll over into Trial 511.84 [U09-3487-01], a 52-week OL extension trial.

The submission contains 2 other Phase III efficacy and safety trials (511.77 and interim data from 511.118). The 511.77 trial [U09-1824-01] was a 24 week study conducted in 13 European Union (EU) countries. Trial 511.118 [U09-1772-01] (EU countries) is an ongoing OL extension study for completers of the EU Phase III Trial 511.77, and is 28 weeks in duration.

For the purpose of this submission, Trial 511.74, 511.71 and 511.75 are considered primary efficacy studies, as these were the North American studies that used the 100mg q.h.s. dose, the dose for which the sponsor is seeking registration. Trials 511.70, 511.77 and 511.84 are considered as supportive as one did not contain the 100mg q.h.s dose (511.70), one was conducted in Europe (511.77) and one was an open label study (511.84).

The trials analyzed entered approximately 5000 women with HSDD who have been treated with flibanserin 50 to 100 mg daily or placebo.

In all of these studies, HSDD was diagnosed by clinicians trained in proper diagnostic techniques utilizing a structured interview, a sexual symptom checklist and a validated screening instrument to rule out current depressive illness. This consistent diagnostic approach is an essential component of the clinical trial program with flibanserin as it ensured women enrolled in the primary efficacy studies exhibited significant loss of desire and accompanying distress. As well, clinicians ascertained the presence or absence of other sexual dysfunctions and ensured that if present, the additional sexual concerns occurred secondarily to the primary HSDD and were considered as “comorbid sexual disorders” by the investigator.

Endpoints assessing sexual desire, sexual distress, sexual function, sexual activity and overall patient benefit were developed and carefully validated in consultation with the FDA. The

assessments provided accurate, relevant, and clinically meaningful measurements of effectiveness of flibanserin in the treatment of HSDD, and taken together provide convergent and compelling evidence of the beneficial change in the hallmark symptoms of HSDD among premenopausal women receiving flibanserin therapy.

1.2 EFFICACY

Premenopausal women with HSDD enrolled in the 5 North American Phase III trials were primarily white (non-Hispanic), married, and on average, 36 years of age. Efficacy results are summarized individually for all Phase III placebo-controlled studies, as well the pooled analysis for pivotal Studies 511.71 and 511.75, which were the North American trials with similar in design and dosing.

Women treated with flibanserin 100 mg once at bedtime (q.h.s.) consistently showed a statistically significant ($p<0.05$) and clinically meaningful benefit on the co-primary endpoint of Satisfying Sexual Events (SSEs) in all three primary efficacy trials and a statistically significant difference ($p<0.05$) on the co-primary eDiary Sexual Desire Score in one of three primary efficacy trials (511.74) while showing positive trends in the other two (511.71 and 511.75). Thus, while of nominal significance in two of the three studies, the Sponsor notes that the additional measure of desire, The Female Sexual Function Index—Desire Items (FSFI–desire) assessing both the frequency and intensity of sexual desire over 28 days showed a highly consistent, although nominally significant ($p<0.01$), clinically meaningful impact of flibanserin treatment versus placebo. This finding demonstrates that flibanserin is more consistently effective in increasing women's global experience of desire than in increasing the intensity of their acute episodes of desire. Distress was also improved; women treated with flibanserin 100 mg q.h.s. consistently showed a nominally significant ($p<0.01$) and clinically meaningful decrease in sexually related distress in all studies.

Women's own perceptions of treatment benefit was assessed using the Patient Global Impression of Improvement (PGI-I); women treated with flibanserin 100 mg q.h.s. consistently showed a nominally significant ($p<0.0001$) improvement in all studies.

Recognizing that statistical significance of any given endpoint alone may not adequately capture the potential benefit of a treatment to the patient, *a priori* responder analyses and post hoc remitter analyses were also performed to more precisely characterize these potential benefits. The methodology for these responder analyses, as agreed with the FDA, was anchored to an individual woman's assessment of her own improvement. This anchor-based assessment of response is an important clinically relevant endpoint, because a result on any given measure that is statistically significant may or may not represent what is truly meaningful to an individual woman taking flibanserin. As well, a woman's assessment of her improvement is based on her impression of all aspects of her treatment experience, some of which may be more or less important to her than to another woman, but ultimately allowing all women in the clinical program to give voice to their personal experience with treatment.

These responder analyses, agreed in advance with the Agency, anchored the endpoints to the Patient Global Impression of Improvement (PGI-I) and confirmed that for each of the co-primary and secondary endpoints Flibanserin 100 mg q.h.s.was statistically significant

superior over placebo, and the difference was clinically meaningful with the exception of the eDiary sexual desire score. This included assessments of sexual desire, sexual distress, sexual activity, sexual function, and overall patient benefit. Proportions of responders ranged from 39 to 57%, depending on the endpoint, with margins of responder superiority consistently 10-15% over the rates of placebo. In addition, sustained efficacy of flibanserin in the treatment of HSDD was demonstrated in a one-year trial (511.74) and supported by an open-label extension trial (511.84), in which improvements in SSEs, FSFI desire, FSDS-R Q13, global impressions, and responder rates were maintained for up to an additional 52 weeks.

Despite the fact that studies of CNS compounds generally demonstrate both a high pleacebo response and variability of results, we note that for all endpoints in all studies flibanserin 100mg q.h.s. results were numerically better than placebo.

In summary, the data demonstrate highly convergent evidence showing sustained clinically significant superiority of flibanserin over placebo on endpoints including SSEs, FSFI- desire items, the FSDS-R total and FSDS-R Q13, and the Patient's Global Impression of Improvement. These consistent, convergent, data assessing multiple components of HSDD demonstrate that flibanserin at 100 mg q.h.s. improves the clinical symptomatology of women suffering from HSDD.

1.3 SAFETY

The assessment of the clinical safety of flibanserin in women with HSDD is based on integrated safety results from four placebo-controlled Phase III clinical trials conducted in North America: 511.70, 511.71, and 511.75, and in the European Union (EU): 511.77, and results of one Phase III, placebo-controlled, randomized withdrawal trial (511.74) conducted in the United States and Canada. In addition, this briefing document presents safety data from two ongoing, open-label, extension Phase III trials in women with HSDD (511.84 in North America, and 511.118 in Europe, data cutoff date of 17 Nov 2009), and two placebo-controlled double-blind Phase II trials of flibanserin in women with HSDD (Trial 511.68 in the United States and 511.69 in Canada). Supportive safety data from 27 Phase I clinical trials with flibanserin and 11 Phase II clinical trials in men and women with major depressive disorder (MDD) are also included. Thus, the safety database includes a total of 47 clinical trials.

The briefing document includes data of flibanserin in 5018 premenopausal women with HSDD: 1175 subjects were treated with flibanserin 100 mg once every evening (q.h.s.) for at least six months, and 213 subjects were treated with flibanserin 100 mg q.h.s. for at least 12 months. Also, a significant number of women (N=2430) with HSDD were exposed to different dose regimens in Phase III placebo-controlled trials, including 25 mg twice-a-day, 50 mg at bedtime, and 50 mg twice-a-day.

Overall, the incidence of adverse events (AEs) in premenopausal women with HSDD taking flibanserin was low with the majority of adverse events mild to moderate in severity. The frequently occurring events were typical of a centrally-acting drug: dizziness, nausea, fatigue, somnolence, and insomnia.

No observations raised concern over the use of flibanserin in premenopausal women with HSDD in regard to cardiac, hepatic, renal, or hematopoietic effects, ophthalmologic safety, hypersexuality, hormonal changes including indices of fecundity, menses, suicide, depression, abuse potential, or withdrawal effects.

No treatment-related deaths occurred. One subject died among all clinical studies (including studies in major depressive disorder) with flibanserin: A subject in Study 511.74 receiving placebo died as a passenger in an airplane crash on Day 19 of the double-blind period.

Serious AEs (SAEs) occurred in <1% of subjects receiving any dose of flibanserin or placebo among the placebo-controlled Phase III studies and in the development program for HSDD only in one subject SAEs (1 ovarian cyst and 1 uterine polyp) were reported by the investigator as related to flibanserin.

As expected for a centrally-acting compound, women treated with flibanserin reported a higher rate of AEs compared with women who received placebo in Phase III placebo-controlled studies (66.2% vs. 57.7%, respectively). The majority of these AEs were mild in intensity and resolved during treatment. The most frequently observed AEs were dizziness, nausea, fatigue, and somnolence (approximately 10-12% each) and insomnia (5%). These AEs, along with dry mouth and anxiety, are considered adverse drug reactions for flibanserin, as they occurred in at least 2% of flibanserin-treated women (100 mg q.h.s.) and occurred at twice the rate observed in the placebo group.

1.4 CONCLUSION

Flibanserin therapy, at the recommended dosing regimen of 100 mg q.h.s., resulted in statistically significant and clinically relevant improvements of the hallmark symptoms of HSDD in premenopausal women based on patient-based assessments of sexual desire, sexual distress, sexual activity, sexual function, and overall patient benefit. In general, flibanserin is well-tolerated as the AEs reported during the development program were non-serious and mild in severity.

Currently, women face extremely limited options when seeking help for HSDD. It is important that women suffering from HSDD and their health care providers have an approved treatment option available to them. As the first pharmacologic therapy for HSDD in premenopausal women, if approved, Flibanserin would appreciably expand the HSDD treatment armamentarium and the choices available to women.

2. OVERVIEW OF CLINICAL EFFICACY

2.1 BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

2.1.1 Design of clinical program

Flibanserin is a 5-HT_{1A} agonist and a 5-HT_{2A} antagonist that is being developed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. In addition to binding to 5-HT_{1A} and 5-HT_{2A} receptors, flibanserin binds with moderate affinity to 5-$HT_{2B,2C}$ where it acts as an antagonist, and dopamine D_4 receptors. Initially tested to treat depression, flibanserin did not meet the primary endpoint for depressive symptoms but was found to be superior to the positive comparator and placebo on the Arizona Sexual Experiences scale (ASEX®), mainly on the "sex drive" item in women. This was the basis for pursuing an indication of HSDD in women.

2.1.1.1 Flibanserin in depression

Nine double-blind placebo-controlled clinical phase II trials of 2- to 8-week duration, a single-dose study, and two 1-year open label safety trials were performed with flibanserin in patients diagnosed with major depressive disorder (MDD) (DSM-IV). A total of 1555 patients diagnosed with MDD received fixed doses of flibanserin ranging from 4–200 mg/day including 112 female (and 82 male) patients treated for six months and 33 female (and 21 male) patients treated for one year. All phase II trials included a selective serotonin reuptake inhibitor (SSRI) active comparator arm (paroxetine or fluoxetine). In each trial, efficacy endpoints included: mean change from baseline in Structured Interview Guide for the Hamilton Depression Scale (SIGH-D) and Clinical Global Impression (CGI) of Severity of Illness at trial end. The primary efficacy endpoint, SIGH-D, was not met for the flibanserin arm in any clinical trials, while the active comparator was positive in three studies.

Flibanserin appeared to have a favorable safety profile and was generally well tolerated in all trials. The main adverse events more frequently associated with flibanserin than with placebo were somnolence, nausea, dizziness and fatigue (11-23% each, respectively).

In the Phase IIa depression trials, in which flibanserin failed to show efficacy on the primary endpoint, virtually no sexual dysfunction was noted. Subsequently a multi dimensional measure of sexual dysfunction, the Arizona Sexual Experiences Scale (ASEX), was included in four Phase IIb depression studies. In one of these four trials, flibanserin was superior in women not only to the positive comparator, as expected, but also to placebo on the ASEX scale, mainly on the item "How strong is your sex drive?". This was the basis for pursuing the indication of HSDD in women.

In conclusion, flibanserin was not effective for treating depression in patients with MDD, leading to the termination of the development as an antidepressant and the initiation of the HSDD development program in women.

2.1.1.2 Flibanserin in HSDD

Two proof-of-concept trials (511.68 and 511.69) were completed in women with HSDD. These trials were identical in design: randomized, double-blind, placebo-controlled, flibanserin (starting with 50 mg twice daily (b.i.d.) and optional up-titration to 100 mg b.i.d.) vs. placebo for 12 weeks of treatment in premenopausal women. Combining the two trials, 149 women were treated with flibanserin and 148 with placebo. The pooled analysis of satisfying sexual events (SSEs) for the two trials combined showed superiority of flibanserin over placebo in the final evaluation period (Weeks 9 to 12). Analyses performed on the full analysis population set (FAS) using the last observation carried forward (LOCF) showed a statistically significant superiority favoring flibanserin ($p<0.05$). The per-protocol population set (PPS) (completers without major protocol violations) showed statistically significant superiority of flibanserin ($p<0.01$) at Weeks 4, 8, and 12. These results were considered promising for Phase III studies in which lower dosages and up-titration to 50 mg b.i.d. or 100 mg q.h.s. were used to attempt to limit AE dropouts. Across a broad variety of measures, including assessments of sexual thoughts and fantasies as well as receptivity to sexual activity, the trials sufficiently demonstrated proof-of-concept to test flibanserin in Phase III for the treatment of HSDD.

Following the FDA draft guidance for a successful registration program in female sexual dysfunction (FSD) [R02-1030], the North American clinical development program consisted of five studies: Trial 511.74 [U08 3394 01] was designed as a randomized withdrawal study in which patients first completed a 24 week open-label (OL) flibanserin treatment period after which patients meeting the predefined enrichment criteria entered a 24 week double-blind (DB), placebo-controlled, randomized withdrawal period. As well, three adequate and well controlled efficacy trials (511.70 [U09-3115-01]; 511.71 [U09-3195-01]; and 511.75 [U09-3194-01]) of 24 week duration were conducted using different dosage regimens. Finally, subjects who completed any one of these 4 trials were allowed to roll over into Trial 511.84 [U09 3487-01], a 52-week OL extension trial.

The submission contains two other Phase III efficacy and safety trials (511.77 and interim data from 511.118). The 511.77 trial [U09-1824-01] was a 24 week study conducted in 13 European Union (EU) countries. Trial 511.118 [U09-1772-01] (EU countries) is an ongoing OL extension study for completers of the EU Phase III Trial 511.77, and is 28 weeks in duration.

The trials analyzed in the NDA and thus included in the briefing document entered approximately 5000 women with HSDD who have been treated with flibanserin 50 to 100 mg daily or placebo. Table 2.1.1.2: 1 provides a general description of the trials analyzed in the briefing document. Table 2.1.1.2: 2 provides the dosing used in these trials. As was noted in the Executive Summary and is extensively documented in the remainder of this document, only the 100mg q.h.s. dosage of flibanserin was found to be consistently effective. Therefore, for the purpose of this submission, Trial 511.74 (24-week double-blind, placebo-controlled randomized withdrawal study) and Trials 511.71 and 511.75 (24-week randomized, placebo-controlled studies) are considered primary efficacy studies, as these were the North American studies that used the 100mg q.h.s. dose, Trials 511.70, 511.77 and

511.84 are considered as supportive as one did not contain the 100mg q.h.s dose (511.70), one was conducted in Europe (511.77) and one was an open label study (511.84).

In addition to the individual trials, pre-specified *a priori* pooled analyses of efficacy data from trials 511.71 and 511.75 are presented for the primary, key secondary and other secondary endpoints. Pooling of these studies provides a more precise estimate of the effect size. Prior to pooling the data, baseline characteristics were assessed to ensure that there were no significant differences between the pooled studies. In addition, sensitivity analyses, testing the treatment by study interaction, were performed in order to assses whether treatment effects differed by study (Section 2.3.4.1) (i.e., test of heterogeneity between studies). These results show that no treatment by study interactions were identified, and the results are prensted in Section 2.3.4.1.

Additionally, non-drug validation studies (511.73, 511.85, 511.106, 511.121, 511.144 and 511.151) were performed to validate the endpoints used in the flibanserin program. Details are provided in Section 2.1.2.5 (Validation of Endpoints).

Table 2.1.1.2: 1 Description of HSDD trials

BI Trial Number	Trial Design/Control	Study & Control Drugs, Dose, Route Regimen	Planned Duration
North American trials			
Phase II – 12-week, placebo-controlled, double-blind			
511.68	Randomized, double-blind, placebo-controlled	50 mg flibanserin tablets; 50 to 100 mg b.i.d. (an increase to 100 mg b.i.d. was possible after 8 weeks of treatment); oral	12 weeks
511.69	Randomized, double-blind, placebo-controlled	50 mg flibanserin tablets; 50 to 100 mg b.i.d. (an increase to 100 mg after 8 weeks treatment was possible); oral	12 weeks
Phase III – Randomized withdrawal – 24-week, open-label, flexible flibanserin regimen, followed by 24-week, placebo-controlled, double-blind, randomized withdrawal			
511.74	Open-label, flexible dose regimen, followed by randomized, double-blind, placebo-controlled fixed dose regimen	50 mg flibanserin tablets; 50 mg q.h.s., 50 mg b.i.d., or 100 mg q.h.s.; oral	48 weeks (24 weeks open-label period + 24 weeks randomized, double-blind period)
Phase III – 24-week, placebo-controlled, parallel group, double-blind			
511.75	Randomized, double-blind, placebo-controlled	25, 50, and 100 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s. for 14 days then up-titration to 50 mg b.i.d. and 50 mg q.h.s. for 14 days then up-titration to 100 mg q.h.s.; oral	24 weeks
511.70	Randomized, double-blind, placebo-controlled	25 and 50 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d.; oral	24 weeks
511.71	Randomized, double-blind, placebo-controlled	50 and 100 mg flibanserin tablets; 50 mg q.h.s., 100 mg q.h.s.; oral	24 weeks
Phase III – Long-term exposure			
511.84	Open-label, uncontrolled	25, 50 and 100 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d., 100 mg q.h.s.; oral	52 weeks
European trials			
Phase III – 24-week, placebo-controlled, parallel group, double-blind			
511.77	Randomized, double-blind, placebo-controlled	50 and 100 mg flibanserin tablets; 50 mg q.h.s., 50 mg q.h.s. for 14 days then up-titration to 100 mg q.h.s.; oral	24 weeks
Phase III – Long-term exposure			
511.118	Open-label, uncontrolled	25, 50 and 100 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d., 100 mg q.h.s.; oral	28 weeks

Table 2.1.1.2: 2 Doses in trials analyzed – HSDD trials

BI Trial Number		Placebo	FLI 25 b.i.d.	FLI 50 q.h.s.	FLI 50 b.i.d.	FLI 100 q.h.s.	FLI 100 b.i.d.
North American trials							
Phase II – 12-week, placebo-controlled, double-blind							
511.68		X			X		X[3]
511.69		X			X		X[3]
Phase III – Randomized withdrawal – 24-week, open-label, flexible flibanserin regimen, followed by 24-week, placebo-controlled, double-blind, randomized withdrawal							
511.74	Open-label			X[5]	X[4]	X[4]	
	Double-blind	X		X	X	X	
Phase III – 24-week, placebo-controlled, parallel group, double-blind							
511.75		X	X		X[1]	X[1]	
511.70		X	X	X	X[1]		
511.71		X		X		X	
Phase III – Long-term exposure							
511.84			X[2]	X[2]	X[2]	X[2]	
European trials							
511.77		X		X		X[1]	
511.118			X[2]	X[2]	X[2]	X[2]	

1 Up-titration from FLI 50 mg q.h.s. after the first 2 weeks of treatment as part of the dosing regimen
2 Dose available as part of a flexible dosing arm
3 Optional up-titration after at least 8 weeks of FLI 50 mg b.i.d. treatment
4 Optional up-titration after at least 4 weeks of FLI 50 mg q.h.s. treatment
5 Patients start on FLI 50 mg q.h.s. and may return to FLI 50 mg q.h.s. after optional down-titration from FLI 50 mg b.i.d. or FLI 100 mg q.h.s.

2.1.2 Definition of efficacy endpoints

HSDD is by definition a condition characterized by the distressing absence or loss of previously adequate sexual desire; however the symptomatology and patient experience of HSDD is not limited to desire alone, necessitating assessments of multiple components of the condition in order to best characterize the potential benefits of a treatment. For this reason both co-primary and secondary endpoints were agreed with the Agency. To assess the behavioural component of HSDD, satisfying sexual events were assessed as a co-primary endpoint. Sexual desire was assessed using an electronic diary.

Sexual desire is inherently challenging to measure as it involves multifaceted aspects of self-assessed experience and performance. There are biological, psychological and interpersonal aspects. It is recognized in the field that sexual desire has both global qualities (i.e., an overall sense of general readiness and specific interest in sexual activity) and more episodic qualities (i.e., days or times of more intense sexual motivation and urges for sexual release), the specific causal pathways are not well known. The degree to which a particular woman is more or less bothered by the infrequency of her desires compared to low intensity of her

desires is likely to vary, and importantly, we have no basis to presume that frequency and intensity are affected in the same way by the imbalance of neurotransmitters thought to influence HSDD. Hence, there is no *a priori* basis on which to presume that flibanserin will work equally on frequency and intensity of sexual desire, and therefore it is important to assess both. It is known from qualitative studies of women with HSDD that both the lack of "acute" experiences of specific desire and the global sense of having "no desire" seem to be important in women's reports of the distress that they experience as a result of HSDD. The period of recall is another dimension that affects a woman's experience and subjective reporting of desire. One week, one day, and one month recall periods were all investigated in the clinical trial program. Qualitative interviews with HSDD patients and controls revealed a preference for one week or one month recall periods as most relevant to assess changes in desire.

Therefore, to adequately assess these different dimensions of HSDD a number of efficacy endpoints were employed. As in all Phase III efficacy studies of pharmaceutical compounds for the treatment of sexual dysfunctions, Patient-Reported Outcome (PRO) measures form the core measures for assessment of efficacy. These PROs utilize varying numbers of items, are scored differently, and differ both in their recall period and their method of data collection (paper vs. electronic). They include:

- Satisfying Sexual Events. This endpoint, which assesses a "downstream" behavioural expression of desire, provides a quantitative measure well suited to assessment by a daily diary measure. However, this behavior-focused proxy of sexual desire is an incomplete assessment of the overall experience of desire given that women may engage in sexual activity without desire or engage/not engage in sexual activity for reasons unrelated to desire. Further, desire may be experienced in the absence of sexual activity.

- eDiary Desire: assesses the more episodic or "day-to-day" experience of the intensity of sexual desire a woman experiences

- FSFI-d: assesses more globally both the frequency and intensity of desire a women experiences over a 28-day period

- FSFI Total Score: assesses global sexual function over a 28-day period

- FSDS-R Total Score (distress): assesses the distress experienced as a result of the presence of sexual concerns such as HSDD

- FSDS-R Q-13 Score (distress): assesses specifically being bothered by low sexual desire

- Patient Global Impression (PGI) of improvement: a bi-directional scale assessing the patient's overall improvement, specifically with regards to the decreased desire and feeling bothered by it, as the participant perceives it, compared to how she felt at the start of the clinical trial compared to how she felt the start of the clinical trial.

It is the totality of these endpoints that provide the most accurate characterization of the effects of a compound for the treatment of HSDD, as illustrated in the hierarchical model below [Figure 2.1.2: 1].

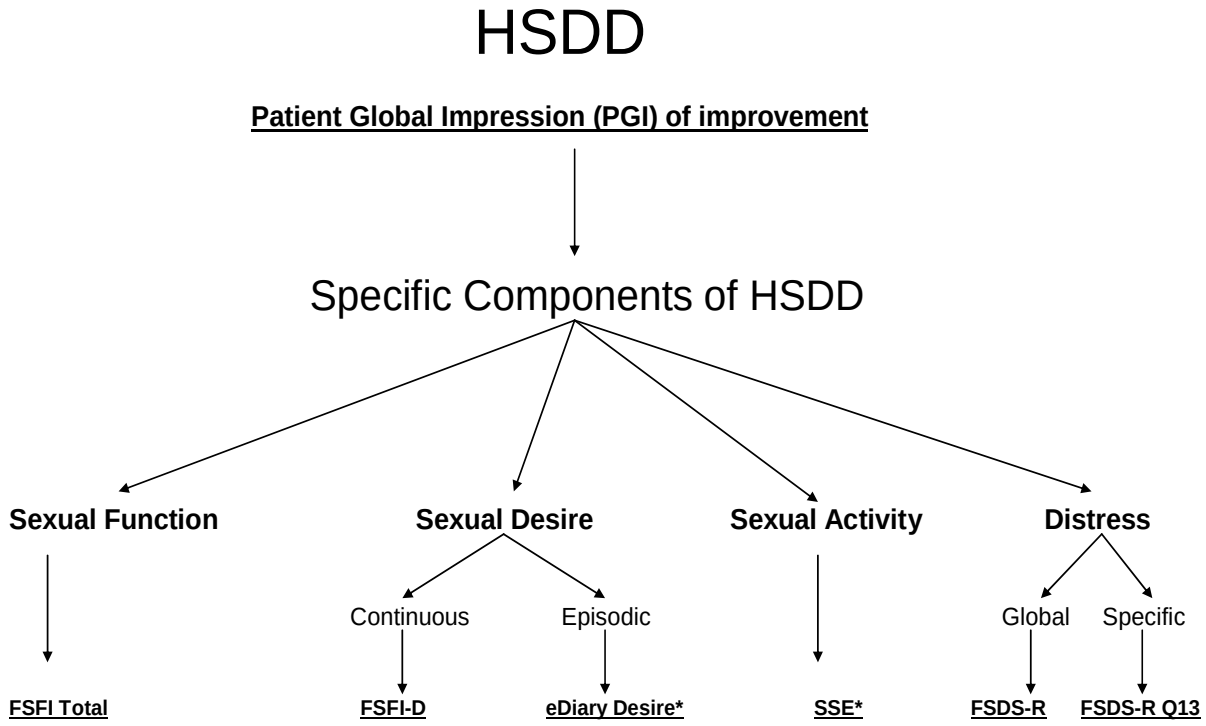


Figure 2.1.2: 1 Mapping of specific HSDD components to clinical endpoints

The PRO endpoints utilized in the flibanserin phase III program were discussed and agreed upon with the Division and are summarized in the following table (Table 2.1.2: 1), which illustrates key features of each, including clinical cut points and normative scores in healthy women, where such values have been established:

Table 2.1.2: 1 Description of endpoints used in HSDD trials

	# items	Score range	Clinical cut point[1]	Direction indicating improvement	Source Data Capture	Recall period (days)	Volunteers without FSD
Satisfying sexual event	2	Y/N	-	↑	electronic	1 - 3	13.9 ± 8.8
eDiary sexual desire score	1	0-3 (0-84/mo)	-	↑	electronic	1	48.7 ± 18.3
FSDS-R total score	13	0 – 52	<15	↓	paper	7	2.2 ± 4.1
FSDS-R Item 13	1	0 – 4	-	↓	paper	7	0.3 ± 0.6
FSFI total score	19	2 – 36	>26.55	↑	paper	28	33.0 ± 4.2
FSFI desire items	2	1 – 5	>3.0	↑	paper	28	4.6 ± 1.1
PGI-I	1	1 – 7	1	↓	paper		
Patient benefit evaluation	1	Y/N	-		paper		

1 Values established to clinically differentiate dysfunctional from non-dysfunctional subjects

Table 2.1.2: 2 summarizes the primary, key secondary and other secondary efficacy endpoints that are presented in Section 2.3.2 (Comparison of efficacy results of all studies/doses). The primary and key secondary endpoints are considered in the statistical inference strategy to control for Type I error. The primary (or both co-primary) endpoint(s) must be statistically significant before testing the key secondary endpoint(s). More details are provided in Section 2.1.3.2.

For Trials 511.68 and 511.69, the ASEX Item 1 was the primary endpoint. Female Sexual Function Index© (FSFI©) desire items and total scores were secondary endpoints.

For Trials 511.74, SSE and electronic diary (eDiary) desire score were the primary endpoints.

For Trials 511.70, 511.71, and 511.75, SSE and electronic diary (eDiary) desire score were the co-primary endpoints and Female Sexual Distress Scale-Revised© (FSDS-R©) was a key secondary endpoint. Additionally for Trials 511.71 and 511.75, Female Sexual Function Index© (FSFI©) desire items was a key secondary endpoint.

For Trial 511.77, SSE was the primary endpoint and FSFI desire items and FSDS-R total were key secondary endpoints.

Trial 511.84 and 511.118 are long-term safety studies and do not have a primary efficacy endpoint; all efficacy endpoints are considered secondary.

Table 2.1.2: 2 Summary of select endpoints in the HSDD trials

	North America				Europe	
	511.68, 511.69	511.74	511.70, 511.71, 511.75	511.84	511.77	511.118
Primary endpoints						
Satisfying sexual event		X	X		X	
eDiary sexual desire score		X	X			
ASEX sex drive (Item 1)	X					
Key secondary endpoint						
FSDS-R total score			X		X	
FSFI desire items[1]			X		X	
Other secondary endpoints						
FSFI desire items[1]	X	X	X	X		X
eDiary sexual desire score					X	
FSDS-R Item 13		X	X	X	X	X
FSDS-R total score		X		X		X
FSFI total score	X	X	X	X	X	X
PGI-I		X	X		X	
Patient benefit evaluation		X	X	X	X	X
CGI of efficacy index				X		X
Satisfying sexual event (count)		X	X		X	
Responder endpoints						
PGI-I of '1' or '2'			X		X	
PGI-I of '1', '2' or '3'			X		X	
Patient benefit evaluation			X		X	
PGI-I anchored responder endpoints[2]						
SSE			X		X	
eDiary sexual desire score			X		X	
FSDS-R Item 13			X		X	
FSDS-R total score			X		X	
FSFI desire items			X		X	
Remitter endpoints						
FSFI desire items >3.0			X		X	
FSDS-R total score <15			X		X	

1 FSFI desire items were pre-specified as a key secondary endpoint in the TSAP before unblinding for Trials 511.70 and 511.71. For Trial 511.77, FSFI desire items were pre-specified as a key secondary endpoint in Protocol Amendment 2 which was implemented before last patient out.

2 PGI-I anchored responder endpoints are data-driven responder endpoints anchored by PGI-I. See Section 2.1.2.4 for details.

2.1.2.1 Primary endpoints

2.1.2.1.1 Satisfying sexual event

The SSE primary endpoint assesses a behavioural component of the experience of HSDD and measures the change from baseline to the final visit period in the monthly frequency of SSEs as measured by the eDiary question: "Was the sex satisfying for you?" Sexual events or encounters included sexual intercourse, oral sex, masturbation, or genital stimulation by the partner. The patient (not the partner) judged whether the event was satisfying or not.

Patients recorded data on a daily basis in the eDiary throughout the study period. Should a patient not have completed the diary on a given day, the patient was prompted to complete

the missed entry (or entries) during the next diary usage for up to the last three days. During the baseline period, 92.8% of patients entered data into the eDiary at least 26 out of 28 days, and 98.0% of patients entered data into the eDiary at least 21 out of 28 days; during the final visit period (Weeks 21 to 24), these compliance values were 70.9% and 88.3%, respectively.

The SSE primary endpoint standardized the counts based on the number of days a patient recorded data into the eDiary taking the retrospective entries into account. Further description of the SSE derivation for handling of missing data is provided in Section 2.1.3.7. In addition, SSE (count) which does not use any standardization methods and imputes a value of zero for missed days was analyzed as a secondary endpoint.

2.1.2.1.2 eDiary sexual desire score

The eDiary sexual desire score endpoint measures acute, episodic changes in the intensity of desire experienced by women with HSDD and is assessed by the change from baseline in the monthly sum of responses entered into the eDiary in the 28 days prior to the clinic visit for the eDiary daily desire question: "Indicate your most intense level of sexual desire."

Patients recorded data on a daily basis in the eDiary throughout the study period. For the eDiary sexual desire question, patients were only allowed to enter data for the past 24 hours. Therefore, should the patient not have completed an entry on a given day, the patient was not allowed to make retrospective entries for eDiary desire. Further description of the derivation for handling of missing data is provided in Section 2.1.3.7.

As the clinical program progressed, important limitations of the eDiary became evident. These included a) Sub-optimal compliance, b) limited response scale that effectively rendered it only a 3-level measure, and c) reactivity of the measure due to annoyance of daily completion. During the baseline period, 74.9% of patients entered data into the eDiary at least 26 out of 28 days, and 95.8% of patients entered data into the eDiary at least 21 out of 28 days; during the final visit period (Weeks 21 to 24), these compliance values dropped to 43.7% and 74.2%, respectively. Since the SSE question allowed for a 72 hour recall period, compliance for the SSE was less of an issue and accordingly higher (70.9% of patients entered SSE data into the eDiary at least 26 out of 28 days, and 88.3% of patients entered SSE data into the eDiary at least 21 out of 28 days during the final visit period).

2.1.2.2 Secondary endpoints

2.1.2.2.1 Key secondary endpoints

Key secondary endpoints were considered *a priori* in the statistical inference strategy as pre-specified in the TSAP. See Section 2.1.3.2 for more details on the statistical methods.

2.1.2.2.1.1 Female Sexual Function Index (FSFI) desire items

FSFI is an instrument for the assessment of female sexual function and dysfunction in a variety of research applications, including HSDD, consistently demonstrating reliability (test-retest and internal consistency), discriminant, convergent, and divergent validity as well as the ability to detect change during treatment. The sexual desire items of the FSFI scale

(FSFI-d) were found in subsequent validation studies conducted by the instrument's developer to have diagnostic accuracy in identifying women with an independent clinical diagnosis of HSDD. A validation study with a large sample (N=302) identified a minimum clinically important difference (MCID) or change score of 1.2 points on the FSFI-d scale (range 1.2-6). These results are consistent with a large number (>200) of published reports indicating the validity, reliability and utility of the measure in both observational studies and clinical trials of female sexual dysfunction. Taken together, this body of evidence supports the diagnostic accuracy and treatment sensitivity of the FSFI-d items for use as an appropriate global desire endpoint in clinical trials of HSDD.

For Trials 511.70 and 511.71, FSFI desire items were pre-specified as a key secondary endpoint in the TSAP before unblinding. For Trial 511.77, FSFI desire items were pre-specified in Protocol Amendment 2 as the main desire endpoint and a key secondary endpoint. The amendment was implemented during the conduct of the study, prior to database lock and unblinding of the study.

Compared to the eDiary desire score, the FSFI desire items were found in Trial 511.75 to have a lower placebo response, lower variance, higher compliance, and (in separate, non-treatment, studies) better content validity (511.144 and 511.151).

In Trial 511.74, FSFI desire was a secondary endpoint.

2.1.2.2.1.2 Female Sexual Distress Scale-Revised© (FSDS-R)

Distress associated with low desire is another hallmark of HSDD. The Female Sexual Distress Scale (FSDS) is a measure of female personal distress associated with sexual dysfunction. Reliability and validity of the FSDS (12-item version), with a 30-day recall period, has been evaluated in different populations of sexually functional and dysfunctional women. For the FSDS, results indicated a unidimensional factor structure, a high degree of internal consistency, and test–retest reliability. The FSDS showed a high degree of discrimination between sexually dysfunctional and functional women in the validation studies.

To strengthen the content validity of the FSDS for use in women with HSDD, the Developer added an additional question (Item 13) to the validated FSDS. This question is about distress specifically related to sexual desire. FSDS plus Item 13 comprises FSDS-R which makes the FSDS-R a self-administered 13-item questionnaire. The maximum total score of the FSDS-R ("52") indicates the maximum level of sexual distress. A score of 15 has been demonstrated to discriminate between women with and without FSD [R04-1068]. The FSDS-R© was modified to use a 7-day recall period; in validation studies by the sponsor, performance of the scale was not affected by this change. Since a higher value on this scale denotes greater distress, a decrease from baseline indicates improvement.

The Female Sexual Distress Scale-Revised© (FSDS-R) total score change from baseline to the final visit was analysed. The FSDS-R Item 13 change from baseline to the final visit was also analyzed along side the FSDS-R total as the FDA stated preference for this endpoint as the distress measure as indicated as part of the Pre-NDA meeting on 10 October 2007.

Item 13 and the total score of the FSDS-R are given the same level of importance in the analysis because of results of the content validity study of this measure (511.121): Item 13 was most relevant to women with HSDD, and scored highest (was the type of distress most frequently experienced), and almost half of the women found it adequate as a single measure of their sexual distress, whereas they found all items of the scale relevant and comprehensive.

In Trial 511.74, FSDS-R was a secondary endpoint.

2.1.2.3 Other secondary endpoints

2.1.2.3.1 Female Sexual Function Index (FSFI) total score

The FSFI is a self-administered questionnaire to assess overall sexual experience that consists of 19 questions that are scored from 0 to 5 [R00-1134]. The scale contains six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI total score is a weighted average of the six domains with each contributing a maximum of six points to the total (maximum score of 36). The change from baseline at the final visit of the FSFI total was analyzed. A cutoff of 26.55 has been demonstrated to discriminate between women with and without FSD [R07-1418].

2.1.2.3.2 Patient Global Impression (PGI) of improvement

The Patient Global Impression of Improvement (PGI-I) is a simple evaluation completed by the patient to assess the patient's overall improvement of her HSDD condition (specifically with regards to the decreased desire and feeling bothered by it) compared to the start of study medication. The PGI-I is rated ordinally from 1 ("very much improved") to 7 ("very much worse"); therefore, a lower value indicates improvement. Since this instrument evaluates improvement, the instrument is not collected at baseline, and the actual value as opposed to change from baseline is used in the analysis.

2.1.2.3.3 Patient benefit evaluation responder endpoint

The patient benefit evaluation is a single question asking the patient whether or not she experienced a meaningful benefit from the study medication during the trial. The question, "Overall, do you believe that you have experienced a meaningful benefit from the study medication?" was only asked upon treatment discontinuation.

2.1.2.4 Secondary responder/remitter endpoints

<u>Responder endpoints</u>

A priori responder analyses were performed in order to assess the clinical relevance of the results. The methodology for these responder analyses, agreed with the Agency, were anchored to a woman's individual assessment of her improvement in SSEs and desire using the Patient's Global Impression of Improvement (PGI-I). The anchor-based assessment of response may in fact be the most clinically relevant endpoint, because these results are linked to a subjects' determination of treatment benefit, e.g., anchoring change in the endpoints to the responses of the subjects on the PGI of Improvement (PGI-I) instrument.

Responder endpoints for Trials 511.70, 511.71, 511.75 and 511.77 include two types of endpoints:

1) Data-driven responder endpoints for which the responder criterion method, rather than a specific value, was pre-specified.

2) Pre-defined responder endpoints for which the responder criterion value was pre-specified.

For each trial, as well as for the pooled analysis, 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 criteria were considered a responder.

PGI-I anchor based responder endpoints have been defined for the following endpoints: SSE, eDiary sexual desire score, FSFI desire items, FSFI total score, FSDS-R total, and FSDS-R Item 13. These responder criteria are displayed in Table 2.1.2.4: 1. The PGI-anchored values showed a high level of consistency across trials for each endpoint.

Table 2.1.2.4: 1 PGI-I anchoring of select endpoints – Trials 511.70, 511.71, 511.75, 511.77 and pooled (FAS, LOCF)

	Difference between Minimally improved and No change				
Endpoint	511.70	511.71	511.75	511.77	Pooled
SSE	1.55	1.22	1.25	1.55	1.24
eDiary sexual desire score	8.15	7.80	7.91	7.25	7.87
FSFI desire items	0.83	0.83	0.74	0.88	0.78
FSDS-R Q 13	-0.47	-0.44	-0.41	-0.51	-0.42
FSDS-R total score	-4.89	-5.63	-5.07	-5.86	-5.27
FSFI total score	4.64	4.52	3.87	5.66	4.10

Using SSEs from the above table as an example, in Study 511.75, the mean change from baseline that correlated with the difference between "no change" and "minimally improved" was 1.25. To be considered a responder in this study, a woman had to have a mean SSE value greater than 1.25. For the pooled analysis of SSEs, in order to be considered a responder she would need to have reported a mean value greater than 1.24 which differs from any individual trial value as a result of the pooling of data. Analyses were then conducted comparing the percentages of women in the flibanserin and placebo arms who met the aforementioned criteria.

Further post-hoc analyses using additional responder criteria thresholds were analyzed as sensitivity analyses to examine the distribution of responses. These additional cut-offs were used to explore the consistency of the results across a broad range of values. The following cutoffs were analyzed:

- SSE change from baseline: >=1, >=2, >=3, >=4

- eDiary sexual desire score change from baseline: >8, >10, >12, >14
- FSDS-R total change from baseline: <-5, <-8, <-11, <-14
- FSDS-R item 13 change from baseline: <= -1, <= -2, <= -3
- FSFI desire change from baseline: >=0.6, >=1.2, >=1.8, >=2.4
- FSFI total score change from basleine: >=4, >=6, >=8, >=10

In addition to the PGI-I anchored responder criteria, the following secondary responder endpoints are presented:

- PGI-I score of 1 or 2 ("very much improved" or "much improved")
- PGI-I score of 1, 2 or 3 ("very much improved", "much improved" or "minimally improved")
- Patient Benefit Evaluation (yes/no)

Remitter endpoints

In addition to responder endpoints, several remitter endpoints based on published literature were also examined. A remitter is a patient who returned to non-clinical levels and thus remitted from symptoms of HSDD. These endpoints were defined post-hoc.

The following remitter endpoints were analyzed:

- FSFI desire items greater than 3.0 [U09-3526-01], indicating remission of desire symptomatology into the non-clinical range
- FSDS-R total score less than 15 [R04-1068], indicating remission of sexually-related distress into the non-clinical range.

2.1.2.5 Validation of endpoints

Trials 511.73, 511.85, and 511.106 were 4-week, non-drug methodology trials conducted to establish discrimant validity of the endpoints used in the efficacy trials. Trials 511.73 and 511.106 were performed in North America whereas Trial 511.85 was conducted in the EU. Discriminant validity analyses of the pooled North American validation studies are presented in Table 7.1.2.1: 1 in which clear discrimination can be seen in the mean scores of the eDiary, FSDS-R total and Q 13, FSFI total and FSFI desire items between women with HSDD and both women with other forms of FSD as well as women with no FSD ($p<0.0001$)

Content validity of the FSDS-R total score and FSDS-R Item 13 was provided in Studies 511.121. Content validity of FSFI total score and FSFI desire items was provided in 511.144 and 511.151.

Study 511.121 showed that the FSDS-R was understandable, clear, and comprehensive, and that all of its items (and responses) were relevant to the 25 women with HSDD who were interviewed. Item 13, identified by FDA as most relevant for individual analysis, was endorsed by the patients as the most relevant (and highest scored, i.e., most frequently experienced problem), and about half of them, when asked pointedly, said that it could replace the entire scale to convey their negative feelings about HSDD adequately.

Studies 511.144 and 511.151 were identical in design and evaluated the content validity of the FSFI in 15 and 30 premenopausal women with HSDD, respectively. Trial 511.151 was conducted to collect data in more women to confirm the results of Trial 511.144. In these studies, the FSFI desire items (Items 1 and 2) were clear, easy to understand, and both items were relevant to over 90% in both trials. For assessing the FSFI desire items, over 90% of women in both Trials 511.144 and Trial 511.151 thought that a 24-hour recall was not relevant. Almost two-thirds of the women in Trial 511.144 and about 80% of the women in Trial 511.151 preferred a recall period of one to two weeks (or longer), but there was no clear preference for a 1-, 2-, or 4-week recall period.

The results of Trial 511.144 and the replication of the results in Trial 511.151 confirm and further extend the evidence supporting the content validity of the FSFI desire items in premenopausal women with HSDD. Overall, the FSFI in general, and the items in the desire domain in particular, were well understood and applicable to premenopausal women with HSDD, and patients thought that recall periods greater than 24 hours were most relevant.

2.1.3 Statistical methods

2.1.3.1 Analysis sets

The full analysis set (FAS) analyses are presented. In Trial 511.74, the FAS for the double-blind period was labelled as FAS2. The FAS uses the intent-to-treat principles and consists of 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 defined are consistent with the FAS definitions stated in the International Conference on Harmonization E9 Statistical Principles for Clinical Trials, Section 5.2.1 (Full Analysis Set).

2.1.3.2 Primary and key secondary endpoints

The details of the statistical analyses are presented in greater detail in the Appendix 7.1.1. A brief description of the statistical analyses and inference strategy are provided below:

Trial 511.74

For Trial 511.74, two co-primary endpoints were defined: SSE and eDiary sexual desire score. This trial had a different trial design from the other Phase III trials and used different statistical methods for the primary analyses. Trial 511.74 was a randomized withdrawal study where patients first completed a 24-week open-label period in which all patients received flibanserin after which patients meeting the enrichment criteria (defined as patients who had an increase of 2 SSEs or more or an increase of 4 desire days or more) entered a 24-week double-blind placebo-controlled randomized withdrawal period. For SSE, a repeated measures Poisson regression model correcting for overdispersion with baseline as a covariate using an unstructured (UN) correlation structure with the number of days as an offset was performed, and the results at Week 48 (conclusion of the double-blind period) were presented. For eDiary sexual desire score, mixed model repeated measures (MMRM) analysis with baseline as a covariate using an unstructured (UN) correlation structure was performed, and the results from the contrast at Week 48 (conclusion of the double-blind period) were presented. Additional analyses for both co-primary endpoints were performed using an ANCOVA model using baseline as a covariate with treatment as a main effect. Details of the statistical inference strategy and the walk through of the results are provided in Section 7.1.1.1.

Trials 511.70, 511.71 and 511.75

For Trials 511.70, 511.71, and 511.75, two co-primary endpoints were defined: SSE change from baseline at Week 24 and eDiary sexual desire score change from baseline at Week 24. SSE was analyzed using Wilcoxon rank sum test stratified by pooled centre. The eDiary sexual desire score was analyzed using analysis of covariance (ANCOVA) using baseline as a covariate and adjusting for pooled centre. The Hochberg procedure was used to adjust for multiple comparisons [R97-1003]. Adjusted p-values will be presented where the appropriate p-values as per the Hochberg procedure will be calculated so as to always compare against a 0.05 level (as opposed to varying levels of p-value thresholds compared using unadjusted p-values). SSE was analyzed first for each dose compared to placebo, and the eDiary sexual desire endpoint was analyzed for the dose(s) that were significant on SSE. If both of the endpoints were statistically significant for a given dose, the key secondary endpoint of FSDS-R total score was analyzed. For Trials 511.70 and 511.71, the FSFI desire items change from baseline at Week 24 was defined as an additional key secondary endpoint in the TSAP before unblinding. For Trials 511.70, 511.71 and 511.75, FDA stated preference for the FSDS-R item 13 as the distress measure. As such, the FSDS-R item 13 results are presented along side the FSDS-R total score. Details of the statistical inference strategy and the walk through of the results for Trials 511.75, 511.71 and 511.70 are provided in Section 7.1.1.2, 7.1.1.3, 7.1.1.5, respectively. Below is a brief summary of the inference strategy:

Trial 511.75

Primary endpoints

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

For dose(s) that was positive on SSE, proceed to test the eDiary sexual desire score. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If both primary endpoints are positive for the same dose, then proceed to testing the key secondary endpoint

Key secondary endpoint

For dose(s) that was positive on both primary endpoints, proceed to test the FSDS-R total score. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

FSDS-R total score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

Trial 511.71

Primary endpoints

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

For dose(s) that was positive on SSE, proceed to test the eDiary sexual desire score. If both doses were positive, then start the testing at Step 1. If one dose was positive, then start the testing for that dose at Step 2; furthermore, $p_{(2)}$ will be multiplied by 2.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If both primary endpoints are positive for the same dose, then proceed to testing the key secondary endpoints.

Key secondary endpoints

For dose(s) that was positive on both primary endpoints, proceed to test the key secondary endpoints. If both doses were positive, then start the testing at Step 1. If one dose was positive, start the testing for that dose at Step 2; furthermore, $p_{(2)}$ will be multiplied by 2.

FSDS-R total score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else that no dose comparisons to placebo are statistically significant.

FSFI desire items - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

Trial 511.70

Primary endpoints

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

For dose(s) that was positive on SSE, proceed to test the eDiary sexual desire score. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If both primary endpoints are positive for the same dose, then proceed to testing the key secondary endpoints.

Key secondary endpoints

For dose(s) that was positive on both primary endpoints, proceed to test the key secondary endpoints. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

FSDS-R total score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else if $p_{(3)} > 0.05$, proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

FSFI desire items - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

Trial 511.77

For Trial 511.77, only one primary endpoint was defined: SSE change from baseline at Week 24. SSE was analyzed using Wilcoxon rank sum test stratified by pooled centre. Two key secondary endpoints were defined. In Trial Protocol Amendment 2, FSFI desire items change from baseline at Week 24 replaced eDiary sexual desire score as a key secondary endpoint. In the original trial protocol, the Hochberg procedure was used to adjust for multiple testing similar to the North American trials (511.70, 511.71 and 511.75). In the

amended inference strategy, an *a priori* hierarchical test procedure was used to control for multiplicity testing. SSE for the comparison of flibanserin 100 mg q.h.s. vs. placebo was tested first. If successful, the key secondary endpoints of FSFI desire times and FSDS-R total score for flibanserin 100 mg q.h.s. vs. placebo were tested in that order. Additionally, if the flibanserin 100 mg q.h.s. vs. placebo was statistically significant, then the SSE for the comparison of flibanserin 50 mg q.h.s. vs. placebo was tested. If successful, the key secondary endpoints of FSFI desire times and FSDS-R total score for flibanserin 50 mg q.h.s. vs. placebo were tested in that order. Details of the statistical inference strategy and the walk through of the results for Trial 511.77 for both the original and amended statistical analyses are provided in Section 7.1.1.4. Below is a brief summary of the inference strategy:

Trial 511.77

Primary endpoints (Defined in Trial Protocol Amendment 2)

SSE

Step 1: If flibanserin 100 mg q.h.s. vs placebo is statistically significant with $p \leq 0.05$, then reject the null hypothesis and proceed to Step 2

Step 2: If flibanserin 50 mg q.h.s. vs placebo is statistically significant with $p \leq 0.05$, then reject the null hypothesis

Key secondary endpoints (Defined in Trial Protocol Amendment 2)

Flibanserin 100 mg q.h.s. vs placebo

Before proceeding to test the key secondary endpoints, flibanserin 100 mg q.h.s. vs placebo must be significant for the primary endpoint

Step 1: FSFI desire items – if statistically significant with $p \leq 0.05$, then reject the null hypothesis and proceed to Step 2

Step 2: FSDS-R total score – if statistically significant with $p \leq 0.05$, then reject the null hypothesis

Flibanserin 50 mg q.h.s. vs placebo

Before proceeding to test the key secondary endpoints, flibanserin 50 mg q.h.s. vs placebo for SSE must be significant for the primary endpoint

Step 1: FSFI desire items – if statistically significant with $p \leq 0.05$, then reject the null hypothesis and proceed to Step 2

Step 2: FSDS-R total score – if statistically significant with $p \leq 0.05$, then reject the null hypothesis

Multiple dose adjustments

Acknowledging that the formal testing procedure and the strict statistical inference ends after failing to meet statistical significance via the Hochberg or hierarchical testing procedure, we nonetheless adjusted for multiple dose comparisons for all subsequent tests including the secondary endpoints by using the threshold of the final step in the Hochberg procedure following a discussion with the FDA during the April 26, 2010 Type C meeting. While this does not circumvent the failed endpoint and the calculated p-values thereafter should be considered nominal and exploratory, the use of this conservative adjustment elevates the rigor of these additional analyses.

As only the flibanserin 100 mg q.h.s dose group showed consistent efficacy results replicated across multiple trials, adjustment using the final step of the Hochberg procedure is equivalent to a Bonferroni adjustment where the study wise alpha is divided equally among all tested treatment arms. Instead of comparing the unadjusted p-value against alpha divided by the number of treatment arms, p-value adjustments are made by multiplying the unadjusted

p-values by the number of flibanserin treatment arms in the study so as to always compare the adjusted p-values against a level of 0.05. Therefore, for Trials 511.70 and 511.75 (trials with 3 flibanserin treatment arms), the unadjusted p-value is multiplied by a factor of 3 to calculate the adjusted p-value. For Trials 511.71 and 511.77 (trials with 2 flibanserin treatment arms), the unadjusted p-value is multiplied by a factor of 2 to calculate the adjusted p-value. Associated confidence intervals were also adjusted accordingly.

2.1.3.3 Pooled analyses

Pooled analyses will be presented for the main analyses (primary, key secondary and other secondary endpoints) along side the trial by trial results. The pooled analyses were pre-planned prior to unblinding, but after assessment of baseline comparability of any of the North American pivotal trials. Pooling of studies provides a more precise estimate of the effect size. To further examine potential between study differences, treatment by study interaction was tested as a sensitivity analysis to test of heterogeneity between studies. This sensitivity analysis demonstrated that there were no study-by-treatment interaction (Section 2.3.4.1).

As there were no formal testing procedures defined for these analyses, these analyses should be considered exploratory. Even though these analyses were exploratory, p-value were adjusted for multiple dose comparisons. As the pooling was performed for Trials 511.71 and 511.75 which in total consisted of 3 flibanserin treatment arms, all p-values for the pooled analyses were adjusted by multiplying the unadjusted p-value by a factor of 3 to calculate the adjusted p-value. For the onset of response and sub-population analyses, only the pooled results will be presented. The pooling allows for an increased sample size for greater power in performing these two analyses. For the onset of response analyses, greater power is needed to detect earlier and smaller effect size differences. For the sub-population analyses, a larger sample size is needed for small sub-populations such as race, ethnicity and other factors examined in the sub-population section.

The pooled analyses presented are for 511.71 and 511.75 combined examining placebo and flibanserin 100 mg q.h.s. For the pooled ANCOVA (and analysis of variance [ANOVA]) analyses, the following additional terms were included in the model: study and pooled centers nested in study. For the pooled analyses, the treatment by study interaction was examined to make sure that there was no treatment by study interactions. Further details are provided in Section 2.1.3.6.3 (Sensitivity analysis).

2.1.3.4 Other secondary endpoints

The additional analyses for the secondary endpoints are the same as the analyses performed for the primary and key secondary endpoints (as described in Section 2.1.3.2) but using the secondary endpoints. Other secondary endpoints were not included in the statistical inference strategy. Therefore, these analyses are exploratory analyses. Even though these secondary analyses were exploratory, all p-value were adjusted for multiple dose comparisons.

2.1.3.5 Responder and remitter endpoints

For the responder/remitter analyses, Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre was used. Responder and remitter endpoints were not included in the statistical inference strategy. Therefore, these analyses are exploratory analyses.

2.1.3.6 Supporting analyses

These are exploratory analyses. As with other secondary analyses, p-values were adjusted for multiple dose comparisons.

2.1.3.6.1 Onset of response

To fully characterize the time course of response, the primary and key secondary endpoints were evaluated at all time points. The methods for these analyses were the same as the analyses performed on the primary and key secondary endpoints but were performed for each visit. Onset of response analyses were not included in the statistical inference strategy. Therefore, these analyses are exploratory analyses.

2.1.3.6.2 Comparison in sub-population

Analyses within sub-populations were performed using the same methods as described in the primary and key secondary endpoints section (Section 2.1.3.2). Sub-population analyses were not included in the statistical inference strategy. Therefore, these analyses are exploratory analyses.

The following sub-populations were examined:

- Race: white, black, Asian
- Ethnicity: Hispanic, non-Hispanic
- Baseline hormone and protein levels
  - Baseline free testosterone: <1.1, ≥1.1
  - Baseline DHEA-S: <60.0, ≥60.0
  - Baseline SHBG: <80, ≥80 to <150, ≥150
- Baseline severity
  - Baseline SSE: >2 , ≤2
  - Baseline FSFI desire items: >1.8, ≤1.8
  - Baseline FSDS R total: >30, ≤30
- Presence of a secondary FSD diagnosis

- Female sexual arousal disorder (FSAD)
- Female orgasmic disorder (FOD)

- Presence of hormonal contraceptive use
- Completers

2.1.3.6.3 Sensitivity analysis

Two different types of sensitivity analyses were performed: 1) examine treatment by study interaction and 2) examine the impact of missing data due to early discontinuation.

The treatment by study interaction was examined to make sure that there were no treatment by study interactions, thereby, confirming that these studies can be pooled and that there were no differences in the treatment effect across trials. To assess treatment by interaction for the pooled analyses, an ANCOVA model with baseline as a covariate with the main effect terms study and pooled centre nested in study as well as the treatment by study interaction term was examined for the pooled analysis. Even though SSE was analyzed using the Wilcoxon rank sum test stratified by pooled centre, SSE was analyzed using the same model for the purposes of examining the interaction. For PGI-I, the same model was applied without the baseline covariate, since this endpoint is not collected at baseline.

The sensitivity analyses to assess the impact of missing data are explained in the following section on handling of missing data (Section 2.1.3.7).

2.1.3.7 Handling of missing data

<u>Handling of missing in endpoint derivation</u>

For SSE, patients were allowed to enter data for up to the last 3 days. If a patient missed more than 3 consecutive days, patients were not allowed to enter data beyond the last 3 days; thus, any days beyond the last 3 days would be missing. In order to calculate the SSE over a 4 week period, the total number of SSEs were divided by the number of enterable days (days for which the patient could have entered in data including the 3 day retrospection). This was then standardized to a 28 day period by multiplying by 28. As a sensitivity analyses, SSE was derived using an alternative method of simply summing the number of SSEs over the last 28 days. This endpoint was referred to as SSE (count) and was analysed as one of the other secondary endpoints.

For eDiary sexual desire score, patients were only allowed to enter data for the last 24 hours. If a patient skipped days, then those days were considered missing. In order to calculate the eDiary sexual desire score, the average of the entered values were multiplied by a constant of 28 days to derive the eDiary sexual desire score endpoint.

Handling of missing data across visits

In general, the following two methods were used: 1) last observation carried forward (LOCF), and 2) observed cases (OC).

In addition, sensitivity analyses to assess the impact of the missing data imputation methods were examined in two ways: 1) baseline observation carried forward and 2) mixed model repeated measures (MMRM). The results of these analyses are provided in Section 2.3.4.2.

In the first method, baseline observation carried forward was applied to the change from baseline endpoints and was thus termed "LOCFZERO" as these analyses imputed a value of zero representing no change from baseline for the missing visits. Baseline observation carried forward is a conservative estimation for missing data particularly if the flibanserin treatment group has 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.

In the second method, MMRM analyses were performed without any data imputation using only the observed cases. The MMRM analysis was performed to mirror the ANCOVA analysis (except for repeated measures aspect); therefore, the analysis was performed using baseline as a covariate with study and pooled centre 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 will be used. If AR(1) does not converge, the unstructured (UN) and compound symmetry (CS) covariance structures were examined.

2.2 SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

As was previously noted in the Executive Summary and is extensively documented in the remainder of this document, only the 100mg q.h.s. dosage of flibanserin was found to be consistently effective. Therefore, for the purpose of this submission, Trial 511.74 (24-week double-blind, placebo-controlled randomized withdrawal study) and Trials 511.71 and 511.75 (24-week randomized, placebo-controlled studies) are considered primary efficacy studies, as these were the North American studies that used the 100mg q.h.s. dose, Trials 511.70, 511.77 and 511.84 are considered as supportive as one did not contain the 100mg q.h.s dose (511.70), one was conducted in Europe (511.77) and one was an open label study (511.84).

Primary Efficacy Trials Supporting Application

- North American placebo-controlled randomized withdrawal: 511.74
- North American randomized, placebo-controlled parallel groups: 511.71, 511.75

Supportive Efficacy Trials

- North American randomized, placebo-controlled parallel groups: 511.70
- European randomized, placebo-controlled parallel groups: 511.77
- North American open-label extension: 511.84

2.2.1 Primary efficacy trials

2.2.1.1 Trial 511.74

Objective: To assess the efficacy of continued flibanserin treatment on sexual desire and satisfying sexual events (SSE) in premenopausal women with generalized acquired HSDD.

Design and Methods: Patients were treated with open-label, flexible-dose flibanserin for 24 weeks. At Week 24, patients meeting enrichment criteria (defined as an increase in SSE of 2 or more or an increase in eDiary desire days of 4 or more) were randomized to 24 weeks' continued flibanserin therapy at optimized dosage, or placebo. Co-primary endpoints were change from Week 24 (randomization) baseline in the number of SSE and total desire score/month, as recorded daily by patients in an electronic diary (the e-Diary For HSDD Trials©). Additional details regarding the statistical inference strategy are provided in Appendix 7.1.1.1 (Trial 511.74 statistical inference strategy).

Results: 738 patients entered the open-label phase of the study. Of these, 333 patients met enrichment criteria and were randomized to flibanserin (n = 163) or placebo (n = 170). Over the 24 weeks of open-label flibanserin treatment, the mean number of SSE and total desire score/month increased 2-fold and there was a 3-fold increase in the number of days in which desire was rated as moderate to strong. From Weeks 45-48, women randomized to flibanserin reported 28% more SSEs than women randomized to placebo (95% CI 1.1-1.5, $p<0.01$). From Week 29 (four weeks after randomization) to Week 48, daily desire score favored flibanserin over placebo ($p<0.05$). From Weeks 45-48, women randomized to flibanserin reported a statistically significant difference on FSFI desire items (0.3, $p<0.001$). The summary of the results are provided in Table 2.2.1.1: 1.

Conclusions: In the 24-week randomized withdrawal phase of a 48-week trial in premenopausal women with HSDD, flibanserin was superior to placebo on both of the primary endpoints, SSEs and eDiary sexual desire score.

Table 2.2.1.1: 1 Placebo-corrected mean change from baseline for select endpoints – Trials 511.74 (FAS, LOCF)

Endpoint	Placebo		Flibanserin			
	N	Δ from baseline	N	Δ from baseline	Diff from placebo	P-values
Primary endpoints						
SSE[1]	153		161		1.28	0.0064**
SSE[2] (secondary analysis)	170	-2.33	163	-1.37	0.96	0.0141##
eDiary sexual desire score[3]	158	25.42	146	29.23	3.80	0.0283*

1 P-value based on a repeated measures Poisson regression model correcting for overdispersion with baseline as a covariate using an unstructured (UN) correlation structure with the number of days as an offset. The model uses Week 48 as the reference group and includes the following terms: time (week), SSE Week 24 baseline and time by treatment interaction term. The value presented is the ratio of flibanserin to placebo. For this analysis OC was used.

2 For comparability purposes, the secondary analysis using the ANCOVA model using baseline as a covariate with treatment as a main effect is also presented.
3 P-values are based on MMRM with baseline as a covariate using an unstructured (UN) correlation matrix. For this analysis OC was used.
* p<0.05; ** p<0.01 ; # nominal p<0.05 ; ## nominal p<0.01

2.2.1.2 Trial 511.75

Objective: To assess the efficacy of flibanserin as a treatment for generalized acquired Hypoactive Sexual Desire Disorder (HSDD) in premenopausal North American women enrolled in Trial 511.75.

Design and Methods: Premenopausal women with clinician-diagnosed generalized acquired HSDD were randomized to 24-weeks' treatment with flibanserin 25 mg b.i.d. (n = 396), flibanserin 50 mg b.i.d. (n = 392), flibanserin 100 mg q.h.s. (n = 395), or placebo (n = 398). Co-primary endpoints were change from 4-week baseline to study end (Weeks 21–24) in the number of satisfying sexual events (SSE) and sexual desire score, measured using a daily electronic diary (eDiary). Secondary endpoints included change from baseline (Week 0) to study end (Week 24) in Female Sexual Distress Scale-Revised (FSDS-R) total, FSDS-R Item13, Female Sexual Function Index (FSFI) total and FSFI desire domain scores. Additional details regarding the statistical inference strategy are provided in Appendix 7.1.1.2 (Trial 511.75 statistical inference strategy).

Results: Mean (SD) baseline data were: SSE 2.8 (2.8) and eDiary desire score 11.3 (9.3) [maximum: 84]. Compared with placebo, flibanserin 100 mg q.h.s. improved the number of SSE by 73% (adjusted p<0.05). There was a numerically but not statistically significant improvement in eDiary desire score in favor of flibanserin (by 25%). Flibanserin 25 mg b.i.d. and 50 mg b.i.d. improved the number of SSE and eDiary desire score at study end; however, none of these differences was significant versus placebo. The flibanserin 100 mg q.h.s. regimen significantly improved FSDS-R total, FSDS-R Item 13, FSFI total and FSFI desire domain scores versus placebo at study end (adjusted p<0.01). The flibanserin 50 mg b.i.d. regimen significantly improved FSDS-R total, FSFI total and FSFI desire domain scores, but the FSDS-R item 13 showed trend levels at adjusted p-value of 0.0697. The flibanserin 25 mg b.i.d. regimens significant improved FSFI total and FSFI desire domain scores, but the FSDS-R total and FSDS-R item 13 showed trend levels at adjusted p-value of 0.1315 and 0.0857, respectively. The summary of the results are provided in Table 2.2.1.2: 1 showing the adjusted p-values.

Conclusions: In premenopausal women with HSDD, flibanserin 100 mg q.h.s. was associated with significant improvements in the number of SSE, sexual desire (measured by FSFI desire), distress associated with sexual dysfunction (measured by FSDS-R and Item 13) and sexual function (measured by FSFI) but did not significantly improve eDiary desire score, compared with placebo. The SSE primary endpoint was statistically significant as per the formal statistical inference procedures, but the other primary endpoint, eDiary sexual desire score was not; therefore, the interpretation of significance on secondary endpoints should be regarded as nominal significance.

Table 2.2.1.2: 1 Placebo-corrected mean change from baseline for select endpoints – Trials 511.75 (FAS, LOCF)

	Placebo		FLI 25 b.i.d.				FLI 50 b.i.d.				FLI 100 q.h.s.			
Endpoint	N	Δ from baseline	N	Δ from baseline	Diff from placebo	Adjusted P-values	N	Δ from baseline	Diff from placebo	Adjusted P-values	N	Δ from baseline	Diff from placebo	Adjusted P-values
Primary														
SSE	381	1.11	376	1.38	0.27	0.2896	369	1.44	0.34	0.3978	371	1.86	0.75	0.0244*
eDiary sexual desire score	381	6.77	376	7.95	1.18	0.8276	369	8.84	2.07	0.1716	371	8.48	1.71	0.3461
Key secondary[1]														
FSDS-R total	389	-5.22	384	-6.67	-1.45	0.1315	379	-7.15	-1.93	0.0225#	380	-7.77	-2.54	0.0012##
Other secondary														
FSFI desire items	388	0.56	384	0.76	0.20	0.0286#	379	0.79	0.23	0.0078##	379	0.89	0.33	<0.0001##

1 Since both primary endpoints were not statistically significant, the p-values for the key secondary endpoints should be regarded as nominal p-values and significance.

NOTE: For SSE, p-values are based on the Wilcoxon rank sum test stratified by pooled center.
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.
Adjusted p-values : * p<0.05; ** p<0.01; # nominal p<0.05 ; ## nominal p<0.01

2.2.1.3 Trial 511.71

Objective: To assess the efficacy of flibanserin as a treatment for generalized acquired Hypoactive Sexual Desire Disorder (HSDD) in premenopausal North American women enrolled in Trial 511.71.

Design and Methods: Premenopausal women with clinician-diagnosed generalized acquired HSDD were randomized to 24-weeks' treatment with placebo (n = 295), flibanserin 50 mg q.h.s. (n = 295) or 100 mg q.h.s. (n = 290). Co-primary endpoints were change from 4-week baseline period to study end (Weeks 21–24) in the number of satisfying sexual events (SSE) and sexual desire score, measured using a daily electronic diary (eDiary). Secondary endpoints included change from baseline (Week 0) to study end (Week 24) in Female Sexual Distress Scale-Revised (FSDS-R) (key secondary), FSDS-R Item 13, Female Sexual Function Index (FSFI) total and FSFI desire domain scores (key secondary). Additional details regarding the statistical inference strategy are provided in Appendix 7.1.1.3 (Trial 511.70 statistical inference strategy).

Results: Mean (SD) baseline data were: SSE 2.8 (2.7) and eDiary desire score 11.9 (9.7) [maximum: 84]. Compared with placebo, flibanserin 100 mg q.h.s. and 50 mg q.h.s. improved the number of SSE by 100% (adjusted $p<0.01$) and 75% (adjusted $p<0.05$), respectively, at study end. There were numerical but not statistically significant improvements in eDiary desire score in favor of flibanserin 100 mg q.h.s. (by 32%) and 50 mg q.h.s. (19%), respectively, at study end. Both flibanserin regimens significantly improved FSDS-R total, FSDS-R Item 13, FSFI total and FSFI desire domain scores versus placebo at study end ($p<0.05$, for all comparisons), except for flibanserin 50 mg q.h.s. on FSDS-R total and Item 13 scores. The summary of the results are provided in Table 2.2.1.3: 1 displaying adjusted p-values.

Conclusions: In premenopausal women with HSDD, flibanserin 100 mg q.h.s. was associated with significant improvements in the number of SSE, sexual desire (measured by FSFI desire), distress associated with sexual dysfunction (measured by FSDS-R and Item 13) and sexual function (measured by FSFI) but did not significantly improve eDiary desire score, compared with placebo. The SSE primary endpoint was statistically significant as per the formal statistical inference procedures, but the other primary endpoint, eDiary sexual desire score was not; therefore, the interpretation of significance on secondary endpoints should be regarded as nominal significance.

Table 2.2.1.3: 1 Placebo-corrected mean change from baseline displaying adjusted p-values - Trials 511.71 (FAS, LOCF)

	Placebo		FLI 50 q.h.s.				FLI 100 q.h.s.			
Endpoint	N	Δ from baseline	N	Δ from baseline	Diff from placebo	Adjusted P-values	N	Δ from baseline	Diff from placebo	Adjusted P-values
Primary										
SSE	285	0.83	291	1.38	0.56	0.0454*	275	1.58	0.75	0.0047**
eDiary sexual desire score	285	6.90	291	8.25	1.35	0.2606	275	9.14	2.24	0.1320
Key secondary[1]										
FSDS-R total	289	-4.93	293	-6.13	-1.20	0.3202	280	-8.86	-3.94	<0.0001##
FSFI desire items[2]	290	0.55	293	0.76	0.21	0.0345#	280	0.90	0.35	0.0002##

1 Since both primary endpoints were not statistically significant, the p-values for the key secondary endpoints should be regarded as nominal p-values and significance.

2 FSFI desire items was elevated from Other secondary endpoints to Key secondary endpoints in the TSAP before unblinding.

NOTE: For SSE, p-values are based on the Wilcoxon rank sum test stratified by pooled center.
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.
Adjusted p-values : * p<0.05; ** p<0.01; # nominal p<0.05 ; ## nominal p<0.01

2.2.2 Supportive trials

2.2.2.1 Trial 511.77

Objective: To assess the efficacy of 24 weeks' treatment with flibanserin for generalized acquired Hypoactive Sexual Desire Disorder (HSDD) in European premenopausal women enrolled in trial 511.77.

Design and Methods: This was a randomized placebo-controlled trial. Primary endpoint was change from baseline to study end in the number of satisfying sexual events (SSE). Secondary endpoints included: eDiary desire (measured using a daily electronic diary), Female Sexual Function Index (FSFI) desire domain, FSFI total, Female Sexual Distress Scale-Revised (FSDS-R) total and FSDS-R Item 13 scores. Additional details regarding the statistical inference strategy are provided in Appendix 7.1.1.5 (Trial 511.77 statistical inference strategy).

Results: At study end, mean increases in SSE were 0.9, 1.2 and 1.5 in the placebo, flibanserin 50 mg q.h.s., and 100 mg q.h.s. groups, respectively, and mean increases in eDiary desire score were 5.4, 5.6, and 7.7 in the placebo, flibanserin 50 mg q.h.s., and 100 mg q.h.s. groups, respectively. The summary of the results are provided in Table 2.2.2.1: 1 displaying adjusted p-values.

Conclusions: In this European dose-response trial in premenopausal women with HSDD, flibanserin 100 mg q.h.s. was associated with a numerically but not statistically significant improvement in SSE in favor of flibanserin and significant improvements in sexual desire measured by the eDiary and distress associated with sexual dysfunction (FSDS-R and Item 13) for the 100 mg flibanserin group. There were trends toward improving the sexual desire measured by FSFI desire domain, and sexual functioning (FSFI total score) compared with placebo. Since the primary endpoint, SSE, was not statistically significant; the interpretation of significance on secondary endpoints should be regarded as nominal significance.

Table 2.2.2.1: 1 Placebo-corrected mean change from baseline for select endpoints – Trials 511.77 (FAS, LOCF)

	Placebo		FLI 50 q.h.s.				FLI 100 q.h.s.			
Endpoint	N	Δ from baseline	N	Δ from baseline	Diff from placebo	Adjusted P-values	N	Δ from baseline	Diff from placebo	Adjusted P-values
Primary										
SSE	307	0.90	297	1.23	0.33	1.0000	299	1.48	0.57	0.1403
Key secondary[1]										
eDiary sexual desire score[2]	307	5.39	297	5.56	0.18	1.0000	299	7.71	2.33	0.0481#
FSFI desire items[2]	313	0.54	305	0.54	-0.01	1.0000	308	0.69	0.14	0.1633
FSDS-R total	313	-3.73	304	-4.78	-1.05	0.3925	308	-6.42	-2.69	0.0020##

1 Since the primary endpoint was not statistically significant, the p-values for the key secondary endpoints should be regarded as nominal p-values and significance.

2 eDiary sexual desire score was replaced by FSFI desire items as the Key secondary endpoints in Trial Protocol Amendment 2 while the trial was still on-going.

NOTE: For SSE, p-values are based on the Wilcoxon rank sum test stratified by pooled center.
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.
Adjusted p-values: * $p<0.05$; ** $p<0.01$; # nominal $p<0.05$; ## nominal $p<0.01$

2.2.2.2 Trial 511.70

Objective: To assess the efficacy of flibanserin as a treatment for generalized acquired Hypoactive Sexual Desire Disorder (HSDD) in premenopausal North American women enrolled in trial 511.70.

Design and Methods: Premenopausal women with clinician-diagnosed generalized acquired HSDD were randomized to 24 weeks' treatment with placebo (n = 335) or flibanserin 25 mg b.i.d. (n = 324), 50 mg q.h.s. (n = 342), or 50 mg b.i.d. (n = 315). Co-primary endpoints were change from 4-week baseline to study end (Weeks 21–24) in the number of satisfying sexual events (SSE) and sexual desire score, measured using a daily electronic diary (eDiary). Secondary endpoints included change from baseline (Week 0) to study end (Week 24) in Female Sexual Distress Scale-Revised (FSDS-R) total, FSDS-R Item 13, Female Sexual Function Index (FSFI) total and FSFI desire domain scores. Additional details regarding the

statistical inference strategy are provided in Appendix 7.1.1.3 (Trial 511.70 statistical inference strategy).

Results: Mean (SD) baseline data were: SSE 2.5 (2.6) and eDiary desire score 11.5 (9.4) [maximum: 84]. At study end, mean (SE) increases in SSE were 1.6 (4.3), 1.5 (3.4), 1.6 (4.2) and 1.6 (3.5) in the placebo, flibanserin 25 mg b.i.d., 50 mg q.h.s., and 50 mg b.i.d. groups, respectively, and mean increases in eDiary desire score were 7.5 (0.9), 8.8 (0.9), 7.0 (0.9), and 7.7 (0.9) in the placebo, flibanserin 25 mg b.i.d., 50 mg q.h.s., and 50 mg b.i.d. groups, respectively. No flibanserin group differed significantly from placebo on either co-primary endpoint, FSDS-R total, or Item 13 score at study end. At study end, flibanserin 25 mg b.i.d. significantly improved FSFI desire domain and FSFI total score versus placebo (adjusted $p<0.05$). The summary of the results are provided in Table 2.2.2.2: 1 displaying adjusted p-values.

Conclusions: Flibanserin 25 mg b.i.d., 50 mg q.h.s., and 50 mg b.i.d. did not improve the number of SSE or eDiary sexual desire score versus placebo.

Table 2.2.2.2: 1 Placebo-corrected mean change from baseline for select endpoints – Trials 511.70 (FAS, LOCF)

	Placebo		FLI 25 b.i.d.				FLI 50 q.h.s.				FLI 50 b.i.d.			
Endpoint	N	Δ from baseline	N	Δ from baseline	Diff from placebo	Adjusted P-values	N	Δ from baseline	Diff from placebo	Adjusted P-values	N	Δ from baseline	Diff from placebo	Adjusted P-values
Primary endpoints														
SSE	325	1.55	320	1.45	-0.10	1.0000	334	1.55	-0.00	0.6981	291	1.65	0.10	0.7550
eDiary sexual desire score	325	7.51	320	8.82	1.32	0.7880	334	7.03	-0.47	1.0000	291	7.72	0.21	1.0000
Key secondary endpoints[1]														
FSDS-R total	335	-6.21	324	-7.25	-1.04	0.6069	342	-5.76	0.46	1.0000	315	-7.46	-1.24	0.3886
FSFI desire items[2]	335	0.59	324	0.81	0.22	0.0262#	342	0.59	-0.00	1.0000	315	0.77	0.18	0.1094

1 Since the primary endpoints were not statistically significant, the p-values for the key secondary endpoints should be regarded as nominal p-values and significance.
2 FSFI desire items was elevated from Other secondary endpoints to Key secondary endpoints in the TSAP before unblinding.
NOTE: For SSE, p-values are based on the Wilcoxon rank sum test stratified by pooled center.
For other endpoints, p-values are based on an ANCOVA model using baseline as a covariate with main effect terms treatment and pooled center.
Adjusted p-values: * p<0.05; ** p<0.01; # nominal p<0.05 ; ## nominal p<0.01

2.2.2.3 Trial 511.84

Objective: To assess in a prospective, multi-center, 52-week, open-label trial the long term safety and tolerability of flibanserin in premenopausal women with HSDD.

Design and Methods: Premenopausal women with clinician-diagnosed generalized acquired HSDD who have completed one of the previous flibanserin trials (511.70, 511.71, 511.75, 511.74 or 511.105) were exposed to flibanserin at flexible dosages to optimize efficacy and tolerability. All subjects were initially started on flibanserin 50 mg q.h.s.; the dose and regimen was subsequently flexibly titrated within the range of 25 mg flibanserin b.i.d., 50 mg flibanserin q.h.s., 50 mg flibanserin b.i.d., or 100 mg flibanserin q.h.s., to individualize dose-optimization. The primary endpoints are the AE safety endpoints: the proportion of patients with the common, expected AE for flibanserin (somnolence, sedation, fatigue, dizziness, nausea, vomiting) individually and collectively; the proportion of discontinuations due to AEs; and the proportion of serious AEs (SAEs). Secondary endpoints included a number of efficacy measures, including mean change from baseline in the FSDS-R© (total and Question 13) and FSFI© (total and subscales).

Results: At the cut-off date for this document, 1723 patients were treated, 667 (38.7%) had completed the trial, 737 (42.8%) had discontinued and 319 patients (18.5%) were ongoing. About twice as many patients stabilized their dose regimen for 26 weeks on 100 mg (48% of patients entering the trial) as those who stabilized on 50 mg q.h.s. (27% of those entering the trial), while 50 mg b.i.d. and 25 mg b.i.d. were used for this duration by very few patients (2% and 4% of those entering trial, respectively). Combining the 100 mg q.h.s. and 50 mg b.i.d. exposures, 1136 patients were exposed to a flibanserin dosage of 100 mg/day for at least 6 months. At the time of this data cut-off, 1010 completed at least one year of flibanserin exposure.

The AEs resulting in discontinuation were comparable to the parallel placebo-controlled Trials 511.70, 511.71, 511.75, and 511.77.

Remitter categorization at the time of study entry (FSFI total >26.55, FSFI-desire >3.0) was used to differentiate patients, as these groups may show differential response in efficacy with continued exposure or new exposure (if patient was on placebo in the previous trial) to flibanserin. The subgroup of 81.0% of patients who entered the trial in the FSFI dysfunctional category and had FSFI follow-up scores (1377 patients) had a baseline mean FSFI-desire score of 1.8, and FSDS-R Q13 of 3.1. Of those meeting criteria for sexual dysfunction at baseline, the proportion in remission continued to increase, peaking at about 50% by Week 26, and continuing through Week 52. Of those patients in remission at baseline, the proportion remaining in remission during treatment rose from a value near 80% at Week 4 to a stable value of about 90%. Substantial improvement was supported by the results of all other efficacy measures, i.e., FSFI desire, FSDS-R, CGI, PGI, and PBE.

Conclusions: Flibanserin in doses of 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d., or 100 mg q.h.s. 52-week, open-label trial was well tolerated. Mean scores of most efficacy measures continued to improve for the majority of women over time.

2.3 COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

The following studies are presented in this document:

- 511.74: 24-week, open-label flibanserin treatment, followed by 24-week placebo-controlled, double-blind randomized withdrawal (for the purposes of this section, the double-blind placebo-controlled period of the trial are presented)
- 511.70, 511.71, 511.75: 24-week, placebo-controlled, parallel-group, double-blind trials
- 511.77: European 24-week, placebo-controlled, parallel-group, double-blind trial
- 511.84: 52-week, open-label flibanserin treatment, long-term safety trial

Additional analyses for 511.74 and 511.84 are presented in Section 2.5 (Persistence of efficacy and/or tolerance effects).

2.3.1 Study populations

Patient disposition, demographics, HSDD characteristics, and baseline characteristics are displayed in the sections below.

HSDD is characterized by a loss of sexual desire accompanied by personal distress or interpersonal difficulties. The definitions and criteria for HSDD and other FSD diagnoses are described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR®) [R05-1015].

The patient population in the randomized withdrawal Trial 511.74 and in the randomized placebo-controlled efficacy trials (511.70, 511.71, 511.75, and 511.77) were premenopausal women (aged 18 years and older) with a primary diagnosis of generalized, acquired HSDD as defined by the DSM-IV-TR® criteria. Trials 511.84 and 511.118 included women who completed a prior clinical trial of flibanserin whether they remained premenopausal or had become perimenopausal.

The overall population demonstrated manifestly severe symptoms of HSDD as assessed using validated measures (Table 2.3.1.3: 1), with mean FSDS-R scores of 30.2 to 31.7, FSFI total scores of 16.1 to 19.6 and FSFI desire items scores of 1.8 to 1.9, all of which notably exceed the validated cut-off scores (FSDS-R = 15, FSFI = 26.55, FSFI desire items = 3.0) for these measures to categorize dysfunctional from control women.

There is no established severity or baseline criterion for SSEs in women diagnosed with HSDD as SSEs are not a part of the DSM-IV-TR® diagnostic criteria; nevertheless, the baseline mean of 2.5 to 2.7 SSEs and 4.5 to 4.9 sexual activity per month in the Phase III

North American trials (Table 2.3.1.3: 1) appear to be low compared to the data on population norms of sexual activity in healthy women in this age range (6-10 per month) (R09-1488).

No significant differences in the baseline characteristics between the flibanserin and placebo treatment groups were noted across all North American trials.

Based on the demographics of the 945 women who participated in the 511.77 EU trial, fewer married women, black and Hispanic women, or women with higher educational levels participated when compared to women in the North American trials. European women also were, on average, of lower body mass index (BMI) and used hormonal contraceptives at a higher rate than North American women.

The European population (511.77) had scores similar to the North American women for the FSFI measure (total or desire items); however, EU sample scores were approximately 20% more severe, on average, on SSE and eDiary scores and about 10% less severe on distress measures (FSDS-R total and Q13). As such, the focus of the document continues to be on the women treated in the North American clinical development program.

2.3.1.1 Demographics

Patient demographics are displayed in Tables 2.3.1.1: 1 and 2.3.1.1: 2. No significant differences between flibanserin and placebo were noted across all trials.

Compared to the patients in the North American trials, the EU trial entered fewer married women, black and Hispanic women, or women with higher educational levels. European women also were, on average, of lower BMI and used hormonal contraceptives at a higher rate than North American women.

Table 2.3.1.1: 1 Demographic characteristics – Trials 511.70, 511.71, 511.75 (Treated Set)

		511.70		511.71		511.75		Pooled (511.71/.75)	
		Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Number of patients		349	1036	295	585	398	1183	693	1768
Age Group [N (%)]	18-34	158 (45.3)	468 (45.2)	126 (42.7)	261 (44.6)	157 (39.4)	531 (44.9)	283 (40.8)	792 (44.8)
	35-44	164 (47.0)	471 (45.5)	136 (46.1)	243 (41.5)	195 (49.0)	529 (44.7)	331 (47.8)	772 (43.7)
	>= 45 yrs	27 (7.7)	97 (9.4)	33 (11.2)	81 (13.8)	46 (11.6)	123 (10.4)	79 (11.4)	204 (11.5)
Age [years]	Mean	34.9	35.0	35.5	36.0	36.2	35.3	35.9	35.5
	SD	6.9	7.0	7.0	7.4	6.6	6.9	6.8	7.1
Race [N (%)]	White	297 (85.1)	912 (88.0)	256 (86.8)	512 (87.5)	370 (93.0)	1076 (91.0)	626 (90.3)	1588 (89.8)
	Black	49 (14.0)	105 (10.1)	33 (11.2)	66 (11.3)	22 (5.5)	90 (7.6)	55 (7.9)	156 (8.8)
	Asian	3 (0.9)	19 (1.8)	6 (2.0)	7 (1.2)	6 (1.5)	17 (1.4)	12 (1.7)	24 (1.4)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnic Origin-Hispanic	No	328 (94.0)	969 (93.5)	272 (92.2)	536 (91.6)	370 (93.0)	1126 (95.2)	642 (92.6)	1662 (94.0)
	Yes	21 (6.0)	66 (6.4)	23 (7.8)	48 (8.2)	28 (7.0)	57 (4.8)	51 (7.4)	105 (5.9)
	Missing	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Current Marital Status	Unmarried	73 (20.9)	228 (22.0)	58 (19.7)	142 (24.3)	60 (15.1)	270 (22.8)	118 (17.0)	412 (23.3)
	Married	276 (79.1)	808 (78.0)	237 (80.3)	443 (75.7)	338 (84.9)	913 (77.2)	575 (83.0)	1356 (76.7)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
How long in present relationship (years)	Mean	9.9	10.5	10.4	10.8	11.4	10.5	11.0	10.6
	SD	6.2	6.6	6.5	6.7	6.2	6.5	6.3	6.5
Hormonal contraceptive use	HC non-users	205 (58.7)	583 (56.3)	181 (61.4)	346 (59.1)	239 (60.1)	726 (61.4)	420 (60.6)	1072 (60.6)
	HC users	144 (41.3)	453 (43.7)	114 (38.6)	239 (40.9)	159 (39.9)	457 (38.6)	273 (39.4)	969 (39.4)
Smoking history	Never smoked	234 (67.0)	713 (68.8)	200 (67.8)	408 (69.7)	258 (64.8)	769 (65.0)	458 (66.1)	1177 (66.6)
	Ex-smoker	63 (18.1)	197 (19.0)	60 (20.3)	111 (19.0)	91 (22.9)	266 (22.5)	151 (21.8)	377 (21.3)
	Current smoker	52 (14.9)	126 (12.2)	35 (11.9)	66 (11.3)	49 (12.3)	148 (12.5)	84 (12.1)	214 (12.1)

Table 2.3.1.1: 2 Demographic characteristics – Trials 511.74 and 511.77 (Treated Set)

		North American			Europe	
		511.74				
		Open-label period	Double-blind period		511.77	
		Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Number of patients		738	170	163	318	627
Age Group [N (%)]	18-34	245 (33.2)	46 (27.1)	51 (31.3)	148 (46.5)	273 (43.5)
	34-44	365 (49.5)	87 (51.2)	85 (52.1)	147 (46.2)	290 (46.3)
	45 or greater	128 (17.3)	37 (21.8)	27 (16.6)	23 (7.2)	33 (10.6)
Age [years]	Mean	37.3	38.4	37.3	34.6	35.5
	SD	7.0	6.7	7.0	7.3	7.1
Race [N (%)]	White	698 (94.6)	161 (94.7)	150 (92.0)	290 (91.2)	577 (92.0)
	Black	32 (4.3)	9 (5.3)	12 (7.4)	3 (0.9)	5 (0.8)
	Asian	8 (1.1)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	25 (7.9)	43 (6.9)
Ethnic Origin-Hispanic	No	701 (95.0)	166 (97.6)	152 (93.3)	289 (90.9)	564 (90.0)
	Yes	37 (5.0)	4 (2.4)	11 (6.7)	3 (0.9)	15 (2.4)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	26 (8.2)	48 (7.7)
Current Marital Status	Not married	163 (22.1)	33 (19.4)	35 (21.5)	134 (42.1)	244 (38.9)
	Married	575 (77.9)	137 (80.6)	128 (78.5)	183 (57.5)	380 (60.6)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.5)
How long in present relationship (years)	Mean	11.47	12.6	11.6	11.0	11.19
	SD	6.81	7.2	6.8	7.06	6.96
Hormonal contraceptive use	HC non-users	N/A	N/A	N/A	150 (47.2)	291 (46.4)
	HC users	N/A	N/A	N/A	168 (52.8)	336 (53.6)
Smoking history	Never smoked	495 (67.1)	110(64.7)	115(70.6)	196 (61.6)	364 (58.1)
	Ex-smoker	137 (18.6)	34(20.0)	29(17.8)	53 (16.7)	115 (18.3)
	Current smoker	105 (14.2)	26(15.3)	19(11.7)	69 (21.7)	148 (23.6)

NOTE: Hormonal contraceptive use was not collected in 511.74.

2.3.1.2 HSDD characteristics

HSDD characteristics are displayed in Tables 2.3.1.2: 1 and 2.3.1.2: 2.

Women enrolled in the Phase 3 trials underwent rigorous diagnostic assessments requiring a structured interview, completion of a sexual symptom checklist (assessing desire, arousal, orgasm, and sexual pain), and assessment of potential confounding factors before being diagnosed as having HSDD. A validated scale (Beck Depression Inventory) was used to

screen for and rule out current depression and women taking medications known to have an effect on women's sexual function were excluded.

The overall population demonstrated manifestly severe symptoms of HSDD as assessed using validated measures at the baseline visit (Table 2.3.1.3: 1 and 2.3.1.3: 2), with mean FSDS-R scores of 30, FSFI total scores of 19.2 and FSFI desire items scores of 1.8, all of which notably exceed the validated cut-off scores (FSDS-R = 15, FSFI = 26.55, FSFI desire items = 3.0) for these measures to categorize dysfunctional from control women.

There is no established severity or baseline criterion for SSEs in women with HSDD, as SSEs per se are not addressed in the DSM-IV-TR® diagnostic criteria; nevertheless, the North American population mean of 2.7 SSEs and 4.7 sexual activity per month (Table 2.3.1.3: 1) is low in comparison with data of population norms of sexual activity in healthy women in this age range (6-10 per month) (R09-1488).

Concomitant disorders of sexual dysfunction (DSM-IV-TR®-defined) were present in approximately equal proportions across studies, i.e., Secondary FSAD (27.6–30.6%), and Secondary FOD (17.6–21.5%).

Table 2.3.1.2: 1 HSDD diagnostic characteristics – Trials 511.70, 511.71, 511.75 (Treated Set)

		511.70		511.71		511.75		Pooled (511.71/75)	
		Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Number of patients		349	1036	295	585	398	1183	693	1768
HSDD diagnosis	Principal	349 (100.0)	1036 (100.0)	295 (100.0)	585 (100.0)	398 (100.0)	1183 (100.0)	693 (100.0)	1768 (100.0)
	Secondary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HSDD duration (months)	Mean	56.7	57.9	59.7	55.1	64.9	61.0	62.7	59.1
	SD	44.4	44.6	46.0	41.8	49.6	44.6	48.2	43.8
Onset of HSDD	Lifelong	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.1)
	Acquired	349 (100.0)	1036 (100.0)	293 (99.3)	584 (99.8)	398 (100.0)	1183 (100.0)	691 (99.7)	1767 (99.9)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Context of HSDD	Generalized	349 (100.0)	1035 (99.9)	295 (100.0)	585 (100.0)	398 (100.0)	1183 (100.0)	693 (100.0)	1768 (100.0)
	Situational	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FSAD diagnosis	No diagnosis	227 (65.0)	689 (66.5)	214 (72.5)	408 (69.7)	291 (73.1)	897 (75.8)	505 (72.9)	1305 (73.8)
	Principal	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Secondary	122 (35.0)	345 (33.3)	74 (25.1)	161 (27.5)	106 (26.6)	283 (23.9)	180 (26.0)	444 (25.1)
	Missing	0 (0.0)	0 (0.0)	7 (2.4)	15 (2.6)	1 (0.3)	3 (0.3)	8 (1.2)	18 (1.0)
FOD diagnosis	No diagnosis	276 (79.1)	819 (79.1)	229 (77.6)	467 (79.8)	322 (80.9)	986 (83.3)	551 (79.5)	1453 (82.2)
	Principal	2 (0.6)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
	Secondary	68 (19.5)	213 (20.6)	59 (20.0)	103 (17.6)	75 (18.8)	192 (16.2)	134 (19.3)	295 (16.7)
	Missing	3 (0.9)	2 (0.2)	7 (2.4)	15 (2.6)	1 (0.3)	4 (0.3)	8 (1.2)	19 (1.1)

Table 2.3.1.2: 2 HSDD diagnostic characteristics by the defined study groupings – Trials 511.74 and 511.77 (Treated Set)

		North America			Europe	
		511.74				
		Open-label period	Double-blind period		511.77	
		Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Number of patients	N (%)	738	170	163	318	627
HSDD diagnosis	Principal	736 (99.7)	170 (100.0)	163 (100.0)	318 (100.0)	626 (99.8)
	Secondary	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
HSDD duration (months)	Mean	61.6	62.8	57.8	65.6	65.6
	SD	48.8	47.0	48.7	50.2	54.3
Onset of HSDD	Lifelong	5 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Acquired	733 (99.3)	170 (100.0)	163 (100.0)	318 (100.0)	626 (99.8)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Context of HSDD	Generalized	734 (99.5)	169 (99.4)	161 (98.8)	318 (100.0)	624 (99.5)
	Situational	4 (0.5)	1 (0.6)	2 (1.2)	0 (0.0)	2 (0.3)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
FSAD diagnosis	No diagnosis	532 (72.1)	123 (72.4)	111 (68.1)	227 (71.4)	432 (68.9)
	Principal	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.5)
	Secondary	206 (27.9)*	47 (27.6)	52 (31.9)	89 (28.0)	192 (30.6)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FOD diagnosis	No diagnosis	589 (79.8)	136 (80.0)	128 (78.5)	260 (81.8)	509 (81.2)
	Principal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Secondary	149 (20.2)*	34 (20.0)	35 (21.5)	56 (17.6)	117 (18.7)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

2.3.1.3 Baseline characteristics for efficacy endpoints

Baseline characteristics for efficacy endpoints are displayed in Table 2.3.1.3: 1 and 2.3.1.3: 2. The baseline efficacy characteristics were similar across groups in North America with the exception of the eDiary, but baseline severity differed somewhat in Europe.

Table 2.3.1.3: 1 Baseline characteristics for efficacy endpoints – Trials 511.70, 511.71 and 511.75 (Treated Set)

		511.70		511.71		511.75		Pooled (511.71/.75)	
		Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Number of patients		349	1036	295	585	398	1183	693	1768
Baseline SSE	Mean	2.7	2.5	2.7	2.8	2.7	2.8	2.7	2.8
	SD	3.2	2.4	2.8	2.7	2.8	2.7	2.8	2.7
Baseline eDiary sexual desire score	Mean	11.8	11.5	11.9	11.9	10.3	11.8	11.0	11.8
	SD	9.1	9.4	9.7	9.7	8.8	9.5	9.2	9.6
Baseline FSDS-R total	Mean	31.5	31.7	30.2	30.7	30.2	30.8	30.2	30.8
	SD	10.0	9.9	9.9	9.8	10.0	9.4	9.9	9.5
Baseline FSDS Item 13	Mean	3.3	3.3	3.2	3.2	3.2	3.2	3.2	3.2
	SD	0.8	0.7	0.8	0.8	0.8	0.8	0.8	0.8
Baseline FSFI desire items	Mean	1.8	1.8	1.9	1.8	1.8	1.8	1.9	1.8
	SD	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Baseline FSFI total	Mean	16.1	18.7	19.8	19.1	19.5	19.6	19.6	19.5
	SD	6.8	6.5	7.1	6.5	6.4	6.2	6.7	6.3
Baseline sexual activity	Mean	4.6	4.5	4.5	4.9	4.8	4.9	4.6	4.9
	SD	4.1	3.7	3.7	3.8	4.1	4.2	3.9	4.1

Table 2.3.1.3: 2 Baseline characteristics for efficacy endpoints – Trials 511.70, 511.71, 511.75, 511.77, 511.74 (Treated Set)

		North America			Europe	
		511.74				
		Open-label period	Double-blind period[1]		511.77	
		Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Number of patients		738	170	163	318	627
Baseline SSE	Mean	2.7	7.2	6.9	2.3	2.3
	SD	2.6	5.9	5.9	2.5	2.5
Baseline eDiary sexual desire score	Mean	12.2	34.2	35.5	9.0	9.7
	SD	9.5	16.2	16.6	8.2	9.3
Baseline FSDS-R total	Mean	30.2	15.2	17.1	28.2	28.2
	SD	9.1	10.4	11.3	10.1	9.8
Baseline FSDS Item 13	Mean	3.2	1.8	1.9	3.0	3.0
	SD	0.7	1.2	1.1	0.9	0.9
Baseline FSFI desire items	Mean	1.9	3.6	3.6	1.8	1.9
	SD	0.7	1.1	1.1	0.8	0.8
Baseline FSFI total	Mean	19.6	28.8	28.6	18.5	18.9
	SD	6.6	4.9	4.8	7.7	7.4
Baseline sexual activity	Mean	4.6	7.9	8.1	4.2	4.0
	SD	3.7	5.9	5.9	3.5	2.6

1 The baseline of the 511.74 double-blind period is from an enriched population which occurs after 24 weeks of open-label flibanserin treatment.

2.3.1.4 Patient disposition

Tables 2.3.1.4: 1 and 2.3.1.4: 2 display the patient disposition. The disposition table displays the number of patients who were entered (randomized), prematurely discontinued along with the reason for discontinuation, and completed.

The disposition of patients differed somewhat by treatment. In the North American trials, the rate of completing trial with placebo was 71.5%. The highest completion rate with the flibanserin dose groups was with 50 mg flibanserin q.h.s. (71.9%), followed by 25 mg b.i.d. (69.4%), and 100 mg q.h.s. (65.7%), and the lowest completion rate was with 50 mg b.i.d. (60.3%). Lack of efficacy was identified as the factor leading to discontinuation in only 2-3%, and showed no dose-relationship (Table 2.3.1.1: 1). Dropouts for AEs were clearly dose and regiment related, as will be discussed in the safety section of this overview.

Disposition in the EU study, 511.77, was similar with completion rates of 76.4% with placebo, 69.5% with 50 mg flibanserin, and 63.9% with 100 mg flibanserin. Lack of efficacy dropouts were 5.7-6.6% per treatment group, and AE dropouts were dose-related.

Table 2.3.1.4: 1 Patient disposition – 511.70, 511.71, 511.75 and pooled (511.71, 511.75)

	511.70		511.71		511.75		Pooled (511.71/.75)	
	Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Entered/randomized	350	1042	295	585	399	1185	694	1770
Not treated	1	6	0	0	1	2	1	2
Treated	349 (100.0)	1036 (100.0)	295 (100.0)	585 (100.0)	398 (100.0)	1183 (100.0)	693 (100.0)	1768 (100.0)
Not prematurely discontinued from trial medication	224 (64.2)	658 (63.5)	234 (79.3)	429 (73.3)	287 (72.1)	784 (66.3)	521 (75.2)	1213 (68.6)
Prematurely discontinued from trial medication	125 (35.8)	378 (36.5)	61 (20.7)	156 (26.7)	111 (27.9)	399 (33.7)	172 (24.8)	555 (31.4)
Adverse event	29 (8.3)	146 (14.1)	10 (3.4)	56 (9.6)	43 (10.8)	159 (13.4)	53 (7.6)	215 (12.2)
Lack of efficacy	9 (2.6)	21 (2)	8 (2.7)	11 (1.9)	11 (2.8)	32 (2.7)	19 (2.7)	43 (2.4)
Non compliant with protocol	11 (3.2)	27 (2.6)	3 (1.0)	14 (2.4)	7 (1.8)	31 (2.6)	10 (1.4)	45 (2.5)
Lost to follow-up	24 (6.9)	58 (5.6)	14 (4.7)	23 (3.9)	13 (3.3)	62 (5.2)	27 (3.9)	85 (4.8)
Consent withdrawn (not due to AE)	40 (11.5)	102 (9.8)	22 (7.5)	32 (5.5)	33 (8.3)	93 (7.9)	55 (7.9)	125 (7.1)
Other	12 (3.4)	24 (2.3)	4 (1.4)	20 (3.4)	4 (1.0)	22 (1.9)	8 (1.2)	42 (2.4)

Table 2.3.1.4: 2 Patient disposition – 511.74 and 511.77

	North American			Europe	
	511.74				
	Open-label period	Double-blind period		511.77	
	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin
Entered/randomized	749	170	163	318	943
Not treated	11	0	0	0	0
Treated	738 (100.0)	170 (100.0)	163 (100.0)	318 (100.0)	627
Not prematurely discontinued from trial medication	525 (71.1)	146 (85.9)	132 (81.0)	243 (76.4)	418(66.7)
Prematurely discontinued from trial medication	213 (28.9)	24 (14.1)	31 (19.0)	75 (23.6)	209 (33.3)
Adverse event	83 (11.2)	7 (4.1)	4 (2.5)	15 (4.7)	86 (13.7)
Lack of efficacy	54 (7.3)	0 (0.0)	5 (3.1)	18 (5.7)	39 (6.2)
Non compliant with protocol	13 (1.8)	2 (1.2)	4 (2.5)	20 (6.3)	40 (6.3)
Lost to follow-up	13 (1.8)	5 (2.9)	7 (4.3)	5 (1.6)	10 (1.6)
Consent withdrawn (not due to AE)	41 (5.6)	7 (4.1)	6 (3.7)	8 (2.5)	23 (3.7)
Other	9 (1.2)	3 (1.8)	5 (3.1)	9 (2.8)	11 (1.8)

2.3.2 Comparison of efficacy results of all studies

For the efficacy analyses, the FAS analysis set were used as explained in Section 2.1.3.1 (Analysis sets) using LOCF as explained in Section 2.1.3.7 unless otherwise specified.

The results of the individual trials are reported as well as the pooled analyses. In addition to the individual trials, pooled analyses of efficacy data from Trials 511.71 and 511.75 are presented in order to better characterize and more confidently assess the overall effect of flibanserin, as well as to assess subgroups and the effect of flibanserin over time. These pooled analyses were pre-planned for those clinical trials that were similar with respect to patient characteristics, data collection, dose of flibanserin and endpoints prior to unblinding as documented in the briefing package sent to the FDA as part of the Pre-NDA meeting. These pooled analyses in addition to the individual trial results form the most integrative evidence of the overall effect of flibanserin.

A summary of the results are displayed in Table 2.3.2: 1. The flibanserin 100 mg q.h.s. group consistently showed meaningful, positive differences from placebo for the majority of the displayed endpoints. The co-primary endpoint SSE was statistically significant in all three primary efficacy trials. The co-primary endpoint eDiary sexual desire score although showing supportive trends, failed to reach statistical significance in two of the three primary efficacy trials. All of the additional endpoints are thus considered to be exploratory but

demonstrate a consistent positive effect of flibanserin on the hallmark symptoms of HSDD. Further details of the results for each of these endpoints are presented in the sections below for each trial.

Table 2.3.2: 1 Placebo-corrected mean change from baseline using adjusted p-values – Trials 511.74, 511.71, 511.75, 511.77 (FAS, LOCF)

	North America				Europe
	Double blind			Pooled	
	511.74	511.71	511.75	511.71/.75	511.77
Endpoint	FLI	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.
Primary endpoints					
SSE	1.0[3] **	0.75 **	0.75 *	0.75 **	0.57
eDiary sexual desire score[2]	3.8 *	2.24	1.71	1.90 *	2.33 #
Key secondary endpoints[1]					
FSFI desire items	0.3 ##	0.35 ##	0.33 ##	0.34 **	0.14
FSDS-R total	-2.9 ##	-3.94 ##	-2.54 ##	-3.19 **	-2.69 ##
Other secondary endpoints					
FSDS-R Item 13	-0.3 ##	-0.36 ##	-0.26 ##	-0.30 ##	-0.20 #
FSFI total	2.1 ##	2.54 ##	1.51 ##	1.94 ##	0.91
PGI-I	-0.3 ##	-0.35 ##	-0.40 ##	-0.37 ##	-0.15
SSE (count)	1.0 #	0.62 ##	0.73 #	0.68 ##	0.46

1 For Trials 511.71 and 511.75, since both co-primary endpoints were not statistically significant, the interpretation of the p-values for the key secondary and other secondary endpoints should be regarded as nominal p-values and significance. For Trial 511.74, both of the primary endpoints, SSE and eDiary sexual desire score, were statistically significant; however, the trial did not specify key secondary endpoints.

2 For Trial 511.77, since the primary endpoint was not statistically significant, the p-values for the key secondary and other secondary endpoints should be interpreted as nominal p-values and significance. The eDiary sexual desire score is presented under the primary endpoint set in this table since it was a primary endpoint in all other trials presented in this table, but this endpoint was a key secondary endpoint in Trial 511.77.

3 For Trial 511.74, SSE was analyzed using Poisson regression as the primary analysis for which the result was statistically significant with a ratio of 1.28 favoring flibanserin. For the purposes of this table, the results displayed are the mean difference from placebo for comparability purposes.

NOTE: Analysis methods are described in Section 2.1.3.2
Adjusted p-values : * p<0.05; ** p<0.01 ; # nominal p<0.05; ## nominal p<0.01.

2.3.2.1 Primary and key secondary endpoints

SSE

In the double-blind period of the randomized withdrawal Trial 511.74, the difference between Flibanserin and placebo at end of the trial was statistically significant with a 1.28-fold difference in the rate of SSEs (as per the pre-specified Poisson regression detailed in Section 2.1.3.2 and Section 2.2.1.1); for comparability purposes, the table displays the mean difference from placebo of 1.0 which was also statistically significantly different from placebo.

In the North American placebo-controlled trials that included the flibanserin 100 mg q.h.s. group (Trials 511.71, 511.75), the comparison of flibanserin 100 mg q.h.s. to placebo for the SSE change from baseline was statistically significant (Table 2.3.2: 1).

In Trial 511.71, patients on placebo had a change from baseline of 0.83 and patients on flibanserin 100 mg q.h.s had a change from baseline of 1.58. The difference was 0.75 with a Hochberg adjusted p-value of 0.0024 (Table 2.2.1.3: 1).

In Trial 511.75, patients on placebo had a change from baseline of 1.11 and patients on flibanserin 100 mg q.h.s had a change from baseline of 1.86. The difference was 0.75 with a Hochberg adjusted p-value of 0.0244 (Table 2.2.1.3: 2).

The comparison of flibanserin 100 mg q.h.s. versus placebo was not statistically significant in the European Trial 511.77, though patients on flibanserin had a numerically higher increase in SSEs over placebo. Patients on placebo had a change from baseline of 0.90 and patients on flibanserin 100 mg q.h.s had a change from baseline of 1.48. The difference was 0.57 with an adjusted p-value of 0.2806 (Table 2.2.2.1: 1).

eDiary sexual desire score

The comparisons of the flibanserin treatment groups to placebo was statistically significant for the eDiary sexual desire score in Trial 511.74 with a difference from placebo of 3.8 at the end of the double-blind period.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. versus placebo was not statistically significant with adjusted p-values of 0.1320 and 0.3461 for Trials 511.71 and 511.75, respectively (Table 2.3.2: 1).

In Trial 511.71, patients on placebo had a change from baseline of 6.90 and patients on flibanserin 100 mg q.h.s had a change from baseline of 9.14. The difference was 2.24 with an adjusted p-value of 0.1320 (Table 2.2.1.3: 1).

In Trial 511.75, patients on placebo had a change from baseline of 6.77 and patients on flibanserin 100 mg q.h.s had a change from baseline of 8.48. The difference was 1.71 with an adjusted p-value of 0.3461 (Table 2.2.1.2: 1).

eDiary sexual desire score was considered as an other secondary endpoint in Trial 511.77. This endpoint was nominally significant favoring flibanserin 100 mg q.h.s. over placebo. Patients on placebo had a change from baseline of 5.39 and patients on flibanserin 100 mg q.h.s had a change from baseline of 7.71. The difference was 2.33 with an adjusted p-value of 0.0481 (Table 2.2.2.1: 1).

FSFI desire items

In the double-blind period of the randomized withdrawal trial 511.74, the difference between flibanserin and placebo at end of the trial was statistically significant with a difference from placebo of 0.3.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. to placebo for the FSFI desire items change from baseline was nominally significant (Table 2.3.2: 1). The difference between flibanserin 100 mg q.h.s. and placebo was 0.4 and 0.3 in Trials 511.71, 511.75.

In Trial 511.71, patients on placebo had a change from baseline of 0.55 and patients on flibanserin 100 mg q.h.s had a change from baseline of 0.90. The difference was 0.35 with an adjusted p-value of 0.0002 (Table 2.2.1.3: 1).

In Trial 511.75, patients on placebo had a change from baseline of 0.56 and patients on flibanserin 100 mg q.h.s had a change from baseline of 0.89. The difference was 0.33 with an adjusted p-value of <0.0001 (Table 2.2.1.2: 1).

The comparison of flibanserin 100 mg q.h.s. versus placebo in Trial 511.77 was not statistically significant although there was a trend with an adjusted p-value of 0.1633. Patients on placebo had a change from baseline of 0.54 and patients on flibanserin 100 mg q.h.s had a change from baseline of 0.69. The difference was 0.14 with an adjusted p-value of 0.1633 (Table 2.2.2.1: 1).

FSDS-R total score

In the double-blind period of the randomized withdrawal Trial 511.74, the difference between flibanserin and placebo at end of the trial was statistically significant with a difference from placebo of -2.9.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. to placebo for FSDS-R total score change from baseline was nominally significant (Table 2.3.2: 1). For FSDS-R, lower values represent less distress, thus negative values indicate improvement.

In Trial 511.71, patients on placebo had a change from baseline of -4.93 and patients on flibanserin 100 mg q.h.s had a change from baseline of -8.86 (lower values indicate less distress). The difference was -3.94 with an adjusted p-value of <0.0001 (Table 2.2.1.3: 1).

In Trial 511.75, patients on placebo had a change from baseline of -5.22 and patients on flibanserin 100 mg q.h.s had a change from baseline of -7.77. The difference was -2.54 with an adjusted p-value of 0.0012 (Table 2.2.1.2: 1).

The comparison of flibanserin 100 mg q.h.s. versus placebo in Trial 511.77 was nominally significant. Patients on placebo had a change from baseline of -3.73 and patients on flibanserin 100 mg q.h.s had a change from baseline of -6.42. The difference was -2.69 with an adjusted p-value of 0.0020 (Table 2.2.2.1: 1).

FSDS-R Item 13

In the double-blind period of the randomized withdrawal Trial 511.74, the difference between flibanserin and placebo at end of the trial was statistically significant with a difference from placebo of -0.3.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. to placebo for FSDS-R Item 13 score change from baseline was nominally significant (Table 2.3.2: 1). For FSDS-R Item 13, lower values represent less distress related to HSDD, thus, negative values indicate improvement. The difference between flibanserin 100 mg q.h.s. and placebo was -0.36 and -0.26 in Trials 511.71 and 511.75.

In Trial 511.71, patients on placebo had a change from baseline of -0.46 and patients on flibanserin 100 mg q.h.s had a change from baseline of -0.82. The difference was -0.36 with an adjusted p-value of 0.0002.

In Trial 511.75, patients on placebo had a change from baseline of -0.48 and patients on flibanserin 100 mg q.h.s had a change from baseline of -0.74. The difference was -0.26 with an adjusted p-value of 0.0019.

The comparison of flibanserin 100 mg q.h.s. versus placebo in Trial 511.77 was nominally significant. Patients on placebo had a change from baseline of -0.35 and patients on flibanserin 100 mg q.h.s had a change from baseline of -0.55. The difference was -0.20 with an adjusted p-value of 0.0326.

2.3.2.2 Other secondary endpoints

As explained in Section 2.1.3.4 under Statistical methods for other secondary endpoints. All analyses performed for other secondary endpoints are considered exploratory.

PGI-I

In the double-blind period of the randomized withdrawal Trial 511.74, the difference between flibanserin and placebo at end of the trial was statistically significant with a difference from placebo of -0.3. For PGI-I, lower values indicate improvement, since a score of 1 indicates “very much improved” and 7 indicates “very much worse”.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. to placebo for PGI-I was nominally significant (Table 2.3.2: 1). The difference between flibanserin 100 mg q.h.s. and placebo was -0.35 and -0.40 in Trials 511.71 and 511.75, respectively.

In Trial 511.71, patients on placebo had a change from baseline of 3.71 and patients on flibanserin 100 mg q.h.s had a change from baseline of 3.36. The difference was -0.35 with an adjusted p-value of <0.0001.

In Trial 511.75, patients on placebo had a change from baseline of 3.72 and patients on flibanserin 100 mg q.h.s had a change from baseline of 3.33. The difference was -0.40 with an adjusted p-value of <0.0001.

The comparison of flibanserin 100 mg q.h.s. versus placebo in Trial 511.77 was not statistically significant. Patients on placebo had a change from baseline of 3.72 and patients on flibanserin 100 mg q.h.s had a change from baseline of 3.57. The difference was -0.15 with an adjusted p-value of 0.0978.

SSE (count)

As described in Section 2.1.2.1.1, SSE (count) is alternative derivation of SSE that does not use any standardization; instead, missing days are imputed with a value of zero. This endpoint was analysed as a sensitivity analysis to the primary SSE endpoint.

In the double-blind period of the randomized withdrawal Trial 511.74, the difference between flibanserin and placebo at end of the trial was nominally significant with a difference from placebo of 1.0 per month.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. to placebo for SSE (count) was nominally significant (Table 2.3.2: 1). The difference between flibanserin 100 mg q.h.s. and placebo was 0.62 and 0.73 in Trials 511.71 and 511.75, respectively.

In Trial 511.71, patients on placebo had a change from baseline of 0.66 and patients on flibanserin 100 mg q.h.s had a change from baseline of 1.28. The difference was 0.62 with an adjusted p-value of 0.0138.

In Trial 511.75, patients on placebo had a change from baseline of 0.86 and patients on flibanserin 100 mg q.h.s had a change from baseline of 1.59. The difference was 0.73 with an adjusted p-value of 0.0044.

The comparison of flibanserin 100 mg q.h.s. versus placebo was not statistically significant in the European Trial 511.77, although there was a numerical trend indicating efficacy. Patients on placebo had a change from baseline of 0.71 and patients on flibanserin 100 mg q.h.s had a change from baseline of 1.17. The difference was 0.46 with an adjusted p-value of 0.3461.

FSFI total score

In the double-blind period of the randomized withdrawal Trial 511.74, the difference between flibanserin and placebo at end of the trial was nominally significant with a difference from placebo of 2.1.

In Trials 511.71 and 511.75, the comparison of flibanserin 100 mg q.h.s. to placebo for FSFI total score was nominally significant (Table 2.3.2: 1). The difference between flibanserin 100 mg q.h.s. and placebo was 2.5 and 1.5 in Trials 511.71 and 511.75, respectively.

In Trial 511.71, patients on placebo had a change from baseline of 2.43 and patients on flibanserin 100 mg q.h.s had a change from baseline of 4.98. The difference was 2.54 with an adjusted p-value of <0.0001.

In Trial 511.75, patients on placebo had a change from baseline of 2.57 and patients on flibanserin 100 mg q.h.s had a change from baseline of 4.08. The difference was 1.51 with an adjusted p-value of 0.0030.

The comparison of flibanserin 100 mg q.h.s. versus placebo was not nominally significant in the European Trial 511.77, although there was a numerical trend indicating efficacy. Patients on placebo had a change from baseline of 2.52 and patients on flibanserin 100 mg q.h.s had a change from baseline of 3.44. The difference was 0.91 with an adjusted p-value of 0.2795.

2.3.2.3 Responder and remitter endpoints

The PGI-I based anchoring method was used to determine the responder criterion for each endpoint for Trials 511.70, 511.71, 511.75 and 511.77. PGI-I anchored responder endpoints were not defined for the randomized withdrawal trial, 511.74. Further details on the PGI-I anchoring method are provided in Section 2.1.2.4. The PGI-I anchored responder criterion for each endpoint are presented in Table 2.1.2.4: 1. The section below provides results for both the PGI-I anchored responder endpoints as well as the responder endpoints using pre-specified values as explained in Section 2.1.2.4.

In the North American trials, the flibanserin 100 mg q.h.s. group consistently showed a nominally significant difference from placebo for all of the displayed endpoints with the exception of the responder endpoints based on the eDiary sexual desire score and the FSFI remitter endpoint with differences from placebo of over 10% on nearly all responder and remitter endpoints (Table 2.3.2.3: 1). Responder analyses using additional cut points are presented in Table 7.1.2.2: 1.

Table 2.3.2.3: 1 Difference from placebo for responder endpoint analysis – Trials 511.71, 511.75, 511.77 and pooled (FAS, LOCF)

	North America									Europe		
	511.71			511.75			Pooled 511.71/.75			511.77		
Endpoint	FLI 100 q.h.s. %	PBO %	Diff	FLI 100 q.h.s. %	PBO %	Diff	FLI 100 q.h.s. %	PBO %	Diff	FLI 100 q.h.s. %	PBO %	Diff
PGI-I anchored responder endpoints												
SSE	47.6	33.0	14.7 **	44.2	34.1	10.1 *	45.7	33.6	12.0 **	36.1	30.3	5.8
eDiary sexual desire score	41.1	38.2	2.8	38.0	32.0	6.0	39.3	34.7	4.6	31.8	27.0	4.7
FSFI desire items	42.9	30.7	12.2 **	45.6	32.7	12.9 **	44.5	31.9	12.6 **	36.7	27.8	8.9 *
FSFI total	46.8	31.5	15.3 **	48.3	35.9	12.4 **	47.6	34.0	13.6 **	30.8	25.9	4.9
FSDS-R Q13	54.6	42.9	11.7 **	49.5	40.1	9.4 *	51.7	41.3	10.4 **	44.5	35.1	9.3 *
FSDS-R total	58.6	47.8	10.8 *	56.6	45.2	11.3 **	57.4	46.3	11.1 **	44.2	30.7	13.5 **
Remitter endpoints												
FSFI desire items remitter (>3.0)	33.2	21.0	12.2 **	32.5	21.3	11.1 **	32.8	21.2	11.6 **	28.2	19.8	8.4 *
FSDS-R total remitter (<15)	31.4	18.0	13.4 **	27.6	20.6	7.1	29.2	19.5	9.8 **	25.0	20.1	4.9
Other responder endpoints												
PGI-I (very much/much improved)	21.8	10.0	11.8 **	20.6	9.8	10.8 **	21.1	9.9	11.2 **	14.0	6.4	7.6 **
PGI-I (very much/much/minimally improved)	50.0	30.3	19.7 **	47.0	30.3	16.6 **	48.3	30.3	17.9 **	35.7	28.8	7.0
Patient Benefit Evaluation	38.6	26.7	11.9 *	41.9	24.2	17.7 **	40.5	25.2	15.2 **	27.2	15.8	11.4 **

Note: P-value based on comparison vs placebo using the Cochran-Mantel-Haenszel test stratified by pooled centre: adjusted p-values: * nominal p<0.05; ** nominal p<0.01

SSE responder analyses

In all of the North American trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for the SSE responder endpoint was statistically significant (Table 2.3.2.3: 1). For the SSE responder endpoint, 47.6% and 44.2% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 14.7% and 10.1% for Trials 511.71 and 511.75, respectively. Responder analyses using additional cut points (>= 1, >= 2, >= 3, >= 4) are presented in Table 7.1.2.2: 1.

FSFI desire items responder analyses

In all of the North American trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for FSFI desire responder endpoint was statistically significant (Table 2.3.2.3: 1). For the FSFI desire items responder endpoint, 42.9% and 45.6% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 12.2% and 12.9% for Trials 511.71 and 511.75, respectively. Responder analyses using additional cut points (>= 0.6, >= 1.2, >= 1.8, >= 2.4) are presented in Table 7.1.2.2: 1.

FSFI desire items remitter analyses

In all of the trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for the FSFI desire items remitter endpoint of greater than 3.0 was statistically significant (Table 2.3.2.3: 1). For the FSFI desire items remitter endpoint, 33.2% and 32.5% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 12.2% and 11.1% for Trials 511.71 and 511.75, respectively.

FSFI total score responder analyses

In all of the North American trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for FSFI total score responder endpoint was statistically significant (Table 2.3.2.3: 1). For the FSFI total score responder endpoint, 46.8% and 48.3% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 15.3% and 12.4% for Trials 511.71 and 511.75, respectively. Responder analyses using additional cut points (>= 4, >= 6, >= 8, >= 10) are presented in Table 7.1.2.2: 1.

eDiary sexual desire score responder analyses

Within the individual trials, none of the comparisons of flibanserin 100 mg q.h.s. to placebo for the PGI-I anchor-based responder criteria for the eDiary sexual desire score were statistically significant (Table 2.3.2.3: 1). Responder analyses using additional cut points (>8, >10, >12, >14) are presented in Table 7.1.2.2: 1.

FSDS-R Item 13 responder analyses

In all of the trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for the FSDS-R Item 13 responder endpoint was statistically significant (Table 2.3.2.3: 1). For the FSDS-R Item 13 responder endpoint, 54.6% and 49.5% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 11.7% and 9.4% for Trials 511.71 and 511.75, respectively. Responder analyses using additional cut points (<= -1, <= -2, <= -3) are presented in Table 7.1.2.2: 1.

FSDS-R total score responder analyses

In all of the trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo was statistically significant for the PGI-I anchor-based responder criteria for the FSDS-R total score (Table 2.3.2.3: 1). For the FSDS-R total score responder endpoint, 58.6% and 56.6% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 10.8% and 11.3% for Trials 511.71 and 511.75, respectively. Responder analyses using additional cut points (< -5, < -8, < -11, < -14) are presented in Table 7.1.2.2: 1.

FSDS-R total score remitter analyses

In Trials 511.71 and Ttrials 511.71 and 511.75 pooled, the comparison of flibanserin 100 mg q.h.s. to placebo for the FSDS-R total score remitter endpoint of less than 15 was statistically significant (Table 2.3.2.3: 1). For the FSDS-R total score remitter endpoint, 31.4% and 27.6% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 13.4% and 7.1% for Trials 511.71 and 511.75, respectively.

PGI-I “very much improved” or “much improved” responder analyses

In all of the trials that included the flibanserin 100 mg q.h.s. group, the comparison of the flibanserin 100 mg q.h.s. to placebo for the PGI-I responder endpoint of “very much improved” or “much improved” was statistically significant (Table 2.3.2.3: 1). For the PGI-I responder endpoint of “very much improved” or “much improved”, 21.8% and 20.6% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 11.8% and 10.8% for Trials 511.71 and 511.75, respectively.

PGI-I “very much improved”, “much improved”, or “minimally improved” responder analyses

In all of the trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for the results of PGI-I responder endpoint of “very much improved”, “much improved” or “minimally improved” was statistically significant (Table 2.3.2.3: 1). For the PGI-I responder endpoint of “very much improved”, “much improved” or “minimally improved”, 50.0% and 47.0% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 19.7% and 16.6% for Trials 511.71 and 511.75, respectively.

Patient benefit evaluation responder analyses

In all of the trials that included the flibanserin 100 mg q.h.s. group, the comparison of flibanserin 100 mg q.h.s. to placebo for the results of the patient benefit evaluation was statistically significant (Table 2.3.2.3: 1). For the patient benefit evaluation, 38.6% and 41.9% of patients on flibanserin 100 mg q.h.s. responded representing a difference from placebo of 11.9% and 17.7% for Trials 511.71 and 511.75, respectively.

2.3.2.4 Summary of the pooled efficacy results

Overall, the flibanserin 100 mg q.h.s. compared with placebo in the analysis of the pooled North American studies demonstrated improvements to the following endpoints that are the defining characteristics of HSDD:

- A statistically significant and clinically meaningful improvement in SSE between flibanserin 100 mg q.h.s. and placebo of 0.75 as well as for the PGI-I anchored responder in which there was a 12.0% difference between flibanserin 100 mg q.h.s. and placebo which was statistically significant (Table 2.3.2: 1 and 2.3.2.3: 1).
- A statistically significant but not clinically meaningful improvement in eDiary desire score between flibanserin 100 mg q.h.s. and placebo of 1.90. The difference between flibanserin 100 mg q.h.s. and placebo for the PGI-I anchored responder endpoint was 4.6% and was not statistically significant (Table 2.3.2: 1 and 2.3.2.3: 1).
- A statistically significant and clinically meaningful improvement in FSFI desire items between flibanserin 100 mg q.h.s. and placebo of 0.3 as well as for the PGI-I anchored responder in which there was a 12.6% difference between flibanserin 100 mg q.h.s. and placebo which was statistically significant (Table 2.3.2: 1 and 2.3.2.3: 1).
- A statistically significant and clinically meaningful improvement in FSFI total score between flibanserin 100 mg q.h.s. and placebo of 1.94 as well as for the PGI-I anchored responder in which there was a 13.6% difference between flibanserin 100 mg q.h.s. and placebo which was statistically significant (Table 2.3.2: 1 and 2.3.2.3: 1).
- A statistically significant and clinically meaningful reduction in FSDS-R Item 13 between flibanserin 100 mg q.h.s. and placebo of 0.3 as well as for the PGI-I anchored responder in which there was a 10.4% difference between flibanserin 100 mg q.h.s. and placebo which was statistically significant (Table 2.3.2: 1 and 2.3.2.3: 1).
- A statistically significant and clinically meaningful reduction in FSDS-R total score between flibanserin 100 mg q.h.s. and placebo of 3.2 as well as for the PGI-I anchored responder in which there was a 11.1% difference between flibanserin 100 mg q.h.s. and placebo which was statistically significant (Table 2.3.2: 1 and 2.3.2.3: 1).

These results capture the clinically meaningful effect of flibanserin 100 mg as assessed by and anchored to each individual woman's assessment of her impression of improvement. These blinded assessments by women may represent the most meaningful endpoint within the flibanserin program, as each woman is her own best judge of what is meaningful to her and her experience of HSDD, irrespective of hierarchical endpoint testing.

2.3.3 Onset of response

The onset of response for flibanserin 100 mg q.h.s. was established by Week 4, the earliest time point for which efficacy was assessed. Thus, although it is possible that flibanserin effect is established sooner, no data are available to address this. For the North American trials pooled, the flibanserin 100 mg q.h.s. group consistently showed a statistically significant difference from placebo by Week 4 for all displayed endpoints (Table 2.3.3: 1 and 2.3.3: 2).

Table 2.3.3: 1 Placebo-corrected mean change from baseline over time for flibanserin 100 mg q.h.s. – Pooled (511.71, 511.75) (FAS, LOCF)

Visit	SSE	eDiary desire	FSFI desire items	FSDS-R total	FSDS-R Item 13	PGI-I	FSFI total
Week 4	0.33	1.1	0.2 **	-1.8 **	-0.1 *	-0.2 **	0.9 **
Week 8	0.69 **	2.3 **	0.3 **	-2.7 **	-0.3 **	-0.4 **	1.3 **
Week 12	0.41	2.0 *					
Week 16	0.52 *	2.0 *	0.3 **	-3.1 **	-0.3 **	-0.4 **	1.8 **
Week 20	0.64 **	1.6					
Week 24	0.75 **	1.9	0.3 **	-3.2 **	-0.3 **	-0.4 **	1.9 **

NOTE: Analysis methods are described in Section 2.1.3
Adjusted p-values: * nominal p<0.05; ** nominal p<0.01.
All endpoints other than the eDiary endpoints were captured only at the clininc visits which took place at Week 4, 8, 16 and 24. eDiary endpoints have calculated Week 12 and 20 even though clinic visits were not conducted.

Table 2.3.3: 2 Placebo-corrected percentages in responder analyses for flibanserin 100 mg q.h.s. over time – Pooled (511.71, 511.75) (FAS, LOCF)

	PGI-I anchored responder endpoints					
Visit	SSE	eDiary desire	FSFI desire items	FSDS-R Item 13	FSDS-R total	FSFI total
Week 4	6.4	4.9	9.0 **	7.7 **	6.9 **	7.9 **
Week 8	9.1 **	8.7 **	14.1 **	13.4 **	9.2 **	13.7 **
Week 12	6.4	5.1				
Week 16	8.3 **	4.8	11.7 **	12.0 **	11.9 **	12.3 **
Week 20	10.9 **	5.5				
Week 24	12.0 **	4.6	12.6 **	10.4 **	11.1 **	13.6 **

	Remitter endpoints		Other responder endpoints	
Visit	FSFI desire items remitter	FSDS-R total remitter	PGI-I of 1 or 2	PGI-I of 1, 2, or 3
Week 4	8.7 **	6.0 **	6.4 **	12.6 **
Week 8	11.7 **	8.3 **	9.5 **	20.1 **
Week 12				
Week 16	11.9 **	10.2 **	10.4 **	16.7 **
Week 20				
Week 24	11.6 **	9.8 **	11.2 **	17.9 **

Note: Analysis methods are described in Section 2.1.3
Adjusted p-values: * nominal p<0.05; ** nominal p<0.01
All endpoints other than the eDiary endpoints were captured only at the clininc visits which took place at Week 4, 8, 16 and 24. eDiary endpoints have calculated Week 12 and 20 even though clinic visits were not conducted.

2.3.4 Sensitivity analysis

Two different types of sensitivity analyses were performed: 1) examine treatment by study interaction and 2) examine the impact of missing data due to early discontinuation. The

details of these sensitivity analyses are presented in the following sections, and the summary of these findings are presented below:

- No treatment by study interactions were found.
- Results for LOCF are robust and the same conclusions are reached using alternative methods such as baseline carried forward and mixed model repeated measures.

2.3.4.1 Treatment by study interaction

For the pooled analyses, treatment by study interactions were examined by using an ANCOVA model with baseline as a covariate with the main effect terms study and pooled centre nested in study as well as the treatment by study interaction term. Even though SSE was analyzed using the Wilcoxon rank sum test stratified by pooled centre, SSE was analyzed using the same model for the purposes of examining the interaction. For PGI-I, the same model was applied without the baseline covariate, since this endpoint is not collected at baseline.

There was no evidence of a treatment by study interaction. FSFI total score was the only endpoint where the p-value for the treatment by study interaction term was 0.1571; however, the by-trial analysis shows that this was a quantitative interaction meaning that both trials had results in the same direction showing flibanserin 100 mg q.h.s. superior to placebo with differences in the magnitude of the difference. Likewise for FSDS-R total score the p-value of the treatment by study interaction term was 0.2210. Again, the by-trial analysis had results in the same direction showing flibanserin 100 mg q.h.s. superior to placebo with differences in the magnitude of the difference.

2.3.4.2 Missing data due to early discontinuation

Missing data due to early discontinuation is an issue in many clinical trials. A higher premature discontinuation rate was observed in the flibanserin 100 mg q.h.s. group compared to placebo. In Trial 511.71, 31.4% of patients on flibanserin 100 mg q.h.s. prematurely discontinued compared to 20.7% on placebo prematurely. In Trial 511.75, 36.5% of patients on flibanserin 100 mg q.h.s. prematurely discontinued compared to 27.9% on placebo. Particularly when differences in the dropout rates between treatment arms are observed, the potential impact of missing data imputation methods should be evaluated.

Therefore, sensitivity analyses to assess the impact of the missing data imputation methods were examined in multiple ways: 1) last observation carried forward, 2) baseline observation carried forward and 3) mixed model repeated measures (MMRM).

Last observation carried forward (LOCF)

LOCF was used as the method for handling missing data. For these trials, LOCF was determined to be an acceptable approach. The theoretical concern over LOCF would be any systematic bias favoring flibanserin over placebo which can occur if a patient drops out of the study at a time when the patient had an improved value. To assess such bias, the values of patients who remained in the trial were compared to the values of patients who dropped out

of the trial. Table 7.1.2.3: 1 displays results for flibanserin 100 mg q.h.s. and placebo for Trials 511.71 and 511.75 showing that the values for patients who dropped out are similar to the value of those patients who stayed in the trial.

Baseline observation carried forward

Baseline observation carried forward is a method that imputes missing data with the baseline value. This analysis was performed as an exploratory analysis. For change from baseline endpoints, the use of this method would mean that the patient had no change from baseline. Using this method, flibanserin 100 mg q.h.s. is consistently statistically significantly different from placebo for all of the endpoints except for the eDiary sexual desire score (Table 2.3.4.2: 2). The consistency of the results suggests that the results from the preplanned analysis using the LOCF method are robust and are not impacted by missing data imputation methods.

Table 2.3.4.2: 2 Placebo-corrected mean change from baseline for select endpoints at Week 24 – Trials 511.71, 511.75, 511.77 and pooled (FAS, LOCFZERO)

	North America			Europe
	511.71	511.75	Pooled 511.71/.75	511.77
Endpoint	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.
SSE	0.9 **	0.5 **	0.7 **	0.4
eDiary sexual desire score	1.7	1.3	1.4	2.1 *
FSFI desire items	0.3 **	0.2 **	0.2 **	0.1
FSDS-R total	-2.7 **	-2.4 **	-2.5 **	-2.1 **
FSDS-R item 13	-0.3 **	-0.2 *	-0.2 **	-0.2
FSFI total	1.9 **	1.1 *	1.4 **	0.9
SSE (count)	0.8 **	0.5 *	0.7 **	0.4

NOTE: Analysis methods are described in Section 2.1.3
Adjusted p-values: * nominal $p<0.05$; ** nominal $p<0.01$

Mixed model repeated measures

MMRM is based on observed cases (OC). The analysis method will estimate the missing data using a model based approach. The results are summarized in Table 2.3.4.2: 3 showing consistent results as previously shown using the Wilcoxon rank sum and ANCOVA/ANOVA analyses.

Table 2.3.4.2: 3 MMRM analysis of change from baseline for select endpoints at Week 24 – Trials 511.71, 511.75, 511.77 and pooled (FAS, OC)

	North America			Europe
	511.71	511.75	Pooled 511.71/.75	511.77
Endpoint	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.
SSE	1.0[a] **	1.1 **	1.0 **	0.7 *
eDiary sexual desire score	2.5	2.5	2.5 **	3.1 **
FSFI desire items	0.4 **	0.4 **	–[b]	0.2
FSDS-R total	-4.4 **	-3.5 **	–[b]	-3.5 **
FSDS-R item 13	-0.4 **	-0.3 **	-0.4 **	-0.3 **
FSFI total	3.0 **	1.8[a] **	2.3[a] **	1.4
SSE (count)	0.9[a] **	1.0 **	0.9[a] **	0.6
PGI-I	-0.4 **	0.9[a] **	-0.4 **	-0.2 **

NOTE: Analysis methods are described in Section 2.1.3
a The UN (unstructured) covariance structure was used.
b None of the pre-specified covariance structures (AR(1), UN, CS) converged for these endpoints.
Adjusetd p-values : * nominal p<0.05; ** nominal p<0.01

2.3.5 Comparison of results in sub-populations

Sub-population analyses for the endpoints SSE and FSFI desire items using pooled data from Trials 511.71 and 511.75 for the comparison between flibanserin 100 mg q.h.s. and placebo were performed for the following factors listed below. To put the sample size of the sub-populations into perspective, the total number of patients and the percentage in the sub-population are provided along side the categories; the number of patients was balanced for the sub-populations across flibanserin 100 mg q.h.s. and placebo (number of patients with missing data are not presented below). Details of the sub-population analyses are provided in the Appendix Figure 7.1.2.4: 1.

- Race: white [N=1201(89.7%)], black [N=113(8.4%)], Asian [N=25(1.9%)]

  Although population-representative proportions of black women were recruited, the number of patients entered in the trials are too small to draw meaningful conclusions between placebo and flibanserin 100 mg q.h.s.

- Ethnicity: Hispanic [N=92(6.9%)], non-Hispanic [N=1246 (93.1%)]

  The number of patients entered in the trials are too small to draw meaningful conclusions between placebo and flibanserin 100 mg q.h.s.

- Baseline hormone and protein levels: Free testosterone, dehydroepiandrosterone (sulphate) (DHEA-S) and sex hormone binding globulin (SHBG)

  The relationship between sex steroid and protein levels and women's sexual function remains inconclusive. Three hormones/protein frequently cited in the literature as having

a putative relationship include free testosterone, DHEA-S and SHBG, hence these sub-population analyses were conducted.

- Baseline free testosterone: <1.1, lower limt of normal [N=459(34.3%)], ≥1.1 [N=862(64.4%)]

  Baseline free testosterone levels had no significant effect on flibanserin 100 mg q.h.s. efficacy regarding SSE and FSFI-Desire.

- Baseline DHEA-S: <60.0, lower limit of normal [N=375(28.0%)], ≥60.0 [N=960(71.7%)]

  Baseline DHEA-S levels had a significant effect on flibanserin 100 mg q.h.s. efficacy regarding both SSE and FSFI-Desire.

- Baseline SHBG: <80, lowest tertile [N=416(31.1%)], ≥80 to <150 [N=503(37.6%)], ≥150 [N=415(31.0%)]

  No consistent effect of SHBG examined by tertiles was seen on flibanserin 100 mg q.h.s. efficacy.

- Baseline severity: Baseline SSE, FSFI desire items, FSDS-R total

  Nominally significant flibanserin 100 mg q.h.s. efficacy was noted regardless of baseline severity:

  - Baseline SSE: >2 [N=585(43.7%)], ≤2 [N=748(55.9%)]

  - Baseline FSFI desire items: >1.8 [N=498(37.2%)], ≤1.8 [N=840(62.7%)]

  - Baseline FSDS-R total: >30 [N=681(50.9%)], ≤30 [N=658(49.1%)]

- Secondary diagnosis of female sexual arousal disorder (FSAD) [N=342(25.5%)]

  Nominally significant flibanserin 100 mg q.h.s. efficacy was noted regardless of a secondary diagnosis of FSAD.

- Secondary diagnosis of female orgasmic disorder (FOD) [N=241(59.5%)]

  Nominally significant flibanserin 100 mg q.h.s. efficacy was noted regardless of a secondary diagnosis of FOD.

- Presence of hormonal contraceptive use [N=542(40.5%)]

  Women not using hormonal contraception experienced a greater increase in SSE than women using hormonal contraception. No difference was seen regarding an effect of hormonal contraception on FSFI-Desire, FSDS-R total score or FSDS-R Q13. Furthermore, no consistent relationship was noted in the North American studies for these

efficacy variables when examining steroid levels of free testosterone or SHBG, the putative mechanism by which hormonal contraception might plausibly affect sexual function. These exploratory analyses suggest that the aforementioned finding may be related to other variables (e.g., age, reason for using hormonal contraception, duration of partner relationship) other than HC use. Therefore, further exploration of this hypothesis is warranted before concluding what impact HC use has on SSEs (Table 2.3.5: 1).

Table 2.3.5: 1 SSE and FSFI desire items at Week 24 by presence or absence of hormonal contraceptive use – Pooled (511.71, 511.75) (FAS, LOCF)

					Change from baseline		
	Hormonal			Baseline		Diff from placebo	
Endpoint	contraceptive use	Treatment	N	Mean (SD)	Mean	Diff	P-value
SSE	No	Placebo	400	2.7 (2.8)	1.2 (3.6)		
		FLI 100 q.h.s.	380	2.7 (2.9)	2.1 (5.3)	0.9	0.0020
	Yes	Placebo	266	2.6 (2.7)	0.7 (3.0)		
		FLI 100 q.h.s.	266	2.9 (2.8)	1.3 (3.8)	0.6	0.7632
eDiary desire score	No	Placebo	400	10.7 (9.2)	7.7 (0.9)		
		FLI 100 q.h.s.	380	12.1 (9.9)	9.5 (0.9)	1.8 (1.1)	0.3111
	Yes	Placebo	266	11.0 (9.2)	6.6 (1.0)		
		FLI 100 q.h.s.	266	12.7 (10.3)	6.3 (1.0)	-0.3 (1.3)	1.0000
FSFI desire items	No	Placebo	408	1.8 (0.7)	0.6 (0.1)		
		FLI 100 q.h.s.	388	1.8 (0.7)	0.9 (0.1)	0.3 (0.1)	<0.0001
	Yes	Placebo	270	1.9 (0.7)	0.6 (0.1)		
		FLI 100 q.h.s.	271	1.8 (0.7)	0.8 (0.1)	0.3 (0.1)	0.0190
FSDS-R Q13	No	Placebo	408	3.2 (0.8)	-0.5 (0.1)		
		FLI 100 q.h.s.	388	3.2 (0.8)	-0.8 (0.1)	-0.3 (0.1)	0.0004
	Yes	Placebo	270	3.2 (0.8)	-0.5 (0.1)		
		FLI 100 q.h.s.	272	3.2 (0.8)	-0.7 (0.1)	-0.2 (0.1)	0.2348
FSDS-R total	No	Placebo	408	30.3 (9.9)	-5.0 (0.6)		
		FLI 100 q.h.s.	388	30.5 (9.5)	-8.3 (0.6)	-3.3 (0.7)	<0.0001
	Yes	Placebo	270	29.9 (9.9)	-5.4 (0.7)		
		FLI 100 q.h.s.	272	30.9 (9.7)	-7.3 (0.7)	-1.9 (0.9)	0.1420

Note: Analysis methods are described in Section 2.1.3
Adjusted p-values are presented. P-values are considered nominal.

- Completers: Patients who did not prematurely discontinue from the trial

  Analyses were performed on patients who were in the FAS and did not prematurely discontinue. Section 2.3.1.1 discusses the patient disposition describing the number of patients who prematurely discontinued and the reasons for discontinuation. The results

among the two-thirds of patients who completed the entire 24 weeks of therapy demonstrate greater effect with consistent nominal statistical superiority of the flibanserin 100 mg q.h.s. over placebo across all endpoints (Table 2.3.5: 2), including the eDiary desire measure.

Table 2.3.5: 2 Placebo-corrected mean change from baseline for select endpoints among patients who did not prematurely discontinue from the trial – Trials 511.71, 511.75, 511.77 and pooled (FAS, LOCF)

	North America			Europe
	511.71	511.75	Pooled 511.71/.75	511.77
Endpoint	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.	FLI 100 q.h.s.
SSE	1.4 **	1.1 **	1.2 **	0.8
eDiary sexual desire score	3.0	2.9	2.8 **	3.1 *
FSFI desire items	0.4 **	0.4 **	0.4 **	0.2 *
FSDS-R total	-4.5 **	-4.2 **	-4.3 **	-3.5 **
FSDS-R Item 13	-0.4 **	-0.4 **	-0.4 **	-0.3 **
FSFI total	3.0 **	2.4 **	2.7 **	2.0 **
PGI-I	-0.4 **	-0.5 **	-0.5 **	-0.3 **
SSE (count)	1.3 **	1.0 **	1.1 **	0.7

NOTE: Analysis methods are described in Section 2.1.3
Adjusted p-values: * nominal $p<0.05$; ** nominal $p<0.01$

2.4 ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Dosing recommendations are as shown below, followed by supporting rationale.

Initial Treatment

Flibanserin should be administered at a dose of 100 mg once daily at bedtime.

Special Populations

As explained in Section 4 (Clinical Pharmacology), flibanserin is not recommended for patients with hepatic impairment, patients taking strong inhibitors of cytochrome P450 3A4, and for patients intolerant to flibanserin 100 mg/day.

Supporting Rationale

Statistically significant flibanserin 100 mg q.h.s. efficacy as compared to placebo was noted regardless of baseline severity of SSE frequency, FSFI desire items score, or FSDS-R total score, and statistically significant flibanserin 100 mg q.h.s. efficacy as compared to placebo was noted regardless of a secondary diagnosis of FSAD or a secondary diagnosis of FOD.

In the fixed dose trials, flibanserin 100 mg q.h.s. showed robust efficacy, whereas each of the three other lower-dose regimens demonstrated mostly non-significant trends in numerical superiority over placebo. The results for the other doses (flibanserin 25 mg b.i.d., 50 mg b.i.d. and 50 mg q.h.s.) are displayed in Section 2 for each individual trial. The inconsistent outcome suggests that daily doses below 100 mg are not likely to be effective.

The rates of the most frequent AE with flibanserin 50 mg q.h.s. were about half of the corresponding rates with flibanserin 100 mg q.h.s.. Taking a morning dose of flibanserin 50 mg as part of a 50 mg b.i.d. regimen was associated with a higher rate of AE than dosing only 100 mg q.h.s. at bedtime. With the flibanserin 50 mg b.i.d. regimen, the rates of the most frequent AE were highest: somnolence, 16-17%, dizziness, 14%-17%, fatigue, 12%-15%, nausea, 11%-14% (the rates with up-titration from 50 mg q.h.s. to 50 mg b.i.d. after 2 weeks are shown separately from, and were mostly marginally lower than, the rates with a fixed dose). Although used in several studies in an attempt to improve tolerability, the use of filbanserin 50 mg q.h.s. as a starting dose was of little benefit compared to starting with flibanserin 100 mg q.h.s. [SCS, Figure 2.1.1.2.1: 1, Moduel 2.7.4]. Therefore, from all tolerability considerations, flibanserin 100 mg q.h.s. is the reasonable starting dose regimen.

Table 2.4: 1 displays the number of patients who received a given dose regimen for at least 3 months (84 days), 6 months (182 days) and 1 year (365 days). Far more patients (N=1138) took flibanserin 100 mg q.h.s. for at least six months than any of the other dose regimens.

Table 2.4: 1 Long term exposure to flibanserin – All HSDD trials

	FLI 25 b.i.d.	FLI 50 q.h.s.	FLI 50 b.i.d.	FLI 100 q.h.s.	FLI Total
Exposure (days)					
>= 84	606	1230	655	2076	3812
>= 182	76	658	97	1138	2101
>= 365	2	75	13	205	1012

NOTE: Includes all HSDD studies that are completed or that are currently ongoing open-label studies: 511.68, .69, .70, 71, .74, 75, .77, .105, .84, .118. In trials involving up- titration, subjects appear in more than one column. The FLI total column differs from the sum of the individual doses within the same row, since it represents cumulative flibanserin exposure to any dose.

In conclusion, flibanserin 100 mg/day, given as a bedtime dose, has shown consistent efficacy across North American primary efficacy trials on multiple, convergent endpoints assessing the components of HSDD including the co-primary endpoint of SSEs and on well-validated secondary endpoints of FSFI sexual desire and FSDS-R sexual distress. The dose regimen 100 mg q.h.s. flibanserin is considered the effective, optimal and maximum dose for patients. The 50 mg q.h.s. used in some trials as the initial dose leading to 100 mg q.h.s., and in other trials as a fixed dose, as a maintenance dose, lacked the consistent efficacy of 100 mg. Conversely, 100 mg flibanserin was consistently effective across sub-groups of women and responder efficacy endpoints pre-selected for the clinical trials. At 100 mg q.h.s. women with HSDD in the North American primary efficacy trials showed consistent, statistically and clinically significant treatment effects, responder rates, and remitter rates.

2.5 PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

Trials 511.74 and 511.84 provide evidence for the persistence of efficacy.

While the primary analyses for 511.74 presented in Section 2.2.1.1 and Section 2.3.2 are the main analyses to support the persistence of efficacy.

Trial 511.84 was an open-label, long-term exposure safety trial where patients received flibanserin treatment for 52 weeks after having completed a previous flibanserin trial (511.70, 511.71, 511.75, 511.74 or 511.105). The efficacy endpoints collected for Trial 511.84 were limited as explained in Section 2.1.2 (Definition of efficacy variables). Trial 511.84 was an open-label trial without the use of a control; therefore, the trial design only allows analyses through descriptive statistics over time.

2.5.1 Trial 511.74

The main analyses for 511.74 used to assess the maintenance of efficacy are presented in Section 2.2.1.1 and Section 2.3.2. These analyses showed a statistically significant superiority of flibanserin over placebo for the primary and secondary endpoints for SSE, eDiary sexual desire score, FSFI desire items, FSFI total score, FSDS-R total score, FSDS-R Item 13 and PGI-I, confirming the maintenance of effect of flibanserin.

2.5.2 Trial 511.84

Trial 511.84 is a North American open-label extension study for patients who have completed one of the previous flibanserin trials (511.70, 511.71, 511.75, 511.74 or 511.105). The main objective of this trial is to assess the long-term safety of flibanserin. As such, the efficacy measures that were collected are limited to the endpoints as shown in Table 2.1.2: 1. The eDiary was not used in this study.

In examining the maintenance of efficacy in this trial, the tables were broken out in two ways: 1) baseline FSFI total score remitter criterion of 26.55 and 2) baseline FSFI desire items remitter criterion of 3.0. The categorization was used to differentiate patients who had already responded before the start of Trial 511.84 from patients who had not responded as they may show differential response in efficacy with continued exposure (which may have been at a lower dose of flibanserin) or new exposure to flibanserin. Non-responders may improve with continued or new exposure to flibanserin whereas patients who already responded may not see further improvement but rather a maintenance of effect.

Since Trial 511.84 only includes the flibanserin treatment arm without a placebo control group, no inferential statistical methods were used in the analyses of this trial. Furthermore, only the observed cases are displayed without the use of last observation carried forward; therefore, the data only from the patients who remained in the trial are displayed.

Several conclusions can be drawn from the interim data from this on-going study:

- There is no discernable decrease in flibanserin efficacy over the subsequent 52 weeks of open label exposure; all efficacy measures continue to improve over the course of the 52 weeks.

- By Week 26 those women who continue treatment with flibanserin demonstrate mean FSFI-D scores (>3.0) indicating remission of intensity and frequency of sexual desire comparable to the population of women without HSDD.

Furthermore, sensitivity analysis was performed to examine the role of differential dropout of patients who performed poorly on continued exposure (and thus biasing the results as patients who improved and/or maintained efficacy stayed in the trial longer). These sensitivity analyses were performed to further support these conclusions by examining the subset of patients who completed 26 weeks of the trial. The results of this subset of patients are identical to the entire population; thereby confirming the above conclusions.

2.6 EFFICACY DISCUSSION

As evident by the evolving literature in the field, the Draft Guidance provided by the FDA on FSD and the ongoing dialog over the last years between the Sponsor and the Division on the flibanserin development program, the science of female sexuality in general and HSDD and its treatment specifically has been constantly evolving. This evolution has led to significantly better understanding of the condition from the patient's perspective which in turn has led to a more appropriate understanding of the results of clinical trials with flibanserin. This section

will summarize the large and complex dataset reported in the previous section, focusing on the three North American primary efficacy trials.

HSDD is by definition a condition characterized by the distressing absence or loss of previously adequate sexual desire; however the symptomatology and patient experience of HSDD is not limited to desire alone, necessitating assessments of multiple components of the condition in order to best characterize the potential benefits of a treatment.

Study 511.74, the first primary efficacy study to be unblinded, demonstrated a significant and meaningful benefit of flibanserin on both co-primary endpoints of SSE and eDiary desire. This benefit on SSE represented a 28% mean increase in the amount of satisfying sexual activity a woman experienced over the last four weeks of treatment when compared to women reciveng placebo. Additionally, the key measure of distress was found to have been improved with significantly and meaningful reductions in women taking flibanserin compared to those receiving placebo.

In the other North American primary efficacy Trials, 511.71 and 511.75, the co-primary endpoint of SSE was also found to be both statistically positive as well as clinically meaningful as defined by the anchoring to the Patient's Global Impression of Improvement. Women taking flibanserin 100mg q.h.s. reported a non placebo-corrected increase with flibanserin 100 mg qhs was 1.66 and 1.86 SSEs in Study 71 and 75, respectively representing an increase of 55% and 72% increase over baseline values.

Although demonstrating consistently positive trends, the comparison of flibanserin 100 mg q.h.s. versus placebo was not statistically significant in the European Trial 511.77 for SSE.

The co-primary eDiary desire score was formally positive in one of the three studies (511.74) while showing consistently positive numeric trends in the other two, although our research has shown that a daily measure of episodic sexual desire, while agreed upon by the sponsor and the FDA, is perhaps not the most relevant nor complete measure of sexual desire in women with HSDD, as subsequent qualitative research conducted in women with HSDD showed that:

- Frequency and intensity measures are capturing different aspects of sexual desire and that a questionnaire measure of the intensity dimension alone would be inadequate as a clinical endpoint for the majority of women with HSDD. Less than half of the sample in two validation studies felt that one of these two FSFI items could be omitted;

- The large majority of women (more than 90%): found the two FSFI desire items simple and clear, easy to understand, and clinically relevant;

- Most women found a recall period of 1-4 weeks for these questions, or longer, to be optimal; most also *thought that a one-day or 24-hour recall period was inappropriate and unsuitable for assessing sexual desire*.

Taken together, this body of evidence provides consistent empirical and conceptual support for the FSFI assessment of sexual desire as a relevant and appropriate endpoint on sexual desire in clinical trials of women with HSDD. Based on these learnings, a decision was taken to formally elevate the FSFI desire items as a key secondary endpoint in the trial statistical analysis plan (TSAP) before unblinding in Trials 511.70 and 511.71. Notwithstanding the hierarchical testing procedures in these trials for which eDiary desire was co-primary, thus formally rendering the FSFI desire and other secondary endpoint statistical results "exploratory", on the basis of the empirical and conceptual strength of the FSFI desire assessment our submission emphasizes the totality and consistent effect of flibanserin on the various components of HSDD.

Improvement in sexual desire as assessed by the FSFI desire items was found to be nominally statistically significant in favor of flibanserin in all three North American studies while showing a positive trend in the European study.

Sexually related distress, as assessed by both the FSDS-R total score and the individual FSDS-R Item 13 (relating to distress related to low desire) was found to be nominally significant in favor of flibanserin 100 mg q.h.s. in all three North American studies as well as in the European study.

Recognizing that statistical significance alone for results may not adequately capture the potential benefit to the patient, *a priori* (responder) analyses and post hoc (remitter) analyses were also performed to better characterize these potential benefits. The intrinsic importance of understanding the clinical meaningfulness of these results is intuitively obvious: How do we know that these positive clinical changes hold any real meaning for the patient's condition, i.e., reflects meaningful improvement? Operationally, this question can be posed as, "How do we know that a statistically significant *mean* difference in response to flibanserin translates into a substantially greater proportion of patients being judged 'clinically improved,' or experiencing 'perceived benefit' from the treatment?"

One prominent approach to answering this is the anchor-based approach [R99-1220] which ties change in the primary outcomes measure(s) to values of an independent measure (anchor) that is typically a patient-rated global measure of perceived change or benefit. The proportions benefiting under regimen A vs. regimen B are then contrasted for significance of differences.

The methodology for these responder analyses assessing the clinical meaningfulness of the flibanserin results were agreed with the Agency to be anchored to an individual woman's assessment of her improvement (PGI-I). This anchor-based assessment of response may in fact be the most clinically relevant endpoint, as a woman's individual assessment of her treatment is based on her impression of all aspects of her treatment experience, some of which may be more or less important to her than to another woman, but which ultimately allows all women in the clinical program to give voice to their personal experience with treatment.

Finally, flibanserin was nominally statistically significant for the PGI-I responder of any improvement (very much/much/minimal). The Patient Global Impression of Improvement is

a single question asking the following question: “How is your condition - meaning decreased sexual desire and feeling bothered by it - today compared to when you started study medication?” where 1=”Very much improved” and 7=”very much worse”. In Trial 511.71, 50.0% of patients on flibanserin 100 mg q.h.s. compared to 30.3% on placebo were PGI-I responders (very much/much/minimal) which is a difference of 19.7% with a p-value of <0.0001. In Trial 511.75, 47.0% of patients on flibanserin 100 mg q.h.s. compared to 30.3% on placebo were PGI-I responders (very much/much/minimal) which is a difference of 16.6% with a p-value of <0.0001.

The assessment of clinical relevance must be derived from two perspectives. First, given the current state of medical practice for HSDD, what would represent a meaningful addition or improvement in the treatment armamentarium of the practicing physician and second, what are the data to support a clinically-relevant effect of flibanserin for women? As there is no pharmacologic therapy approved for the treatment of HSDD, there currently exists an unmet medical need in this clinically relevant and important disorder.

Currently, the state of medical practice results in women being exposed to off-label treatments such as buproprion and testosterone, whose safety and efficacy have not been prospectively assessed in adequate and well controlled trials in women with HSDD. In this context, any compound demonstrating safety and efficacy in the treatment of HSDD would be considered as extremely meaningful and relevant, both to clinicians and to women suffering from HSDD.

Remitter analyses, while post hoc and exploratory in nature, demonstrate that the proportion of women who took 100 mg of flibanserin who remitted (scores indicative of no longer being in the range of clinical disorder) was statistically significantly greater on the FSFI desire and FSDS-R Q 13 than women taking placebo.

An important subgroup are those subjects who complete therapy, as this allows clinicians to advise patients what they may experience if they continue or complete therapy. Analysis of the 65% of patients taking flibanserin 100mg q.h.s. who completed Studies 511.71 and 511.75 demonstrated significant and meaningful improvements in all endpoints including the eDiary desire measure.

In order to better characterize and more confidently assess the overall effect of flibanserin, as well as to assess subgroups and the effect of flibanserin over time, pooled analyses were pre-planned for those clinical trials that were similar with respect to patient characteristics, data collection, dose of flibanserin and endpoints prior to unblinding as documented in the briefing package sent to the FDA as part of the Pre-NDA meeting. These pooled analyses in addition to the individual trial results form the most integrative evidence of the overall clinically meaningful effect of flibanserin.

Table 2.6: 1 illustrates the consistent effect of flibanserin across individual studies and the pooled analyss for a range of endpoints relevant to women with HSDD. The hallmark symptoms of HSDD, low desire and related distress, are improved, leading to a subsequent increase in the behavioural endpoint of SSEs. These observations are confirmed by women in their own assessments of benefit.

Table 2.6: 1 Summary of results – Trials 511.71, 511.75, 511.74 and 511.77 (FAS, LOCF)

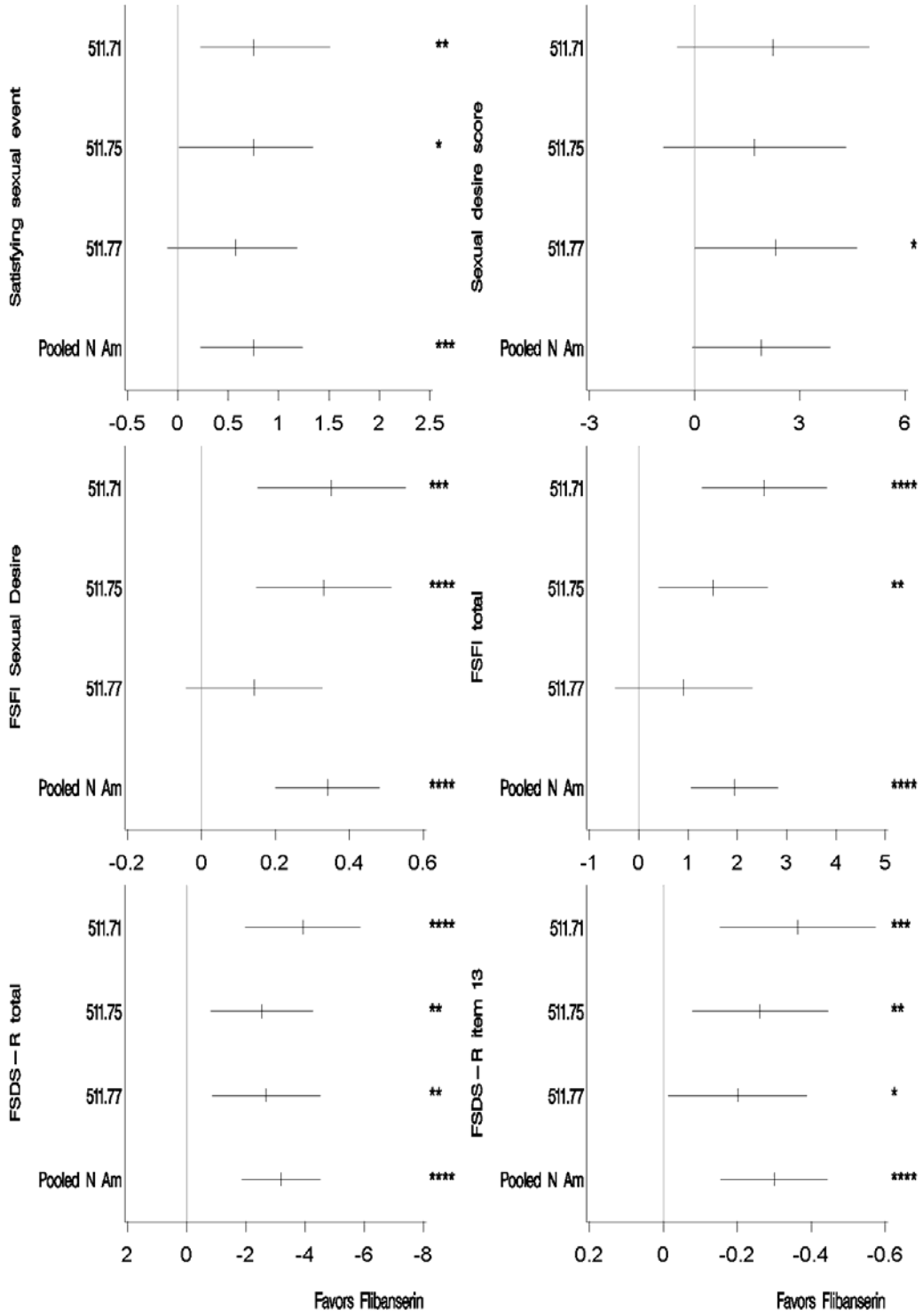
	North America			
	511.74[2]	511.71	511.75	Pooled 511.71/.75
Primary endpoints				
SSE	**	**	*	**
eDiary sexual desire score	*	–	–	*
Key secondary endpoints[1]				
FSFI desire items	##	##	##	**
FSDS-R total	##	##	##	**
Other secondary endpoints				
FSDS-R Item 13	##	##	##	##
FSFI total	##	##	##	##
PGI-I	##	##	##	##
SSE (count)	#	##	#	##
PGI-I anchored responder endpoints				
SSE	N/A	##	#	##
eDiary sexual desire score	N/A	–	–	–
FSFI desire items	N/A	##	##	##
FSFI total	N/A	##	##	##
FSDS-R Q13	N/A	##	#	##
FSDS-R total	N/A	#	##	##
Remitter endpoints				
FSFI desire items remitter (>3.0)	N/A	##	##	##
FSDS-R total remitter (<15)	N/A	##	–	##
Other responder endpoints				
PGI-I (very much/much improved)	N/A	##	##	##
PGI-I (very much/much/minimally improved)	N/A	##	##	##
Patient Benefit Evaluation	N/A	#	##	##

NOTE: Adjusted p-values: – p>0.05; * p<0.05; ** p<0.01; # nominal p<0.05 ; ## nominal p<0.01

1 Since both primary endpoints were not statistically significant in Trials 511.71 and 511.75, the interpretation of the key secondary endpoints should be interpreted as nominal significance.

2 For Trial 511.74, the endpoints listed under key secondary endpoints were not specifically denoted as key secondary endpoints, but rather as secondary endpoints. Furthermore, the responder/remitter endpoints were Not Applicable (N/A) since these responder/remitter endpoints were not defined as secondary endpoints.

Figure 2.6: 1 below provides graphic demonstration of the consistent effect of flibanserin 100mg taken at bedtime on the multiple components of HSDD that were assessed. These figures represent for each efficacy endpoint the point estimates (with 95% confidence intervals) and corresponding adjusted p-values illustrating the replication of the efficacy of flibanserin 100mg across studies and endpoints.

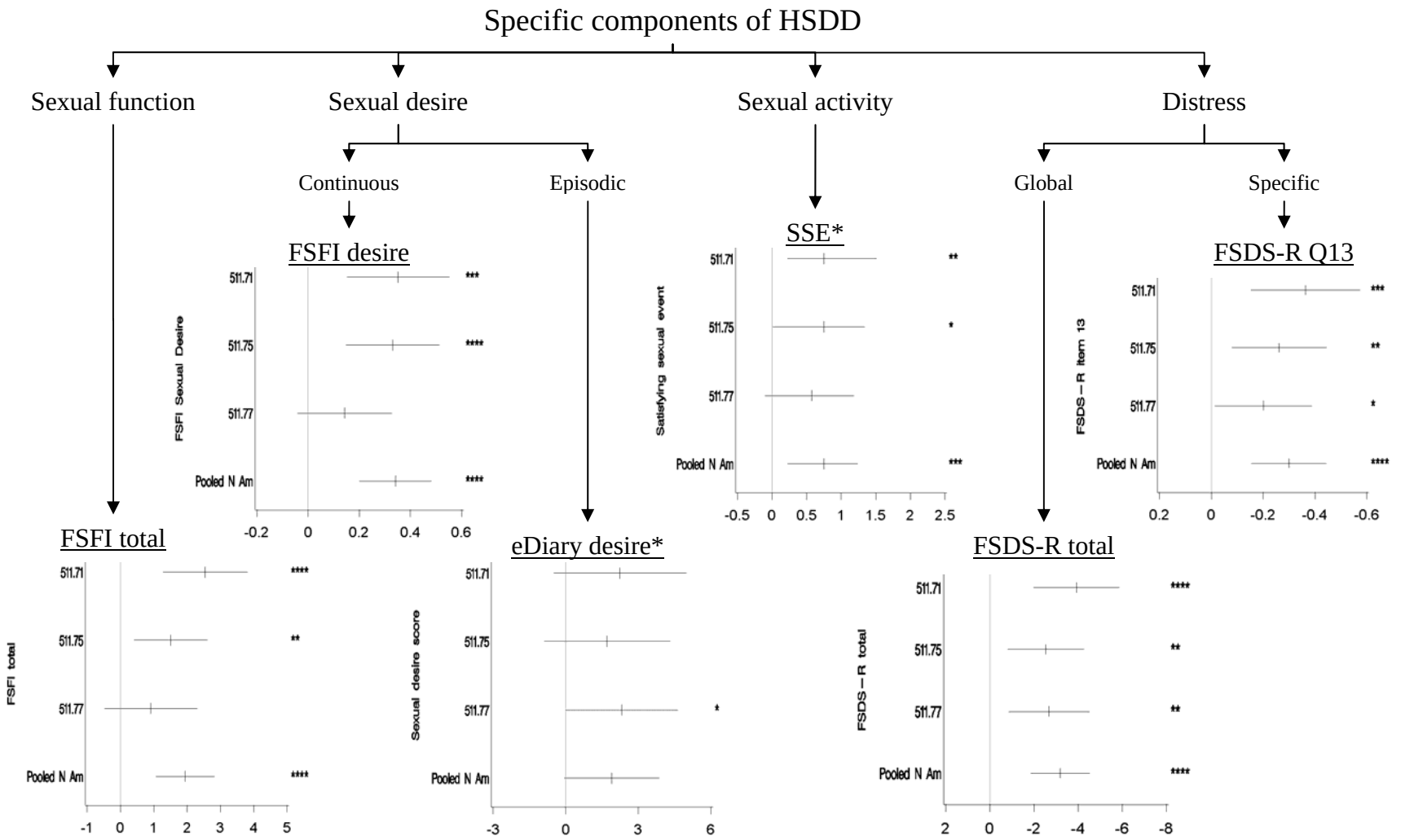


NOTE: Adjusted p-values and adjusted confidence interval: * p<0.05; ** p<0.01; *** p<0.001; ****p<0.0001

Figure 2.6: 1 Placebo-subtracted mean change and 95% confidence interval for flibanserin 100 mg q.h.s. – Trials 511.71, 511.75, 511.77 and pooled (FAS, LOCF)

In summary, the program of flibanserin clinical trials was performed recognizing that the FDA draft guidance calls for SSEs as well as an additional measure assessing desire, in this case, the eDiary desire score, in order to evaluate efficacy. Additionally, the program also recognizes that there are other important dimensions of HSDD that ideally would respond to treatment and therefore the most complete way to characterize the efficacy of flibanserin involves assessments of these other relevant dimensions beyond SSEs and the eDiary. Thus, we assessed a second global measure of desire intensity and frequency (FSFI-d) as well as measures of distress (FSDS-R and FSDS-R Q13) and women's evaluations of their disease status and their response to treatment (PGI-I).

Study 511.75 showed that lower doses and b.i.d formulation did not have sufficient effect on SSEs, while 100 mg qhs was significantly better than placebo. While the eDiary measure assessing episodic desire was not statistically superior, flibanserin 100 mg q.h.s. was significantly superior to placebo for the global measure of intensity and frequency of desire (FSFI-d) as well as for both measures of distress and the measure of patient's global assessment. The results of Trials 511.70 and 511.71, replicated the results of Trial 511.75; flibanserin 100 mg q.h.s. demonstrated efficacy of the same magnitude and statistical significance for every one of the relevant dimensions and every endpoint (FSFI-d, FSDS-R, FSDS-R Q13, PGI-I) within those dimensions, while lower dosages and b.i.d regimens did not. The finding that these relevant pre-specified secondary endpoints demonstrate positive treatment effect of flibanserin in one trial and replicating those findings on the same endpoints in a second trial that includes the same dosage regimen provides evidence of the efficacy of flibanserin. These findings, illustrated by the dimension of HSDD assessed, is illustrated in Figure 2.6: 2.



NOTE: Mean and adjusted 95% CI are displayed. Adjusted p-values: * p<0.05; ** p<0.01; *** p<0.001; ****p<0.0001

Figure 2.6: 2 Mapping of specific HSDD components to clinical endpoints

The totality of evidence supports that flibanserin 100 mg q.h.s. improves desire and related distress in women with HSDD. Flibanserin's effect on HSDD is supported by a comprehensive dataset including the SSEs, eDiary desire, FSFI desire items, the FSDS-R total and FSDS-R Q13, and the Patient's Global Impression of Improvement. These data coupled with a series of sensitivity analyses all demonstrate that flibanserin 100 mg q.h.s. improves the clinical symptomatology of women suffering from HSDD.

3. OVERVIEW OF SAFETY

Overall, the incidence of AEs in premenopausal women with HSDD taking flibanserin was low with the majority of adverse events mild to moderate in severity. The frequently occurring events were typical of a centrally-acting drug: dizziness, nausea, fatigue, somnolence, and insomnia.

No observations raised concern over the use of flibanserin in premenopausal women with HSDD in regard to cardiac, hepatic, renal, or hematopoietic effects, ophthalmologic safety, hypersexuality, hormonal changes including indices of fecundity, menses, suicide, depression, abuse potential, or withdrawal effects.

No treatment-related deaths occurred. One subject died among all clinical studies (including studies in major depressive disorder) with flibanserin: A subject in Trial 511.74 receiving placebo died as a passenger in an airplane crash on Day 19 of the double-blind period.

Serious AEs (SAEs) occurred in <1% of subjects receiving any dose of flibanserin or placebo among the placebo-controlled Phase III studies and in the development program for HSDD only in one subject SAEs (1 ovarian cyst and 1 uterine polyp) were reported by the investigator as related to flibanserin.

As expected for a centrally-acting compound, women treated with flibanserin reported a higher rate of AEs compared with women who received placebo in Phase III placebo-controlled, North American studies (66.2% vs. 57.7%, respectively). The majority of these AEs were mild in severity and resolved during treatment. The most frequently observed AEs were dizziness, nausea, fatigue, and somnolence (approximately 10-12% each) and insomnia (5%). These AEs, along with dry mouth and anxiety, are considered adverse drug reactions for flibanserin, as they occurred in at least 2% of flibanserin-treated women (100 mg q.h.s.) and occurred at twice the rate observed in the placebo group.

3.1 NON-CLINICAL SAFETY

The nonclinical safety of flibanserin was investigated in rodent and non-rodent species. These investigations included studies of safety pharmacology, single- and repeat-dose toxicity, genotoxicity, reproductive toxicity and carcinogenicity.

The acute toxicity of flibanserin in rodents was low, the approximate oral lethal dose being 2000 mg/kg in rats. In oral repeat-dose toxicity studies (up to 26 weeks in rats with dose levels up to 400 mg/kg/day; up to 52 weeks in dogs with dose levels up to 75 mg/kg/day), first adverse effects were mild and considered equivalent to those observed clinically at the recommended human daily dose, e.g. somnolence. Severe clinical signs of toxicity were only observed at exposure levels far in excess of those recommended for human therapy (in dogs at about 28-fold higher than the maximal plasma level at the recommended human dose of 100 mg q.d.). Early signs of toxicity in rats and dogs were detected by marked behavioral changes. Transient corneal opacities observed in dogs at exposures about 28-fold higher than the maximal human exposure were observed in animals that also showed severe signs of behavioral toxicity. In humans, there were no effects on the cornea (or crystalline lens).

Hepatocellular hypertrophy was found in mice and rats (at dose levels ≥80 mg/kg/day) and is considered the morphological correlate to enzyme induction which has been shown for flibanserin in rodents. Flibanserin is not an inducer of cytochrome P450 in humans.

Elevation of prolactin levels in blood has been reported for mice, rats and dogs at exposures in excess of the human exposure (in dogs at plasma levels about 7-fold higher than in humans at 100 mg). In humans, no hyperprolactinemia was observed in clinical trials with flibanserin.

Electrocardiogram (ECG) morphology was normal and no QT-prolongation was observed.

Oral reproductive toxicity studies included a study of fertility and early embryonic development (rat), studies of embryo-fetal development (rat, rabbit), a study of pre- and postnatal development (rat) and a cross fostering study (rat). Flibanserin affected the duration of estrus cycle, led to an increase in the number of corpora lutea, and prolonged the gestation duration in rats. These findings were considered to be related to the aforementioned elevated level of prolactin seen in rodents. Prolactin levels were obtained during the Phase II and Phase III HSDD clinical trials. There was no evidence of hyperprolactinemia in the studies where prolactin levels were measured.

Fertility and early embryonic development prior to implantation were not affected. The flibanserin dosages investigated (20 up to 400 mg/kg/day) produced clear and dose-related maternal toxicity (mainly effects on CNS and body weight). Secondary to the dose-related maternal toxicity, embryo-fetal toxicity was reported with a slightly greater rate of variations and sporadic malformations in the flibanserin treated groups in one strain of rats. In this strain in the study of embryo-fetal development at the dose of 400 mg/kg/day, two pups in one out of 24 litters were diagnosed with anophthalmia, in the study of pre- and postnatal development at 200 mg/kg/day, two pups in two out of 24 litters were affected. However, in the cross fostering study with a different strain of rats, in 50 litters and comparable dosing regimen, there were no cases of anophthalmia. The exposure levels at which the sporadic malformation anophthalmia occurred in rats was in excess of about 15-fold the exposure in humans at the recommended dose of 100 mg q.d. In rabbits no cases of anophthalmia were present up to the maximum tested dosage (exposure about 26-fold higher than the exposure in humans at the recommended dose of 100 mg q.d.). These multiples are considered to be sufficiently in excess of the maximum human exposure to indicate no relevance to clinical use.

Treatment-related maternal toxicity in pregnant rabbits led to embryo-lethality. There was, however, no evidence of a teratogenic effect of flibanserin in rats or rabbits. Maternal toxicity (mainly CNS effects) at high dose levels also affected the postnatal development of offspring. Dams at high doses of flibanserin showed poor maternal care. The postnatal viability rate was markedly impaired, and signs of retardation were noted. The ontogeny of reflexes and sensory functions, however, proceeded at a normal rate. The fertility of the offspring was not impaired. A lactation study in rats showed that flibanserin and metabolites are excreted into milk (about 1-2% of the dose).

Flibanserin did not reveal any genotoxic potential.

Two-year carcinogenicity studies were performed in rats (10, 30, 100 mg/kg/day) and mice (10, 80, 200, 1000/1200 mg/kg/day). No carcinogenic potential of flibanserin was observed. In the mammary gland of female mice, there was an higher incidence of combined carcinomas at 200 and 1200 mg/kg/day (up to 10% in the high-dose). The incidence of mammary gland neoplasms in the two control groups was 0 and 1.4%, close to the lower range of historical control data for this strain of mouse (R08-4790, R10-1208, R07-1045, R10-1209). Compared to this very low incidence in the control groups, the incidence of combined mammary gland carcinomas at the high-dose was statistically significant, however still within the range of historical control data (up to 12.5%.) The absent increase in either hyperplastic lesions or adenomas (as would be expected for induced neoplasia) also provides evidence that the neoplasms were spontaneous (R10-1207). These neoplasms were neither dose- nor compound-related as indicated by the parameters of tumor multiplicity (similar to historical control pattern); time of appearance (first tumor appeared at 80 mg/kg/day); volume at time of appearance (highest at 80 mg/kg/day, lowest at 1200 mg/kg/day); time from appearance of tumor until death (mammary gland tumor-bearing mice at 1200 mg/kg/day lived longer and had a smaller tumor size); Peto score (all tumors were incidental) and the histopathological pattern of metastasis (comparable to historical control data). Overall, these mammary gland neoplasms resembled spontaneous neoplasms in their histopathological features (R10-1207). In rats, the incidence of mammary gland tumors was comparable to concurrent controls.

In addition, in this study a dose-related increase in food consumption and related body weight gain was observed at 200 and 1200 mg/kg/day. Increased body weight gain and body weight are known to increase the propensity for the development of spontaneous neoplasms of the mammary gland in both mice and rats (R97-0537, R10-1209). In addition, in a toxicokinetic bridging study, mice showed elevated prolactin levels. Prolactin is known to increase food consumption and body weight gain in rodents. In clinical studies, no higher incidences of hyperprolactinemia and not significant increase in body weight were observed. Moreover, in rats at the high-dose (100 mg/kg/day), there was a reduction of body weight gain and no mammary gland neoplasia. Therefore, the tumors of the mammary gland in female mice were considered not to be due to a tumorigenic potential of flibanserin.

In summary, taking into account the borderline statistical significance, historical control data, the presence of elevated prolactin levels and the concurrent increase in food consumption and body weight, it was concluded that there is no evidence for a carcinogenic effect of flibanserin in female mice. Together with the lack of genotoxicity of flibanserin, it is concluded that flibanserin does not pose a human cancer risk.

3.2 CLINICAL SAFETY

The assessment of the clinical safety of flibanserin in women with HSDD is based on integrated safety results from 4 placebo-controlled Phase III clinical trials conducted in North America: 511.70, 511.71, and 511.75, and in the European Union (EU): 511.77, and results of one Phase III, placebo-controlled, randomized withdrawal trial (511.74) conducted in the United States and Canada. In addition, this briefing document presents safety data from two ongoing, open-label, extension Phase III trials in women with HSDD (511.84 in North America, and 511.118 in Europe, data cutoff date of 17 Nov 2009), and two

placebo-controlled double-blind Phase II trials of flibanserin in women with HSDD (Trial 511.68 in the United States and 511.69 in Canada). Supportive safety data from 27 Phase I clinical trials with flibanserin and 11 Phase II clinical trials in men and women with major depressive disorder (MDD) are also included. Thus, the safety database includes a total of 47 clinical trials.

The briefing document includes data of flibanserin in 5018 premenopausal women with HSDD: 67 in Phase I trials, 149 in Phase II trials, 3431 in Phase III placebo-controlled trials, 738 in Phase III randomized withdrawal trial, and 633 in opel-label, Phase III extension trials (newly exposed subjects) (Table 3.2: 3). Out of these, 1175 subjects were treated with flibanserin 100 mg once every evening (q.h.s.) for at least 6 months, and 213 subjects were treated with flibanserin 100 mg q.h.s. for at least 12 months. Also, a significant number of women (N=2430) with HSDD were exposed to different dose regimens in Phase III placebo-controlled trials, including 25 mg twice-a-day, 50 mg at bedtime, and 50 mg twice-a-day. A smaller number of patients (N=72) received flibanserin 100 mg b.i.d.; these were women in Phase II HSDD trials. Overall, a total of 2190 subjects were treated with flibanserin for at least 6 months, 1130 subjects were treated for at least 12 months, and 185 subjects were treated with flibanserin for at least 18 months.

In general, flibanserin was shown to be well-tolerated, and the safety profile of flibanserin in HSDD patients was found to be without physical or laboratory changes, with frequent AEs limited to subjective feelings such as sleepiness, dizziness and nausea. No observation was made that would raise concern over the use of flibanserin in premenopausal women with HSDD in regard to suicide, depression, abuse potential, hypersexuality, ophthalmologic safety, hormonal changes including indices of fecundity, or pregnancy outcome in those whose treatment was stopped promptly upon discovery of pregnancy.

The most frequently observed AEs were dizziness, nausea, fatigue, and somnolence, at approximately 10-12% each, and insomnia, at about 5%. The Sponsor considered treatment emergent AEs to be adverse drug reactions (ADRs) to flibanserin if occurring in at least 2% of the study population treated with the active dose of the study drug (100 mg q.h.s.) in the Phase III placebo-controlled trials, and occurring in at least twice the rate observed in the placebo group, as the lower limit of adverse event incidence considered to be clinically meaningful given the denominators. Using these criteria, ADRs for flibanserin include dizziness, nausea, fatigue, somnolence, insomnia, dry mouth and anxiety. Events not meeting these criteria were reviewed for possible relationship with flibanserin administration using criteria such as frequency of reporting, extent of dose response, or the extent to which the AE may have been related to the pharmacology of the drug: based on these assessments constipation, sedation, sleep disorder, palpitations, vertigo and hypotension were also considered treatment emergent AEs. The majority of AEs were mild in severity (Table 7.2.2: 3, Appendix 7.2.2) and resolved during treatment; only one somnolence event was reported as serious.

To date, no clinically significant effects on cardiovascular parameters including PR, QT intervals, or other ECG parameters have been observed in humans. Furthermore, no significant or consistent effects on vital signs or laboratory parameters have been noted in any clinical trial of flibanserin.

No treatment-related deaths occurred in the flibanserin clinical trials; one non-treatment-related death occurred, a subject died in an airplane accident. Less than 1% of serious adverse events (SAEs) were reported in patients in flibanserin trials regardless of whether the patients received placebo or flibanserin. Six SAEs (1 rash, 2 depression, 1 somnolence; all in depressed patients in the MDD studies; 1 ovarian cyst and 1 uterine polyp in the same patient in the HSDD studies) were reported by the investigator as related to flibanserin.

The design of the 9 Phase II/III trials in women with HSDD is summarized in Table 3.2: 1. The following tables display number of subjects in various trial groupings for all clinical trials described in the safety section of the briefing document. For the Phase II/III placebo-controlled trials in woment with HSDD, analyses are displayed in 2 ways: by randomized treatment and by treatment at onset (Tables 3.2: 2 and 3.2: 3). The randomized regimens in supportive MDD trials (Table 3.2: 4) involved flexible dosing, thus, summaries of MDD subjects are displayed by collapsing dose groups (flibasnerin versus placebo).

Table 3.2: 1 Description of HSDD Phase II/III trials analyzed in the SCS

BI Trial Number	Trial Design/Control	Study & Control Drugs, Dose, Route Regimen	Duration
Phase II – 12-week, placebo-controlled, double-blind			
511.68	Randomized, double-blind, placebo-controlled	50 mg flibanserin tablets; 50 to 100 mg b.i.d. (an increase to 100 mg b.i.d. was possible after 8 weeks of treatment); oral	12 weeks
511.69	Randomized, double-blind, placebo-controlled	50 mg flibanserin tablets; 50 to 100 mg b.i.d. (an increase to 100 mg b.i.d. after 8 weeks treatment was possible); oral	12 weeks
Phase III – 24-week, placebo-controlled, parallel group, double-blind North American trials			
511.70	Randomized, double-blind, placebo-controlled	25 and 50 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d.; oral	24 weeks
511.71	Randomized, double-blind, placebo-controlled	50 and 100 mg flibanserin tablets; 50 mg q.h.s., 100 mg q.h.s.; oral	24 weeks
511.75	Randomized, double-blind, placebo-controlled	25, 50, and 100 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s. for 14 days then up-titration to 50 mg b.i.d. and 50 mg q.h.s. for 14 days then up-titration to 100 mg q.h.s.; oral	24 weeks
Phase III – Randomized withdrawal – 24-week, open-label, flexible flibanserin regimen, followed by 24-week, placebo-controlled, double-blind, randomized withdrawal			
511.74	Open-label, flexible dose regimen, followed by randomized, double-blind, placebo-controlled fixed dose regimen	50 mg flibanserin tablets; 50 mg q.h.s., 50 mg b.i.d., or 100 mg q.h.s.; oral	48 weeks (24 weeks open-label period + 24 weeks randomized, double-blind period)
Phase III – Long-term exposure			
511.84	Open-label, uncontrolled	50 and 100 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d., 100 mg q.h.s.; oral	52 weeks
European trials			
511.77	Randomized, double-blind, placebo-controlled	50 and 100 mg flibanserin tablets; 50 mg q.h.s., 50 mg q.h.s. for 14 days then up-titration to 100 mg q.h.s.; oral	24 weeks
511.118	Open-label, uncontrolled	25, 50 and 100 mg flibanserin tablets; 25 mg b.i.d., 50 mg q.h.s., 50 mg b.i.d., 100 mg q.h.s.; oral	28 weeks

b.i.d. = twice daily; q.h.s. = once every evening

Table 3.2: 2 Number of subjects by randomized arm - Placebo-controlled Phase II/III HSDD randomized trials

Trial Grouping	Trials Included	Placebo	25 mg b.i.d.	50 mg q.h.s.	50 mg b.i.d.	100 mg q.h.s.	100 mg b.i.d.	Total Flibanserin
Phase III placebo-controlled	511.70, 71, 75 and 77	1360	733	969	728	1001	0	3431
Broken out by fixed vs. uptitrated (uptit) regimen		1360	733	969	336 (fixed) 392 (uptit)	290 (fixed) 711 (uptit)	0	3431
Phase II placebo-controlled	511.68 and 69	148			149			149
Phase II/III placebo-controlled	511.68, 69, 70, 71, 75 and 77	1508			not combined [a]			3580
Phase III placebo-controlled randomized withdrawal	511.74 (second 24 weeks only)	170						163 [b]

a The 50 mg b.i.d. regimen of the 3-month phase 2 placebo-controlled trials (which had an optional uptitration to 100 mg b.i.d. after 8 weeks of treatment) was considered too different from the 50 mg b.i.d. regimens of the 6-month phase 3 placebo-controlled trials (i.e. fixed for the full 6 months or uptitration from 50 mg q.h.s after 2 weeks) to pool for analyses by randomized dose regimen. Therefore, any pooled analysis of phase 2 and 3 placebo-controlled trials was based on pooling all flibanserin regimens versus placebo.

b Continuation of the optimal dose (50 mg q.h.s., 50 mg b.i.d or 100 mg q.h.s) for each individual subject as determined during the open-label phase of the trial.

Table 3.2: 3 Number of subjects in analyses of adverse events by treatment at onset - HSDD trials

Trial Grouping[a]	Trials Included	Placebo	25 mg b.i.d.	50 mg q.h.s.	50 mg b.i.d.	100 mg q.h.s.	100 mg b.i.d.	Total Flibanserin
Phase III placebo-controlled	511.70, 71, 75 and 77	1360	733	2072 [b]	713[c]	978[d]	0	3431
Phase II placebo-controlled	511.68 and 69	148	0	0	149	0	72[e]	149
Phase II/III placebo-controlled	511.68, 69, 70, 71, 75 and 77	1508	733	2072	862	978	72	3580
Phase III placebo-controlled randomized withdrawal	511.74 (entire trial)	170	0	738	101	552	0	738[f]
Ongoing open-label Phase III uncontrolled	511.84 and 118	0	57	2197	305	1791	0	2203[g]
Phase I	511.105	0	35	32	32	30	0	67
All HSDD[g]	<all of above>	1678	814	3839	1257	2938	72	5018

a In trials involving up-titration, subjects may appear in more than one column.
b Some 50 mg b.i.d. and 100 mg q.h.s. regimens (referred to as up-titration regimens) started with 50 mg q.h.s. uptitrated after 2 weeks to either 50 mg b.i.d or 100 mg q.h.s.
c 15 subjects randomized to the 50 mg b.i.d. up-titration regimen dropped out while receiving 50 mg q.h.s. (i.e., before up-titrating to 50 mg b.i.d.)
d 23 subjects randomized to the 100 mg q.h.s. up-titration regimen dropped out while receiving 50 mg q.h.s. (i.e. before up-titrating to 100 mg q.h.s.)
e The 511.68 and 511.69 trial designs allowed for one month of exposure to 100 mg b.i.d. through an optional up-titration as week 8 of the 12 week trial.
f All subjects began Trial 511.74 receiving 50 mg q.h.s. and were subsequently permitted to titrate to 50 mg b.i.d. or 100 mg q.h.s.
g The tally of open-label uncontrolled extension trials (511.84 and 511.118) reflects double counting of subjects who received flibanserin in a previous trial and subsequently continued treatment in the extension trial.

Table 3.2: 4 Number of subjects in analyses of adverse events by treatment at onset - MDD trials

Trial Grouping[a]	Trials Included	Placebo	< 50 tdd[b]	50 mg q.h.s.	50 mg b.i.d.	100 mg q.h.s.	150 tdd	100 mg b.i.d.	Total Flibanserin
Placebo-controlled	511.10 511.11 511.12 511.18 511.28 511.41 511.42 511.43 511.49 (Women and Men)	718	408	70	521	102	9	211	1210
	Women Only	417	240	33	313	65	4	113	702
Open-label uncontrolled	511.44 511.45 (Women and Men)	0	0	68	439	83	247	161	439[c]
Phase I	511.5	0[d]	14	14		15			43[e]

a In trials involving up-titration, subjects may appear in more than one column.
b The abbreviation tdd stands for total daily dose. Doses within the < 50 tdd category included 2 mg (given as a single dose), 2 mg b.i.d. (given for 8 weeks), 20 mg qd (given for 4 weeks) and 20 mg b.i.d (given for 2-8 weeks).
c The tally of open-label uncontrolled extension trials (511.44 and 511.45) reflects double counting of subjects who received flibanserin in a previous trial and subsequently continued treatment in the extension trial.
d No concurrent placebo group was in the trial.
e Trial 511.5 included single doses of 2 mg, 50 mg and 100 mg and was conducted in male MDD subjects.

3.2.1 Extent of exposure

3.2.1.1 Overall extent of exposure

Flibanserin has been tested in healthy volunteers at single doses ranging from 0.1-150 mg and multiple doses up to 100 mg t.i.d., in depressed patients at doses ranging from 2-100 mg b.i.d., and in women with HSDD at doses ranging from 25-100 mg b.i.d. Over 7000 human subjects have received one or more doses of flibanserin in clinical trials.

Flibanserin exposures included 803 healthy volunteers in Phase I trials, 1210 depressed men and women, and 5018 premenopausal women with HSDD (67 in Phase I, 149 in Phase II, 3431 in placebo-controlled Phase III trials, 738 in the randomized withdrawal trial, and 633 newly exposed to flibanserin in open-label, extension Phase III trials).

When assessed by cumulative interval, 2938 (58.5%) of the 5018 premenopausal women with HSDD received flibanserin 100 mg q.h.s. Of those, 2144 (73.0%) subjects were treated with flibanserin 100 mg q.h.s. for at least 3 months, 1175 (40.0%) subjects were treated for at least 6 months, and 213 (7.2%) subjects were treated with flibanserin 100 mg q.h.s. for at least one year. Thirty-eight (1.3%) women have received flibanserin 100 mg q.h.s. for at least 18 months, and 185 (3.7%) received flibanserin at various doses (50-100 mg/day) for at least 18 months. Mean exposure to flibanserin 100 mg q.h.s. was 189.7 days (>6 months), and mean total flibanserin exposure was 226.9 days (approximately 7.5 months). Median exposure to flibanserin 100 mg q.h.s. was 162 days (approximately 5 months), and was 173 days (nearly 6 months) for flibanserin in total. Table 3.2.1.1: 1 displays the cumulative intervals of exposure for all HSDD trials.

Table 3.2.1.1: 1 Exposure to flibanserin by cumulative interval – All HSDD trials

	FLI 25 bid	FLI 50 qhs	FLI 50 bid	FLI 100 qhs	FLI 100 bid	FLI Total
Number of Subjects	814 (100)	3839 (100)	1257 (100)	2938 (100)	72 (100)	5018 (100)
Exposure (days)						
≥1	814 (100.0)	3839 (100.0)	1257 (100.0)	2938 (100.0)	72 (100.0)	5018 (100.0)
≥7	802 (98.5)	3798 (98.9)	1198 (95.3)	2884 (98.2)	63 (87.5)	4947 (98.6)
≥14	758 (93.1)	3696 (96.3)	1110 (88.3)	2804 (95.4)	55 (76.4)	4863 (96.9)
≥28	730 (89.7)	2968 (77.3)	1017 (80.9)	2643 (90.0)	41 (56.9)	4647 (92.6)
≥56	648 (79.6)	1613 (42.0)	849 (67.5)	2324 (79.1)	0 (0.0)	4217 (84.0)
≥84	605 (74.3)	1255 (32.7)	666 (53.0)	2144 (73.0)	0 (0.0)	3850 (76.7)
≥182	75 (9.2)	691 (18.0)	97 (7.7)	1175 (40.0)	0 (0.0)	2190 (43.6)
≥365	2 (0.2)	89 (2.3)	13 (1.0)	213 (7.2)	0 (0.0)	1130 (22.5)
≥547	0 (0.0)	6 (0.2)	1 (0.1)	38 (1.3)	0 (0.0)	185 (3.7)
Mean	133.5	88.1	105.8	189.7	23.5	226.9
SD	67.4	95.0	83.9	140.0	10.0	173.1
Min	1	1	1	1	2	1
P25%	75	28	34	71	18	86
Median	168	41	89	162	28	173
P75%	172	159	161	313	29	359
Max	518	694	643	697	42	752
Exposure Subject-years	297.5	925.8	364.0	1525.6	4.6	3117.5

a Includes all HSDD studies that are completed or that are currently ongoing open−label studies: 511.68, .69, .70 .71, .74, .75, .77, .84, .105, .118.

b Exposure for subjects who rolled over to 511.84 or .118 is combined with their exposure in the previous double−blind trial as if it were continuous by summing the exposure in the double−blind period and the exposure in the open−label extension trial.

FLI = flibanserin

Includes all data from these trials that is in the project database as of 17 Nov 2009.

3.2.1.2 Phase I trials

A total of 803 subjects received flibanserin and 161 subjects received placebo in the Phase I trials. All subjects received at least one dose of trial medication and had at least one post-dose on-treatment safety assessment. Table 7.2.1: 1 (Appendix 7.2.1) displays the numbers and types of subjects for the Phase I trials. The only Phase I trial which included women with HSDD was 511.105.

3.2.1.3 Placebo-controlled trials in HSDD

In Phase II and III controlled trials of HSDD, 1729 women were exposed to the clinically relevant flibanserin dosage of 100 mg per day (100 mg q.h.s. or 50 mg b.i.d.). When all phase III placebo-controlled HSDD trials were combined, 3431 subjects were exposed to

either 50 mg or 100 mg flibanserin daily for a mean of 137.7 days (approximately 19 weeks), with an exposure of 1293.5 subject years.

The mean duration of treatment exposure during double-blind treatment in the Phase III controlled trials was 145.5 days (approximately 21 weeks) in the placebo group and 137.7 days (19.7 weeks) in the flibanserin group (Table 3.2.1.3: 1). The maximum duration of exposure was 251 days in the placebo group versus 241 days in the flibanserin group.

Table 3.2.1.3: 1 Exposure to flibanserin or placebo - Phase III placebo-controlled HSDD trials

	Placebo	FLI 25 mg b.i.d.	FLI 50 mg q.h.s.	FLI 50 mg b.i.d.	FLI 100 mg q.h.s.	All FLI
Number of Subjects	1360 (100)	733 (100)	969 (100)	728 (100)	1001 (100)	3431 (100)
Exposure (days)						
1 - 28	68 (5.0)	40 (5.5)	53 (5.5)	80 (11.0)	68 (6.8)	241 (7.0)
29 - 60	111 (8.2)	85 (11.6)	82 (8.5)	93 (12.8)	121 (12.1)	381 (11.1)
61 - 90	69 (5.1)	28 (3.8)	56 (5.8)	44 (6.0)	56 (5.6)	184 (5.4)
91 - 135	87 (6.4)	47 (6.4)	59 (6.1)	52 (7.1)	70 (7.0)	228 (6.6)
136 - 180	860 (63.2)	465 (63.4)	605 (62.4)	411 (56.5)	591 (59.0)	2072 (60.4)
181 or greater	165 (12.1)	68 (9.3)	114(11.8)	48 (6.6)	95 (9.5)	325 (9.5)
Mean	145.5	141.4	144.0	127.6	136.2	137.7
SD	51.9	54.8	53.0	62.0	57.3	56.9
Min	2	2	2	2	2	2
P25%	140	119	128	64	93	99
Median	169	169	169	168	169	169
P75%	175	174	175	173	174	174
Max	251	235	241	208	226	241
Exposure Subject-years	541.7	283.8	382.1	254.3	373.3	1293.5

Trials include 511.70, .71, .75, and .77
Subjects may be reflected in multiple columns.

3.2.1.4 Phase III randomized withdrawal Trial 511.74

In Trial 511.74, 68% of 24-week completers stabilized their dosage at 100 mg q.h.s., while 24% used 50 mg q.h.s. and 8% used 50 mg b.i.d.

The duration of the entire Trial 511.74 was 56 weeks, which included a 4-week screening period without treatment (Weeks -4 to 0), 24 weeks of OL treatment (Weeks 1 to 24), and 24 weeks of double-blind treatment (Weeks 25 to 48), and a 4-week post-treatment period (Weeks 49 to 52).

The mean duration of combined exposure to OL and double-blind flibanserin during the entire trial was 168 days (6 months); the median exposure was also 168 days. Of 738 subjects, 184 (25.0%) were exposed for more than 180 days and 22 (3.0%) subjects had an exposure of 12 months. The extent of exposure to flibanserin during the entire trial is displayed in Table 3.2.1.4: 1.

Table 3.2.1.4: 1 Number of subjects (%) exposed to flibanserin in the entire 511.74 trial (combined open-label and double-blind periods)

	FLI 50mg q.h.s.	FLI 50mg b.i.d.	FLI 100 mg q.h.s.	All FLI
Number of Subjects	738 (100)	101 (100)	552 (100)	738 (100)
Exposure (days)				
1	0 (0.0)	2 (2.0)	6 (1.1)	0 (0.0)
2 - 7	11 (1.5)	9 (8.9)	18 (3.3)	10 (1.4)
8 - 15	7 (0.9)	5 (5.0)	25 (4.5)	6 (0.8)
16 - 28	311 (42.1)	23 (22.8)	50 (9.1)	27 (3.7)
29 - 60	238 (32.2)	21 (20.8)	77 (13.9)	74 (10.0)
61 - 90	47 (6.4)	12 (11.9)	41 (7.4)	63 (8.5)
91 - 135	20 (2.7)	10 (9.9)	86 (15.6)	73 (9.9)
136 - 180	70 (9.5)	9 (8.9)	143 (25.9)	301 (40.8)
181 - 350	30 (4.1)	10 (9.9)	106 (19.2)	162 (22.0)
> 350	4 (0.5)	0 (0.0)	0 (0.0)	22 (3.0)
Mean	61.4	77.8	128.4	168.0
SD	68.7	80.9	96.9	97.5
Min	2	1	1	2
P25%	28	28	49	92
Median	29	53	131	168
P75%	57	111	149	180
Max	386	330	349	421
Exposure Subject-years	124.0	21.5	194.0	339.5

All subjects began the trial receiving 50 mg q.h.s. and were subsequently permitted to titrate to 50 mg b.i.d. or 100 mg q.h.s.

3.2.1.5 Open-label, extension Phase III trials (ongoing)

As of the data cutoff date of 17 Nov 2009, 2203 subjects were exposed to flibanserin in the open-label extension trials. The displays of exposure in this section show exposure only for subjects in Trials 511.84 or 511.118, and do not combine their exposure with that from the previous double-blind trials.

When assessed by cumulative interval, a total of 2203 subjects were exposed to flibanserin for a mean of 242.9 days (range: 1 day to 420 days [Table 3.2.1.5: 1]) in the Phase III open-label extension HSDD trials, with 1791 (81.3%) of those receiving flibanserin 100 mg q.h.s. Of those, 1356 (75.7%) subjects were treated with flibanserin 100 mg q.h.s. for at least 84 days, 898 (50.1%) subjects were treated for at least 182 days, and 4 (0.2%) subjects were treated with flibanserin 100 mg q.h.s. for at least 365 days. It is important to note that in Trial 511.84, subjects were required to take flibanserin 50 mg q.h.s. for the first 4 to 8 weeks, and Trial 511.118 is a 28-week trial, thus, the exposure to flibanserin 100 mg q.h.s. in these 2 trials for one year is limited.

Mean exposure to flibanserin 100 mg q.h.s. was 199.0 days (>6 months), and mean total flibanserin exposure was 242.9 days (approximately 8 months). Median exposure to flibanserin 100 mg q.h.s. was 182 days (approximately 6 months), and was 239 days (approximately 8 months) for flibanserin in total.

Table 3.2.1.5: 1 Exposure to flibanserin by cumulative exposure interval – Phase III open-label, uncontrolled extension HSDD trials

	FLI 25 bid	FLI 50 qhs	FLI 50 bid	FLI 100 qhs	FLI total
Number of Subjects	57 (100)	2197 (100)	305 (100)	1791 (100)	2203 (100)
Exposure (days)					
≥ 1	57 (100.0)	2197 (100.0)	305 (100.0)	1791 (100.0)	2203 (100.0)
≥ 7	54 (94.7)	2185 (99.5)	282 (92.5)	1769 (98.8)	2193 (99.5)
≥ 14	51 (89.5)	2168 (98.7)	264 (86.6)	1750 (97.7)	2181 (99.0)
≥ 28	44 (77.2)	1847 (84.1)	233 (76.4)	1669 (93.2)	2145 (97.4)
≥ 56	27 (47.4)	609 (27.7)	175 (57.4)	1475 (82.4)	2024 (91.9)
≥ 84	23 (40.4)	380 (17.3)	119 (39.0)	1356 (75.7)	1849 (83.9)
≥182	9 (15.8)	206 (9.4)	52 (17.0)	898 (50.1)	1505 (68.3)
≥ 365	0 (0.0)	46 (2.1)	0 (0.0)	4 (0.2)	564 (25.6)
≥ 547	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean	96.4	65.1	99.1	199.0	242.9
SD	105.9	80.4	97.2	121.0	124.9
Min	1	1	1	1	1
P25%	28	28	28	86	126
Median	47	31	63	182	239
P75%	121	56	140	331	365
Max	356	395	345	378	420
Exposure Subject-years	15.0	391.6	82.8	975.6	1465.0

Includes exposure only in Trials 511.84 and .118
a Trials 511.70, .71 , .74, .75, and .105 fed into .84, and .77 fed into .118.
b Subjects may appear in multiple columns.
FLI = flibanserin
Includes all data from these trials that are in the project database as of 17 Nov 2009.

3.2.1.6 Long-term exposure

In Trials 511.84 and 511.118 over three times as many patients stabilized their dose regimen for 90 days or longer on 100 mg q.h.s. (72.8% of patients) as did those who stabilized on 50 mg q.h.s. (20.7% of patients), while 50 mg b.i.d. and 25 mg b.i.d. were used for this duration by very few patients (1.3% and 6.2%, respectively). Combining the 100 mg q.h.s. and 50 mg b.i.d. exposures in 1175 and 97 patients, 1272 patients were exposed to a

flibanserin dosage of 100 mg/day for at least 182 days. Relatively few patients had stayed on one dose regimen for 52 weeks, but 1130 had completed at least one full year of flibanserin exposure (using a cut-off of 365 days), and 185 were exposed for at least 18 months (Table 3.2.1.6: 1).

Table 3.2.1.6: 1 Long term exposure to flibanserin, all HSDD trials

	FLI 25 mg b.i.d.	FLI 50 mg q.h.s.	FLI 50 mg b.i.d.	FLI 100 mg q.h.s.	FLI Total
Exposure (days)					
≥84	605	1255	666	2144	3850
≥182	75	691	97	1175	2190
≥365	2	89	13	213	1130

NOTE: Includes all HSDD studies that were completed or that were currently ongoing open-label studies: 511.68, 511.69, 511.70, 511.71, 511.74, 511.75, 511.77, 511.105, 511.84, 511.118. In trials involving up-titration, subjects appear in more than one column. The FLI total column differs from the sum of the individual doses within the same row, since it represents cumulative flibanserin exposure to any dose.

3.2.2 Adverse events

All AEs were pooled and displayed for the following on-treatment groups:

- Phase III Trials 511.70, 511.71, 511.75, and 511.77
- Phase III randomized withdrawal Trial 511.74
- Phase III open-label extension Trial 511.84 and 511.118, ongoing.

This AE overview focuses on flibanserin 100 mg q.h.s. as the recommended dose. Due to the overall study design, the population in the double-blind phase of Trial 511.74 was comprised of responders who already had tolerated a flibanserin run-in treatment for 24 weeks. Therefore, the AEs in this study were analyzed separately.

Patients with MDD exposed to flibanserin 100 mg q.h.s. had similar AEs at similar severities as premenopausal women with HSDD, however the overall duration of exposure in MDD patients was shorter and these 2 diagnostic groups are not compared in detail because of their differences in demographics, dosing, and self-reported health problems. Nevertheless, these safety data can be used to assist in understanding the overall safety profile of flibanserin in women with HSDD. Table 7.2.2: 4 (Appendix 7.2.2) displays the AEs occurring in >=1% of subjects in Phase II placebo−controlled MDD trials by treatment, and Table 7.2.2: 5 (Appendix 7.2.2) displays the AEs for female patients only.

3.2.2.1 Common adverse events

3.2.2.1.1 Placebo-controlled Phase III Trials 511.70, 511.71, 511.75, and 511.77

In the four Phase III placebo-controlled HSDD trials, more patients in the flibanserin groups reported an AE compared to the placebo group (66.2% vs. 57.7%). The investigators rated over 90% of the AE's reported as mild or moderate in severity.

The most frequently reported AEs - those in ≥1% of patients exposed to flibanserin and twice the rate in the placebo group - are in Table 3.2.2.1.1: 1. With 100 mg flibanserin q.h.s., these AEs included dizziness, nausea, fatigue, and somnolence, at approximately 10-12% each, and insomnia, at about 5%.

Table 3.2.2.1.1: 1 Number (%) of subjects with adverse events occurring in ≥1% and at least twice that of placebo in the flibanserin 100-mg groups by preferred term and randomized treatment, Phase III placebo-controlled HSDD trials

Preferred term	Placebo N (%)	FLI 50 mg q.h.s. N (%)	FLI 100 mg q.h.s. N (%)
Number of subjects	1360 (100)	969 (100)	1001 (100)
Dizziness	34 (2.50)	61 (6.09)	120 (11.99)
Nausea	58 (4.26)	68 (7.02)	119 (11.89)
Fatigue	77 (5.66)	59 (6.09)	110 (10.99)
Somnolence	40 (2.94)	55 (5.68)	95 (9.49)
Insomnia	32 (2.35)	19 (1.96)	51 (5.09)
Dry mouth	9 (0.66)	12 (1.24)	23 (2.30)
Anxiety	9 (0.66)	19 (1.96)	20 (2.00)
Abdominal pain	11 (0.81)	17 (1.75)	18 (1.80)
Constipation	4 (0.29)	4 (0.41)	17 (1.70)
Sedation	2 (0.15)	6 (0.62)	17 (1.70)
Nocturia	3 (0.22)	5 (0.52)	12 (1.20)
Sleep disorder	1 (0.07)	3 (0.31)	12 (1.20)
Palpitations	6 (0.44)	5 (0.52)	10 (1.00)
Stress	2 (0.15)	4 (0.41)	10 (1.00)
Vertigo	4 (0.29)	3 (0.31)	10 (1.00)

Includes Trials 511.70, 511.71, 511.75 and 511.77
Percentages were calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 11.1
Sort is in descending order of frequency in flibanserin 100 mg q.h.s.
Rounding to 2 decimal places of accuracy was used to provide confirmation of the table selection criterion (twice that of placebo).

The Sponsor considered treatment emergent AEs to be ADRs to flibanserin if they occurred in at least 2% of the study population treated with the active dose of the study drug (100 mg q.h.s.) in the Phase III placebo-controlled trials, and occurred in at least twice the rate observed in the placebo group. Using these criteria, ADRs of flibanserin included dizziness, nausea, fatigue, somnolence, insomnia, dry mouth and anxiety. Other events not meeting these criteria were reviewed for possible relationship with flibanserin administration using criteria such as frequency of reporting, extent of dose response, or the extent to which the AE may have been related to the pharmacology of the drug: based on these assessments constipation, sedation, sleep disorder, palpitations, vertigo and hypotension were also considered treatment emergent AEs. Each of these AEs was also in excess of placebo-associated rates by a factor of at least 2.

Drug-related AEs typically began during the first week or two of flibanserin treatment. These AEs were dose-related and regimen-related (more with 50 mg b.i.d. than with 100 mg q.h.s.). For 100 mg flibanserin q.h.s. dose groups, the expected AEs showed little relation to whether the dose was fixed or reached by up-titration. Results over the first 4 weeks for the most frequent type of AEs, somnolence/fatigue/sedation, showed little difference between starting with a 100-mg dose or up-titrating to a 100-mg dose: 20.1% of patients had one or more AEs while on a 100-mg fixed dose, compared to 18.2% patients on 100 mg reached by up-titration. Figure 7.2.2: 1 (Appendix 7.2.2) shows a similar pattern on a per-week basis as incidence rates of first onset of one or more of AEs during the first 4 weeks of treatment. Most AEs began in the first week of flibanserin exposure, regardless of whether that exposure was initially 100 mg (15.9% of patients reporting the AE) or 50 mg (12.5% of patients reporting the AE). The other 2 most frequently reported AEs, nausea and dizziness, showed the same pattern.

The duration of the most frequent AEs in these four trials is summarized in Table 3.2.2.1.1: 2. The median duration for nausea was shortest, at 6 days. The median duration for dizziness, insomnia, and all sedative-type effects (fatigue, somnolence, sedation) ranged from 18.5-50 days. The incidence for all sedative type of events was 21.3% with flibanserin 100 mg q.h.s as compared to 9.1% with placebo. In most cases, these adverse events were mild, and dissipated over time. Discontinuations due to the adverse events were infrequent (see Section 3.2.2.2), strengthening the fact that the common adverse events were of mild severity.

Table 3.2.2.1.1: 2 Duration of most frequent adverse events in Trials 511.70, 511.71, 511.75, and 511.77, by treatment at onset

		Number of days with AE		
Frequent AE	Number (%) of patients taking 100 mg flibanserin q.h.s. with AE	25th percentile	median	75th percentile
Treated subjects	978			
Dizziness	76 (7.8)	3	18.5	46
Nausea	75 (7.7)	2	6	15
Fatigue	55 (5.6)	12.5	42.5	85.5
Somnolence	51 (5.2)	18	50	169
Insomnia	40 (4.1)	15	34.5	70

3.2.2.1.2 Phase III randomized withdrawal Trial 511.74

In the open-label period of the Phase III placebo-controlled randomized withdrawal Trial 511.74 in HSDD subjects, 512 subjects (69.4%) experienced AEs while taking flibanserin. Somnolence, fatigue, headache, dizziness, and nausea were the most prevalent, and each event was reported in 8-14% of the subjects. Table 3.2.2.1.2: 1 displays AE that occurred in ≥2% of subjects.

These data do not include the randomized withdrawal period of Trial 511.74, which are evaluated separately for withdrawal effects and presented in Section 3.2.8.3 of this briefing document.

Table 3.2.2.1.2: 1 Adverse events reported in ≥2% of all subjects in the open-label period of Trial 511.74 by MedDRA preferred term

	Flibanserin N (%)
Total treated	738
Total with any AE	512 (69.4)
Preferred term	
Somnolence	104 (14.1)
Fatigue	76 (10.3)
Headache	66 (8.9)
Dizziness	65 (8.8)
Nausea	59 (8.0)
Menorrhagia	40 (5.4)
Nasopharyngitis	34 (4.6)
Insomnia	29 (3.9)
Irritability	28 (3.8)
Urinary tract infection	24 (3.3)
Sinusitis	23 (3.1)
Dysmenorrhea	22 (3.0)
Upper respiratory tract infection	18 (2.4)
Sedation	18 (2.4)
Back pain	16 (2.2)
Depression	15 (2.0)

The most common AEs occurring in subjects in the Phase III randomized withdrawal Trial 511.74 were comparable to those seen in the Phase III Trials 511.70, 511.71, 511.75, and 511.77.

3.2.2.1.3 Open-label, extension Trials 511.84 and 511.118

3.2.2.1.3.1 Overall summary of adverse events

Trials 511.84 and 511.118 comprise subjects who opted to continue into OL, long-term trials following completion of earlier trials. The starting dose was flibanserin 50 mg q.h.s. for the first 4 to 8 weeks, with flexible dosing of 50 or 100 mg q.h.s. or 25 mg b.i.d. or 50 mg b.i.d.

Among the 1791 subjects receiving flibanserin 100 mg q.h.s., 1098 (61.3%) experienced one or more AEs; 121 subjects (6.8%) experienced AEs of severe intensity, and 124 subjects (6.9%) experienced one or more AEs that led to discontinuation of study drug. A summary of all AEs that occurred in the open-label trials is presented in Table 3.2.2.1.3.1: 1. Tables 7.2.2: 1 and 7.2.2: 2 in Appendix 7.2.2 display the common AEs in detail.

Table 3.2.2.1.3.1: 1 Adverse event overall summary - Phase III open-label, uncontrolled extension HSDD trials

	FLI 25 bid N (%)	FLI 50 qhs N (%)	FLI 50 bid N (%)	FLI 100 qhs N (%)
Number of subjects	57 (100.0)	2197 (100.0)	305 (100.0)	1791 (100.0)
Subjects with any AE	27 (47.4)	1001 (45.6)	163 (53.4)	1098 (61.3)
Subjects with severe AEs	3 (5.3)	66 (3.0)	19 (6.2)	121 (6.8)
Subjects with AEs leading to discontinuation of trial drug	8 (14.0)	104 (4.7)	13 (4.3)	124 (6.9)
Subjects with serious AEs	1 (1.8)	9 (0.4)	4 (1.3)	16 (0.9)

FLI = flibanserin
A subject could be counted in more than one seriousness criterion.
Percentages were calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 12.1.
Includes all data from Trials 511.84 and .118 in the project database as of 17 Nov 2009.
AE displayed by treatment at onset.

3.2.2.1.3.2 Common adverse events

In the Phase III open-label extension HSDD trials, somnolence (302, 13.7%), fatigue (200, 9.1%), nasopharyngitis (176, 8.0%), headache (164, 7.4%), dizziness (159, 7.2%), and nausea (150, 6.8%) were the most prevalent AEs. The most common AE among subjects receiving flibanserin 100 mg q.h.s. was somnolence, experienced by 113 (6.3%) subjects.

Other common AEs in the flibanserin 100-mg q.h.s. group included nasopharyngitis (96, 5.4%), dizziness (87, 4.9%), upper respiratory infection (75, 4.2%), nausea (75, 4.2%), and headache (74, 4.1%). Table 7.2.2: 1 (Appendix 7.2.2) displays the common AEs (i.e., occurring in ≥1% of subjects) in the open-label, long-term HSDD trials by treatment, and Table 7.2.2: 2 (Appendix 7.2.2) displays the common AEs by dose.

The common AEs occurring in subjects in the open-label extension Trials 511.84 and 511.118 were comparable to those seen in the Phase III Trials 511.70, 511.71, 511.75 and 511.77.

3.2.2.1.4 Common adverse events in female MDD subjects

The pattern of AEs in the female MDD subject population receiving flibanserin 100 mg daily is consistent with that of the HSDD subjects with higher rates of dizziness, nausea, and insomnia (Table 7.2.2: 5, Appendix 7.2.2).

3.2.2.2 Discontinuations for AE

This section displays other significant AEs (other than those reported as SAEs) that led to premature discontinuation of flibanserin treatment.

3.2.2.2.1 Placebo-controlled Phase III Trials 511.70, 511.71, 511.75, and 511.77

AEs led to treatment discontinuation in 12.9% of the 3431 subjects receiving flibanserin and in 6.8% of the 1360 subjects receiving placebo. The rate of AE discontinuations was highest with 50 mg b.i.d. flibanserin (20.3%; data not shown because this dose regimen was ineffective and had more AEs and AE dropouts, and thus is not recommended for future efficacy-safety studies). The AE discontinuation rate was lower with 100 mg q.h.s., at 14.6% (Table 3.2.2.2.1: 1). The AE discontinuation rates with flibanserin 25 mg b.i.d. (6.8%; not shown) and 50 mg q.h.s. (10.2%) were higher than that with placebo (6.8%).

Table 3.2.2.2.1: 1 displays the AEs that led to treatment discontinuation by preferred term and randomized treatment for Trials 511.70, 511.71, 511.75, and 511.77 (see also Table 7.2.2: 6, Appendix 7.2.2).

Seven (7) AEs led to discontinuation of about 1% each or more on flibanserin 100 mg q.h.s.:

- Nausea, fatigue, dizziness, and insomnia led to discontinuation at rates of about 1-2% each with 100 mg q.h.s. These frequent AEs were the main sources of AE dropouts.
- Somnolence, the other frequent AE, led to slightly less than 1% AE discontinuation with 100 mg (8 patients, 0.8%).
- Anxiety, reported at less than 5% but in excess with flibanserin compared to placebo, also led to about 1% AE discontinuation.
- Headache led to about a 1% rate of discontinuation from all treatment groups, including placebo.

Except for headache, the AE discontinuations were dose-related. Overall, the sedative type of AEs (fatigue, somnolence and sedation) led to discontinuation in 1.0% with placebo, 1.1% with flibanserin 50 mg q.h.s, and 2.0% with flibanserin 100 mg q.h.s.

Table 3.2.2.2.1: 1 Discontinuation rates for adverse events in about 1% or more patients by preferred term and randomized treatment, Phase III placebo-controlled Trials 511.70, 511.71, 511.75, 511.77

	Placebo	Flibanserin 50 mg q.h.s.	Flibanserin 100 mg q.h.s.
Number of patients	1360	969	1001
Total with AEs leading to treatment discontinuation	92 (6.8)	99 (10.2)	146 (14.6)
Dizziness	1 (0.1)	9 (0.9)	18 (1.8)
Nausea	3 (0.2)	5 (0.5)	16 (1.6)
Anxiety	4 (0.3)	10 (1.0)	13 (1.3)
Insomnia	3 (0.2)	3 (0.3)	13 (1.3)
Fatigue	7 (0.5)	7 (0.7)	11 (1.1)
Somnolence	7 (0.5)	4 (0.4)	8 (0.8)
Headache	9 (0.7)	11 (1.1)	6 (0.6)

3.2.2.2.2 Phase III randomized withdrawal Trial 511.74

The AEs resulting in discontinuation in the Phase III randomized withdrawal Trial 511.74 were comparable to the parallel placebo-controlled Trials 511.70, 511.71, 511.75, and 511.77.

Discontinuations due to AEs occurred in 112 subjects (15%) taking open-label flibanserin. The most frequent AEs leading to discontinuation in the open-label period were fatigue (2.0%) and somnolence (1.8%). During the double-blind period, no AE led to discontinuation in 1% or more subjects in a treatment group.

3.2.2.2.3 Open-label, extension Trials 511.84 and 511.118

As of the data cutoff of 17 Nov 2009, 249/2203 (11.3%) subjects had AEs that led to discontinuation of treatment. Subjects receiving flibanserin 25 mg b.i.d. had the highest incidence of AEs that led to treatment discontinuation, but also had the fewest subjects exposed in total.

In subjects treated with flibanserin 100 mg q.h.s., the most common AEs that led to treatment discontinuation were depression (1.0%), dizziness (0.7%), anxiety (0.5%), insomnia (0.4%) nausea (0.4%) and fatigue (0.3%); all of these incidence rates are lower than those in the Phase III placebo-controlled trials with the exception of depression, which is slightly higher (Table 3.2.2.2.3: 1).

Table 3.2.2.2.3: 1 displays the AEs occurring in ≥0.2% of subjects in the flibanserin 100 mg q.h.s. treatment group that led to treatment discontinuation in the OL extension trials.

Table 3.2.2.2.3: 1 Frequency [N (%)] of subjects with adverse events occurring in equal to or greater than 0.2% of subjects in the Flibanserin 100 q.h.s. group leading to treatment discontinuation by treatment, primary system organ class and preferred term - Phase III OL uncontrolled extension HSDD trials

System organ class Preferred term	Fibanserin 100 qhs N (%)
Number of subjects	1791 (100.0)
Total with adverse events leading to treatment discontinuation	124 (6.9)
Psychiatric disorders	50 (2.8)
Anxiety	9 (0.5)
Depression	18 (1.0)
Insomnia	7 (0.4)
Depressed mood	3 (0.2)
Sleep disorder	3 (0.2)
Stress	3 (0.2)
Nervous system disorders	32 (1.8)
Somnolence	4 (0.2)
Dizziness	13 (0.7)
Headache	4 (0.2)
Paraesthesia	3 (0.2)
Ear and labyrinth disorders	4 (0.2)
Vertigo	4 (0.2)
Gastrointestinal disorders	11 (0.6)
Nausea	7 (0.4)
Vomiting	3 (0.2)
General disorders and administration site conditions	10 (0.6)
Fatigue	6 (0.3)

Percentages are calculated using total number of subjects treated with flibanserin 100-mg q.h.s. as the denominator. Includes AEs that led to discontinuation in ≥0.2% of subjects in the flibanserin 100-mg q.h.s. treatment group.
MedDRA version used for reporting: 12.1.
The set of trials used as the basis for this display include 511.84 and .118.
Includes data from these trials in the project database as of 17 Nov 2009.

3.2.3 Vital signs, electrocardiograms, and laboratory findings

In Trial 511.70, fecundity evaluations were conducted by collecting follicular and luteal phase sex hormones pre-, on-, and post-treatment. Ovulatory vs. anovulatory cycle determinations were made for 120 patients on flibanserin and 36 patients on placebo. This showed no indication of loss of fecundity attributable to flibanserin.

3.2.3.1 Vital signs

Vital signs were recorded in all flibanserin studies. No clinically significant changes in blood pressure or pulse rate were found in all Phase III trials despite routine monitoring at all visits (Table 3.2.3.1: 1). No clinically relevant differences between the treatment groups in mean blood pressure scores or pulse rate, or differences in AEs of hypertension, bradycardia or tachycardia, were seen at any time point in the primary efficacy studies conducted to date with flibanserin.

Table 3.2.3.1: 1 Subjects with clinically relevant changes for blood pressure, pulse, and weight - Phase III placebo-controlled HSDD trials (511.70, 511.71, 511.75, 511.77)

Parameter	Placebo N (%)	Flibanserin 100 mg q.h.s. N (%)
Number of subjects	1360 (100.0)	1001 (100.0)
Pulse rate[a]		
Increase	2 (0.1)	0 (0.0)
Decrease	10 (0.7)	3 (0.3)
Systolic BP[b]		
Increase	1 (0.1)	0 (0.0)
Decrease	11 (0.8)	3 (0.3)
Diastolic BP[c]		
Increase	5 (0.4)	3 (0.3)
Decrease	4 (0.3)	3 (0.3)
Weight[d]		
Increase	29 (2.1)	8 (0.8)
Decrease	36 (2.6)	51 (5.1)

a Pulse must have increased or decreased 15 bpm or more from baseline at any subsequent visit and be out of normal range (<50 or >120), or baseline pulse must be above 120 bpm.
b Baseline Systolic BP must have increased or decreased 20 mmHg or more from baseline and be out of normal range (<90 or >180).
c Baseline Diastolic BP must have increased or decreased 15 mmHg or more from baseline and be out of normal range (<50 or >105).
d Weight: change of ≥7% from baseline at any subsequent visit.

3.2.3.2 Electrocardiograms

No clinically significant ECG changes were found in central readings in all North American, placebo-controlled Phase III trials (Table 3.2.3.2: 1), and no signal was seen in a thorough QT trial. In Trial 511.77, the ECGs were read locally only, and therefore, not pooled with the North American trials.

Table 3.2.3.2: 1 Changes in HR, PR and QRS intervals - Phase III placebo-controlled HSDD Trials 511.70, 511.71, and 511.75

	Placebo N (%)	Flibanserin N (%)
Number of subjects	1042	2804
Heart rate [bpm]		
N	898	2397
Mean of change	-0.1	-0.8
SD	8.4	8.5
Notable HR change [bpm][a]		
N	898	2397
No notable change	896 (99.8)	2382 (99.4)
Increase	0 (0.0)	6 (0.3)
Decrease	2 (0.2)	9 (0.4)
PR interval [ms]		
N	898	2396
Mean of change	-0.1	-0.1
SD	11.5	11.5
Notable PR increase[b]		
N	898	2396
No	898 (100.0)	2394 (99.9)
Yes	0 (0.0)	2 (0.1)
QRS interval [ms][c]		
N	898	2397
Mean of change	1.0	0.7
SD	5.6	5.8
Notable QRS increase		
N	898	2397
No	898 (100.0)	2396 (100.0)
Yes	0 (0.0)	1 (0.1)

Trials include 511.70, 511.71, 511.75. Trial 511.77 is not included because ECGs were read locally, unlike Trials 511.70, 511.71, and 511.75, which had central ECG readings

a Notable HR increase defined as ≥25% increase and on-treatment HR >100 bpm and notable HR decrease defined as ≥25% decrease and on-treatment HR <50 bpm (subjects may experience both an increase and a decrease on-treatment.)

b Notable PR interval increase defined as ≥25% increase and on-treatment PR interval >200 ms

c Notable QRS interval increase defined as ≥10% increase and on-treatment QRS interval >110 ms

A thorough QT study, conducted using a protocol that had been reviewed by FDA, of flibanserin 50 mg b.i.d. and 100 mg t.i.d. compared to placebo and moxifloxacinin in 56 male and female healthy volunteers, has shown no effect of flibanserin on the QTc interval.

3.2.3.3 Laboratory findings in Phase III placebo-controlled trials in HSDD (511.70, 511.71, 511.75, 511.77)

3.2.3.3.1 Mean change from baseline

Hematology

There were no clinically important changes from baseline in mean hematology values among the subjects in the placebo-controlled trials in HSDD. Mean changes from baseline to last value on treatment were similar between the flibanserin 100 mg q.h.s. group and the placebo group for all hematologic parameters.

Chemistry

There were no clinically important mean changes from baseline in chemistry values among the subjects in the placebo-controlled trials in HSDD subjects. Mean changes in liver function tests (aspartate aminotransferase [AST/SGOT], alanine aminotransferase [ALT/SGPT], alkaline phosphatase) from baseline to last value on treatment were minimal and similar between the flibanserin 100 mg q.h.s. group and the placebo group.

There were no mean differences in creatinine from baseline to last value on treatment for any of the treatment groups in the Phase III studies. Mean changes in total cholesterol from baseline to last value on treatment were lower for all treatment groups in the Phase III studies: -12.4 mg/dL for the flibanserin 100 mg q.h.s. group, and -7.6 mg/dL for the placebo group.

Urinalysis

There were no clinically important mean changes from baseline in urinalysis values among the subjects in the placebo-controlled trials in HSDD subjects.

Hormones

The hormonal evaluation included follicle stimulating hormone, luteinizing hormone, estradiol, progesterone, testosterone (free and total), DHEA and DHEA-S, SHBG, and prolactin. There were no clinically important mean changes from baseline in hormone values among the subjects in the placebo-controlled trials in HSDD subjects.

Table 7.2.3: 1 (Appendix 7.2.3) displays the mean changes from baseline to last value on treatment for female hormones for the flibanserin 100 mg q.h.s. dose group and the placebo group. Very few subjects had post-baseline thyroid hormone tests performed. Data for those few subjects showing mean change from baseline to last value on treatment are not displayed.

In this population, an unexpectedly large proportion of subjects had baseline values of SHBG above the normal range, and free testosterone and DHEA-S below the normal range. Those values did not change substantially during the treatment period. There were changes in both directions in prolactin, but no significant increase of prolactin levels.

In addition, Trial 511.70 included evaluation of follicular and lutenizing hormones, prolactin, and anovulatory cycles. These data showed no association between flibanserin and clinically important changes in these parameters.

3.2.3.3.2 Transitions among laboratory parameters of interest

Table 7.2.3: 2 (Appendix 7.2.3) displays the transitions outside the normal reference ranges for the dose of flibanserin 100 mg compared with placebo for each of the laboratory parameters of interest. The majority of changes from baseline outside of the normal reference range for the standard laboratory tests (excluding the hormone laboratory tests) occurred in less than 1% of subjects in the flibanserin 100-mg q.h.s. dose group. For those changes that occurred in ≥1% of subjects, few differed among the treatment groups.

There were no clinically important transitions from baseline to outside the reference range for any hematologic parameters.

Similarly, among chemistry parameters, transitions from baseline to outside the reference range were similar for the flibanserin 100 mg q.h.s. group and for the placebo group. Transitions from normal baseline values in ALT to high by end of treatment occurred for 18 (2.0%) for placebo and for 15 (2.4%), respectively, for flibanserin 100 mg q.h.s, and AST for 13 (1.4%) for placebo and 10 (1.6%) for flibanserin 100 mg q.h.s., respectively. Transitions from high baseline values in ALT returned to normal by end of treatment for 20 (2.2%) for placebo and for 20 (3.2%) for flibanserin 100 mg q.h.s, respectively and AST for 12 (1.3%) for placebo and 12 (1.9%) for flibanserin 100 mg q.h.s., respectively.

Most of the transitions from normal to outside the reference range at last value for hormone data were similar between the treatment groups. Similar proportions of subjects in the placebo group and flibanserin groups transitioned from high baseline values to normal values at the end of treatment.

3.2.3.3.3 Possibly clinically significant laboratory abnormalities

Using the project's predefined ranges (e.g., 2-fold UNL for AST and ALT), possibly clinically significant laboratory changes for the standard laboratory tests (excluding the hormone laboratory tests) in individual subjects were few, the majority occurred in <1% of subjects, and in similar proportions to the placebo group.

The investigators reported none of these possibly clinically significant laboratory changes as adverse events.

Four (0.6%) subjects had clinically significant increases in AST while receiving flibanserin 100 mg q.h.s. compared with 2 (0.2%) subjects receiving placebo, and 2 (0.3%) subjects had

clinically significant increases in ALT while receiving flibanserin 100 mg q.h.s. compared with 2 (0.2%) subjects receiving placebo.

Six (1.0%) subjects had clinically significant increases in glucose while receiving flibanserin 100 mg q.h.s. compared to three (0.3%) subjects receiving placebo.

Clinically significant increases in cholesterol occurred in all treatment groups during the studies; 37 (5.9%) subjects had clinically significant increases in cholesterol while receiving flibanserin 100 mg q.h.s., as did 82 (8.9%) subjects receiving placebo.

Clinically significant decreases and increases occurred for sex hormone binding protein in all treatment groups; 12 (1.9%) subjects had clinically significant decreases while receiving flibanserin 100 mg q.h.s., as did 20 (2.1%) subjects receiving placebo. In addition, 51 (8.2%) subjects had clinically significant increases in sex hormone binding protein while receiving flibanserin 100 mg q.h.s. compared with 59 (6.3%) subjects receiving placebo.

Clinically significant decreases in progesterone occurred in all treatment groups during the studies; 89 (14.5%) subjects had clinically significant decreases in progesterone while receiving flibanserin 100 mg q.h.s. and 153 (16.5%) subjects receiving placebo.

Clinically significant increases in prolactin occurred in all treatment groups during the studies; 21 (3.4%) subjects had clinically significant increases in prolactin while receiving flibanserin 100 mg q.h.s., as did 34 (3.6%) subjects receiving placebo.

Table 7.2.3: 3 (Appendix 7.2.3) displays the frequency of subjects with possibly clinically significant laboratory abnormalities among the laboratory parameters of interest with flibanserin 100 mg q.h.s. in the Phase III HSDD trials.

3.2.4 Other safety data

3.2.4.1 Pelvic examinations and cytological smears

Physical examinations were performed in all Phase II trials (MDD and HSDD) and in all Phase III trials in premenopausal women with HSDD. No abnormalities attributable to study medication were found. Follow-up pelvic examinations and Pap smears were performed in Trial 511.84 and also showed no safety signals.

Table 7.2.4: 1 (Appendix 7.2.4) displays the frequency of subjects with clinically relevant changes from baseline in pelvic examinations and cytological smears. Ninety-eight percent or more subjects had normal results of pelvic examinations at baseline, and over 97% had normal cytological smears at baseline.

Post-baseline results indicate that of those with normal baseline results, over 98% continued to have normal results for pelvic examinations, and over 95% had normal cytological smear results. Of the subjects with abnormal results at baseline, the majority had normal results at their final examination.

Of those subjects with normal baseline results, 16 (0.91%) subjects had clinically relevant changes in bimanual examinations, 22 (1.26%) subjects had clinically relevant changes in cervix examinations, two (0.11%) had clinically relevant changes in clitoris examinations, 15 (0.85%) had clinically relevant changes in vagina examinations, 10 (0.56%) had clinically relevant changes in vulva examinations, and 79 (4.63%) had clinically relevant changes in cytological smear results (Appendix 7.2.4, Table 7.2.4: 1).

In conclusion, the transitions from normal at baseline to abnormal post-baseline pap smear results in subjects treated with flibanserin are within the range of what is expected in this subject population during this time frame [R09-1486].

3.2.4.2 Beck Scale for Suicide Ideation®

The Beck Scale for Suicide Ideation (BSS) was used in the flibanserin development mainly for detection purposes rather than quantization. The BSS Ideation is a validated 21-item instrument (self-reported or administered by a paraprofessional) that clinicians use to detect and measure the severity of suicidal ideation in adults. It measures a broad range of attitudes and behaviors that clinicians routinely consider in assessing suicide risk, and reveals characteristics that require greater clinical scrutiny. Of its 21 items, the first 19 items measure severity of suicidal wishes, attitudes, and plans. The statement gradations range from "0" (no inclination to suicidality) to "2" (moderate to strong inclination to suicidality). The last two items [Groups 20 and 21 (if applicable)] are on background characteristics: the number of previous suicide attempts and the seriousness of intention to die associated with the last attempt.

The first five of 21 items serve as a screen for suicidal ideation (Part I). If a subject chose zero statements for Item 4 and/or Item 5 (indicating no active suicidal intention), then she was instructed to skip the next 14 items and answer Group 20 (the number of previous suicide attempts). If a subject chose non-zero statements for Item 4 and/or Item 5 (indicating suicidal ideation), then she was instructed to complete the next 14 items, in addition to Groups 20 and 21. The BSS was performed in Trials 511.70, 511.71, 511.75, 511.77, and 511.74 at Screening, Baseline, on-treatment, and post-treatment visits. At Screening, Week 24- and Week-28 visits, suicidal ideation was elicited by subject completion of the BSS, which may have resulted in increased reporting of suicidal ideation when compared to spontaneous reporting.

Among the Phase III placebo-controlled trials, 0.4% of subjects receiving flibanserin had a BSS score >0 in Part I on treatment, whereas 0.5% of subjects receiving placebo had a score >0 in Part I on treatment (Table 7.2.4: 2; Appendix 7.2.4).

Seven subjects in the flibanserin group were classified on BSS as having suicidal ideation on-treatment, however, those were screening responses that were carried over into the trial. Five of those subjects did not meet inclusion/exclusion criteria due to indicating non-zero responses at Screening, but were incorrectly entered into the trials. The other two subjects each had recorded positive response at Screening on the BSS Group 20 (previous suicide attempt). Four subjects were randomized to flibanserin even though they had non-zero

responses at Screening; none of those subjects had any further non-zero findings on the BSS during the study.

There were no apparent trends in suicidal ideation in the Phase III placebo-controlled trials. 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.

3.2.4.3 Menses evaluation

Phase III flibanserin trials (511.70, 511.71, 511.75, 511.77, and 511.74). At each visit, menses evaluation assessed changes in the subject's menstrual regularity, flow, duration, and symptomatology. All menstrual bleeding AEs reported at 1% or more, i.e., menorrhagia, metrorrhagia, and polymenorrhea, showed AE rates similar between the flibanserin groups and the placebo group. Discontinuations due to these AEs occurred in only 10 (0.3%) subjects who received flibanserin.

The incidence of menorrhagia was similar between the flibanserin 100 mg q.h.s. and the placebo group (3.6% vs. 3.1%, respectively). The incidence of metrorrhagia was also similar between the flibanserin 100 mg q.h.s. and the placebo group (2.0% vs. 1.5%, respectively), and each flibanserin group had <2% of subjects with AEs of metrorrhagia.

3.2.4.4 Ophthalmologic examinations

Full ophthalmologic examinations were performed in Trial 511.71 at the screening and end of treatment and included the best corrected distance visual acuity, tonometry (intraocular pressure measurement), and with pupils dilated, slit lamp evaluation of the anterior segment, including the cornea and lens. Overall, no flibanserin related side effects occurred, and there was no excess of any type of eye abnormalities with flibanserin compared to placebo.

Follow-up full ophthalmologic examinations were also performed on the subjects who completed Trial 511.71 and entered open-label extension Trial 511.84. Rates of eye abnormalities were about the same as in the parent trial, and worsening of intraocular pressure or visual acuity was balanced by equally small numbers of improvements. No corneal abnormalities were imputed to flibanserin by the expert ophthalmologists consulted by the Sponsor.

3.2.5 Adverse events of interest

The following AEs were of interest in this development program due to findings in earlier studies or at the Division's request: depression, suicide/self-injury, hemorrhage, and hypersexuality. Suicidality is of concern to the Division for all centrally acting agents. Depression was a concern of the Sponsor because depression in general may relate to suicidality. Hemorrhage was a concern of the Sponsor because some other serotonergic agents (peripherally acting 5HT-2A inhibitors) have been tested as antiplatelet agents, and because Phase II results, using higher doses of flibanserin, showed an increased incidence of bleeding AEs with flibanserin, particularly in patients using aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) along with flibanserin, compared to placebo. It is important to note when considering the rates of AEs of interest that more women were

randomized to flibanserin than to placebo by a ratio of 2.5 to 1. To provide the largest possible set of subjects from placebo-controlled trials for all doses studied, analyses by treatment at onset were based on Phase II/III placebo-controlled HSDD trials, which included the 2 additional 3-month studies 511.68 and 511.69.

Depression

In the Phase II/III trials, AEs of depression occurred in 41 (4.2%) subjects receiving flibanserin 100 mg q.h.s. compared to 47 (3.1%) subjects receiving placebo. The rate differences for the preferred term depression were not significantly different between flibanserin 100 mg and placebo.

Bleeding/hemorrhage

In the Phase II/III trials, hemorrhage events in the flibanserin 100 mg q.h.s. group were observed in 65 subjects (6.6%) compared to placebo (81 subjects, 5.4%). Events of genital hemorrhage occurred in 7 (1.0%) subjects in the flibanserin 25 mg b.i.d. group and in similar proportions of subjects in each of the other flibanserin dose groups and placebo. Menorrhagia occurred in 34 (3.5%) subjects receiving flibanserin 100 mg q.h.s. compared with 43 (2.9%) subjects receiving placebo. Metrorrhagia occurred in similar proportions of subjects receiving each of the flibanserin doses and placebo (approximately 1.5%). Not more than one subject experiencing each of these AEs discontinued because of these AEs in the flibanserin 100 mg q.h.s. group. Two bleeding-related SAEs were reported in Trial 511.77: Subject 36770, receiving placebo, had an SAE of hematuria of moderate severity, beginning on Day 40 and resolving on Day 41; the event was considered serious because it prolonged the subject's hospitalization. One SAE of moderate metrorrhagia was reported in Subject 38383 receiving flibanserin 50 mg q.h.s.; the event began on Day 91, required hospitalization, and was resolved on Day 92.

In summary, flibanserin at any dose was not associated with an increased risk of hemorrhage.

Suicide/self-injury

In the Phase II/III trials, suicide/self injury (SMQ) was reported by <1% of subjects in any treatment group. Suicide/self injury was reported in 1 (0.1%) subject in the flibanserin 100 mg q.h.s. dose group as attempted suicide, and in 3 (0.1%) subjects in the flibanserin 50 mg q.h.s. as suicidal ideation compared with 1 (0.1%) subject with suicidal ideation in placebo group. In addition, one subject in Trial 511.74 had an SAE of suicidal ideation.

Based on the data in completed Phase II/III studies, there was no increase of suicidal ideation in HSDD subjects treated with any dose of flibanserin compared to placebo.

Anovulation

Anovulatory cycle (user-defined) was reported by <1% of subjects in any treatment group in the Phase II/III trials. Anovulatory cycle was reported in six (0.1%) subjects receiving flibanserin, one of those subjects was receiving flibanserin 100 mg q.h.s. (bleeding

anovulatory). None of the subjects receiving placebo experienced an AE of anovulatory cycle.

In addition, Trial 511.70 included evaluation of follicular and lutenizing hormones, prolactin, and anovulatory cycles. These data showed no association between flibanserin and clinically important changes in follicular and luteal hormones, for prolactin, or for an increased risk of anovulatory cycles.

Hyperprolactineamia

In the Phase II/III trials, hyperprolactinemia (user-defined AE category) was reported by <1% of subjects in any treatment group. Hyperprolactinemia was reported in 9 (0.9%) subjects receiving flibanserin100-mg q.h.s.: 4 subjects (0.4%) experienced AEs coded as PT of hyperprolactinemia; 4 (0.4%) subjects had coded as PT blood prolactin increased, and one (0.1%) subject had an AE coded as PT of prolactinoma. Four (0.3%) subjects receiving placebo experienced AEs of blood prolactin increased.

All the AEs of hyperprolactinemia in subjects receiving flibanserin100 mg q.h.s were of mild severity with the exception of one subject with blood prolactin increased of moderate severity.

No prolactin values were near or greater 100 ng/dL (upper limit of normal [uLN] = 30 ng/dL), considered to be the threshold for further evaluation of hyperprolactinemia.

Prolactin levels vary over a 24-h period, rising during sleep and peaking in the morning. Prolactin increases during times of physical or emotional stress, and many stimuli can elicit its release, including breast manipulation, drugs, and certain foods. In conclusion, flibanserin at any dose was not associated with increased risk of hyperprolactinemia.

Syncope

User-defined AE category related to syncope (hypotension, syncope, blood pressure decreased, circulatory collapse, dizziness postural, loss of consciousness, and syncope vasovagal) occurred in 7 (0.7%) subjects receiving flibanserin 100 mg q.h.s., and in four (0.3%) subjects receiving placebo in the Phase II/III trials. The differences in the rates of the PT syncope were not significant between the flibanserin 100 mg q.h.s. group and the placebo group.

Hypotension

Hypotension occurred in three (0.3%) subjects randomized to the flibanserin 100-mg dose group and in none of the subjects randomized to the placebo group among the Phase III HSDD placebo-controlled trials. None of the hypotension was reported as an SAE, but one subject treated with flibanserin 100 mg q.h.s. had experienced an SAE of circulatory collapse. Two of the hypotension AEs were mild (one with a duration of 1 day and one with a duration of 40 days) and one was moderate.

Liver function

User-defined AE category related to liver function (increased AST, increased ALT, hepatic enzyme increased, and liver function test abnormal) occurred in 2 (0.2%) subjects receiving flibanserin 100 mg q.h.s., and in one (0.1%) subject receiving placebo in the Phase II/III trials. Two subjects in the 100 mg q.h.s group experienced asymptomatic, transient elevations in liver enzymes: one subject had an AE with PT of increased ALT and AST of moderate severity, and one subject had an AE with PT of increased AST of mild severity.

In conclusion, there was no signal that flibanserin 100 mg q.h.s. could lead to increase of liver function tests and potential liver damage.

Sleep disorders

User-defined AE categories related to sleep disorders occurred in 58 (5.9%) in flibanserin 100 mg q.h.s. group and in 52 (3.4%) subjects in the placebo group in the Phase II/III trials. Insomnia occurred in 4.1% of subjects in the flibanserin 100 mg q.h.s. group and in 2.5% of subjects receiving placebo. Differences for other terms related to sleep disorder occurred in less than 1% of subjects.

Eye disorders

The related to eye disorders by SOC occurred in 11 (1.1%) in flibanserin 100 mg q.h.s. group and in 17 (1.1%) subjects in the placebo group in the Phase II/III trials. Thus, there was no signal that flibanserin 100 mg q.h.s. would lead to increase of eye disorders.

Hypersexuality

None of the subjects receiving flibanserin 100 mg q.h.s. experienced AEs of hypersexuality. Adverse events of hypersexuality have been reported in two subjects (0.1%) with HSDD among the Phase III placebo-controlled trials: one subject taking flibanserin 25 mg b.i.d. in Trial 511.70 (mild severity and duration of 86 days), and one subject receiving flibanserin 50 mg q.h.s. in Trial 511.77 (severe intensity, duration of 29 days - this AE led to discontinuation). The subject in Study 511.77 experienced an episode of high desire coupled with what the investigator described as a state of Persistant Genital Arousal Syndrome which frightened the patient with its intensity. On questioning, the patient disclosed that she had experienced such an effect in the past, prior to participation in the study. One subject receiving placebo experienced an AE of "libido increase" in the Phase III trials. There were no AEs of this type in the Phase II HSDD trials. Data to date do not suggest that flibanserin could lead to hypersexuality.

3.2.6 Safety in special groups

3.2.6.1 Pediatric patients

No children and adolescents up to the age of 18 were included in this clinical development program, and HSDD is a diagnosis to be made in adults only. Therefore, flibanserin should not be used in children or adolescents.

3.2.6.2 Use in pregnancy and lactation

Women of childbearing potential were excluded from participation in this program if no medically reliable method of contraception was used or the serum pregnancy test prior to enrollment was positive. However, about 1% of enrolled women became pregnant despite medically accepted contraception (hormonal contraceptives in about 40% of cases). Study drug was stopped in each case as soon as the pregnancy was discovered, and the case was followed up.

The pregnancy rate (contraceptive failure rate) in these trials lasting 6 to 12 months was about 1% regardless of method and treatment, i.e., whether hormonal or non-hormonal, and whether on flibanserin or placebo.

A total of 61 pregnancies have been reported in Phase II/III HSDD trials (17 in subjects receiving placebo and 44 in subjects receiving flibanserin). Outcome is available for 58 of the 61 cases. Of the 44 pregnancies in subjects known to have been receiving flibanserin, 29 have resulted in live births, five in miscarriages and four in a therapeutic abortion, and one reported a congenital anomaly/malformation (hypospadia). Two subjects had an ectopic pregnancy. Outcome of three pregnancies in subjects receiving flibanserin is unknown; the patients were reported to be lost to follow-up by the investigators. Of the 17 pregnancies in subjects receiving placebo, 12 resulted in live births, and four in therapeutic abortion; one of the pregnancies with a known outcome reported a congenital anomaly/malformation (duodenal atresia). In the general population, about 15-20% of known pregnancies terminate in miscarriages [R09-1412]. Using hCG measurements to detect early subclinical pregnancy losses, the percentage increases to 30%. Thus, based on the data available, there is no evidence that flibanserin increases the risk of a miscarriage. Table 7.2.4: 3 (Appendix 7.2.4) displays pregnancies that occurred on treatment in Phase II/III HSDD trials.

One pregnancy occurred in the Phase I trial 511.111: a subject was exposed to single dose of flibanserin 50 mg at about the 4th week post menstruationem. The pregnancy resulted in a live birth of twins, in one of the two children a congenital anomaly (cleft lip) was diagnosed.

There are no adequate and well controlled studies of flibanserin in pregnant women. No direct indication for a teratogenic potential was present in preclinical studies. The effect of flibanserin on labour and delivery are unknown.

The excretion of flibanserin into human milk has not been examined. However, due to the chemical and pharmacokinetic properties of flibanserin, excretion in the human breast milk must be expected. Data obtained in lactating rats after dosing with radiolabeled flibanserin showed a milk to plasma ratio of 2.2-2.3 for drug-related radioactivity including flibanserin.

Flibanserin should not be initiated during pregnancy and should be discontinued if pregnancy is established. Breast feeding while taking flibanserin is not recommended.

3.2.6.3 Elderly patients

The effects of two weeks of flibanserin treatment on cognitive function, safety, and efficacy was evaluated in depressed elderly patients in Trial 511.28. A total of 70 elderly patients

(≥65 years) with MDD were randomized to receive either placebo, 20, 50, or 100 mg flibanserin b.i.d. for two weeks. Cognitive effects were primarily investigated by Critical Flicker Fusion test. In addition, further cognitive tests, psychiatric rating scales, and safety measures and sparse flibanserin plasma concentrations were investigated.

The cognitive tests revealed mild sedative-type effects, mainly for the 100 mg b.i.d. flibanserin group. These effects were maximal at 2 hours but mostly reversed by 6 hours. Plasma concentrations of flibanserin appeared to increase with flibanserin dose. The tolerability of 100 mg flibanserin b.i.d. also appeared to be less than that of the lower dosages, as suggested by the number of patients with dosage decreases due to AEs and by the prevalence of AEs. AEs were of greater frequency but no greater severity or longer duration than in younger patients. Other safety measures (blood pressure, pulse, weight, physical examinations, 12-lead ECGs, and routine laboratory tests) were unaffected by treatment. There was only one clinically relevant change from baseline (severe macular retinal pigment epithelium with trace drusen [preferred term of retinal deposits] in the left eye) detected during day 14 ophthalmological examination. The investigator felt that the event had a reasonable causality to the study medication and the patient did not receive any therapy for this event. However, this observation is typically seen in an otherwise healthy elderly population. There were no deaths in this trial. There was one SAE in the placebo group and one dropout due to AEs in the 20 mg flibanserin group. Flibanserin plasma concentrations in elderly depressed patients were not obviously different from those observed in healthy subjects.

From the cognitive, safety, and tolerability results of this clinical trial, it appeared that flibanserin doses up to and including 100 mg b.i.d. were safe. The dosages of 50 and 100 mg flibanserin b.i.d. were less well-tolerated in elderly patients than in adults with depression.

3.2.6.4 Renally impaired patients

No patient with renal impairment (defined as having significant renal disease or creatinine clearance lower than 50 mL/minute) was allowed to participate in Phase III flibanserin trials. A Phase I study in patients with impaired renal function (Trial 511.96) showed no increase in flibanserin levels or significant increase in metabolite exposure, so no dose adjustment should be required for renally impaired patients.

3.2.6.5 Hepatically impaired patients

For the Phase III analysis, hepatic impairment was defined as serum ALT or serum AST >3 times upper limit of normal. There were no subjects among the Phase III trials with hepatic impairment. There were six subjects with values that met these criteria at screening. However, on repeat testing, three subjects' values were within the normal range, and 3 subjects had hepatic enzyme values that were <2 times the upper limit of normal (which was the limit allowed for inclusion into the trial).

Results of Trial 511.67 indicated the total exposure to flibanserin was up to 4.5-fold higher in subjects with liver disease as evidenced by a Child-Pugh score greater than five compared to healthy subjects as a result of reduced flibanserin clearance. The Child-Pugh score employs

five clinical measures of liver disease: encephalopathy grade, ascites, serum bilirubin, serum albumin, and prothrombin time. Each measure is scored with 1 to 3, with 3 indicating most severe derangement. Chronic liver disease is classified into Child-Pugh class A to C, with A: 5 to 6 (mild), B: 7 to 9 (moderate), and C: 10 to 15 (severe). Flibanserin is not recommended for use in subjects with chronic liver disease classified by Child-Pugh class A to C.

3.2.6.6 Patients with bleeding disorders (gastrointestinal, dysfunctional uterine, coagulopathy, etc.)

Patients with known bleeding disorders were not exposed to flibanserin. They were excluded from Phase III trials because of the excess of dose-related abnormal bleeding in Phase II. No excess of bleeding AEs was seen in the much larger Phase III trials, in which the maximum flibanserin dose was restricted to 100 mg/day.

3.2.6.7 Basic intrinsic factors: BMI, Age, Race

No differences among the most common AEs appeared attributable to flibanserin regarding the intrinsic factors of BMI, age, or race, although the samples of black and Asian subjects receiving flibanserin were small.

3.2.6.8 Extrinsic factors: Drug-Drug Interaction

The incidence of AEs in association with concomitant medications used by at least 100 women per treatment group in Phase III placebo-controlled trials was formally evaluated; hormonal contraceptives, aspirin or NSAID, and antihistamines met the criterion for this evaluation. As the incidence of tobacco users was close to 100, this treatment group was evaluated in addition.

In aspirin/NSAID users and in tobacco users, no synergy between flibanserin and those substances was seen with respect to the occurrence of overall AEs.

Subjects using antihistamines in both flibanserin 100 mg q.h.s. and in placebo treatment groups experienced more AEs than non-users. The data suggest no synergy between flibanserin and antihistamine use relative to the occurrence of overall AEs; the difference between subjects receiving flibanserin using antihistamines and non-users (18.3%) was smaller than the difference between placebo users and non-users (18.7%). Among individual symptoms, the incidence of fatigue, sedation, dry mouth, dizziness, nausea, and somnolence increased in flibanserin 100 mg q.h.s group by 1.3-6.0% whereas the increases in placebo group were up to 3.0%. Table 7.2.4: 4 (Appendix 7.2.4) displays AEs by antihistamine use in Phase III placebo-controlled HSDD trials.

SSRIs and selective noradrenergic reuptake inhibitors (SNRI) were prohibited in trials, but 28 subjects in the flibanserin 100-mg q.h.s. group and 23 subjects in the placebo group used such agents. Such concomitant use appeared to be associated with higher overall AE rates in both flibanserin and placebo treated patients. The difference between users and non-users (24.0%) in flibanserin group was smaller than the difference between users and non-users (29.8%) in placebo group, but the number of subjects with a given AE was too small to make

firm conclusions. The same was true for triptans, which were used by 36 subjects on flibanserin 100 mg q.h.s. and 43 on placebo.

Alcohol use was not evaluated during the study, but the status of drinker/non-drinker was determined at baseline. Among the 1001 subjects in the flibanserin 100 mg q.h.s. group, 759 (75.8%) were classified at baseline as drinkers (over 99% of whom the alcohol use was clinically assessed by the investigator as without potential interference in trial participation), as were 784/1011 (77.5%) subjects in the placebo group. Drinkers at baseline appeared to have a moderately higher incidence of AEs with flibanserin, including, as expected, AE of the nervous and psychiatric System Organ Classes: for nausea, 13.3% vs. 7.4% for non-users; for dizziness, 13.2% vs. 8.3%; for fatigue, 11.9% vs. 8.3%; for somnolence, 10.1% vs. 7.4%; and for insomnia, 5.8% vs. 2.9%. In conclusion, patients should use alcohol with caution while taking flibanserin.

In Phase III trials in women with HSDD, over 40% of subjects used hormonal contraception (HC). Women receiving flibanserin 100 mg q.h.s. and using HC tended to have higher rates of AEs per 100 subject-years compared to placebo. Moderately higher incidences of most of the common AEs were seen: for dizziness, 14.6% in users vs. 9.9% in non-users, for fatigue, 13.7% vs. 8.8%; for somnolence, 11.0% vs. 8.3%; for nausea, 13.5% vs. 10.6%, and for insomnia, 5.2% vs. 5.0%. Hypotension occurred in three (0.7%) subjects in users vs. none in non-users, syncope in two (0.4%) vs. one (0.2%) and circulatory collapse in 1 (0.2%) vs. none. The event circulatory collapse was reported as an SAE. In the placebo group, one subject each reported an AE syncope (non-user) and circulatory collapse (user).
Table 7.2.4: 5 (Appendix 7.2.4) displays AEs by hormonal contraceptive use in Phase III placebo-controlled HSDD trials.

Although higher rates of AEs were seen with some of the extrinsic factors evaluated, an analysis of the rate of discontinuation due to AE in the Phase III controlled trials of women with HSDD does not support that any of these lead to a relevant increase in intolerability. With 100 mg flibanserin q.h.s., the rate of discontinuation due to AE for the sub-groups was:

- for HC users, 15.7% vs. 13.7% for non-users;
- for ASA/NSAID users, 14.0% vs. 14.9% for non-users;
- for CNS-active drug users (mostly antihistamines), 17.8% vs. 13.6% for non-users, about the same difference as in the placebo group: 9.5% in users vs. 6.0% for non-users; and
- for baseline alcohol users, 15.3% vs. 12.4% in non-users.

None of the individual AEs contributing to these totals was reported more frequently than with a difference of 1% in any user group vs. the respective non-user group.

CYP3A4 inhibition

Results of Phase I trials evaluating the metabolic drug-drug interactions of flibanserin indicate that strong CYP3A4 inhibitors can cause 2.7-4.5 fold increase of flibanserin AUC

and 1.7-1.85 fold increase of C_{max} (see also Section 4). Based on these evaluations, flibanserin is not recommended for subjects taking strong CYP3A4 inhibitors, e.g. ketoconazole (Trials 511.37 and 511.111).

Few HSDD women took weak/moderate CYP3A4 inhibitors (e.g., diflucan or fluconazole) other than HC concomitantly in Phase III trials (N=20 on flibanserin 100 mg q.h.s. vs. N=34 on placebo): a higher rate of dizziness (20% vs. 11.8% in non-users), somnolence (15% vs. 9.3% in non-users), and dry mouth (5% vs. 2.3% in non-users) was seen, but no increase of fatigue, sedation, or nausea. However, the number of subjects with a given AE was too small to make firm conclusions. Table 7.2.4: 6 (Appendix 7.2.4) displays AEs by CYP3A4 inhibitor use in Phase III placebo-controlled HSDD trials.

In summary, although moderately higher incidences of most of the common AEs were seen in users of HC, weak/moderate CYP3A4 inhibitors, and alcohol, flibanserin was still well tolerated in these subgroups. As such, CYP3A4 inhibition is one of the most common interaction well known to physicians who are aware how to deal with it. Thus, the sponsor is of the opinion that though strong CYP 3A4 inhibitors are not recommended to be used concomitantly, weak and moderate CYP3A4 inhibitors can be safely used in combination with flibanserin.

3.2.7 Serious adverse events

SAEs that occurred during or within 30 days of terminating flibanserin treatment are included in this section. Other considerations include potential relationships to relevant factors, e.g., flibanserin dose regimen and concomitant medication use.

The SAEs are displayed for the following on-treatment groups:

- Phase III Trials 511.70, 511.71, 511.75, and 511.77
- Phase III randomized withdrawal Trial 511.74
- Phase III open-label extension Trial 511.84 and 511.118, ongoing
- MDD trials
- Phase I trials

Table 7.2.5: 1 (Appendix 7.2.5) displays the subjects with SAEs among all HSDD trials, both placebo-controlled and ongoing, open-label trials.

3.2.7.1 Placebo-controlled Phase III Trials 511.70, 511.71, 511.75, and 511.77

Serious AEs occurred in <1% of subjects receiving any dose of flibanserin or placebo among the placebo-controlled Phase III studies. A total of 29/3431 (0.8%) subjects receiving flibanserin experienced one or more SAEs compared to 8/1360 (0.6%) subjects receiving placebo. Subjects receiving flibanserin 100 mg q.h.s. had the largest proportion of SAEs (9/978, 0.9%). None of the SAEs that occurred in subjects in the Phase III placebo-controlled HSDD trials was judged to be related to flibanserin by any investigator, nor the Sponsor.

The most frequently reported SAE among flibanserin subjects in the placebo-controlled Phase III HSDD studies was appendicitis (six subjects, 0.1%); appendicitis occurred in one (0.1%) subject receiving flibanserin 25 mg b.i.d., in four (0.2%) subjects receiving flibanserin 50 mg q.h.s., and in one (0.1%) subject receiving flibanserin 50 mg b.i.d. None of the subjects receiving flibanserin 100 mg q.h.s. or placebo experienced appendicitis.

As part of a more thorough evaluation of suicidality and hypotension as potentially related to flibanserin, the two relevant SAEs are described in detail below.

Subject 36657, receiving flibanserin 100 mg q.h.s. in Trial 511.77, attempted suicide on Study Day 35. At screening the subject had not reported any significant medical history, concurrent diseases or concomitant medications, however, after the event she disclosed a history of depression. She had a zero score on the BSS at baseline. The subject was admitted to the hospital on Day 35 having ingested 10-15 tablets of Ritalin (methylphenidate) and 10-15 tablets of Remeron (mirtazapin). Study medication was discontinued due to the event on an unknown date. The subject was treated in the hospital and subsequently transferred to the psychiatric unit. The subject recovered from the event. The event was considered not to be related to study medication by the investigator (Narrative, Subject 36657).

Subject 37779 in Trial 511.77, receiving flibanserin 100 mg q.h.s., suffered circulatory collapse on Day 11, fell and suffered a concussion and was hospitalized. Concurrent AEs were nausea, headache, and pain. The subject was 34 year old and had a medical history of hypotension and orthostatic dysregulation. There was no relevant concomitant therapy in this subject. Neither of the SAEs was considered related to flibanserin treatment by the investigator (Narrative, Subject 37779.

Table 3.2.7.1: 1 provides a summary of SAEs among the Phase III placebo-controlled trials by SOC, PT, and treatment.

Table 3.2.7.1: 1 Frequency [N (%)] of subjects with serious adverse events by treatment at onset, primary system organ class and preferred term − Phase III placebo−controlled HSDD trials

System organ class Preferred Term	Placebo N (%)	FLI 25 mg b.i.d. N (%)	FLI 50 mg q.h.s. N (%)	FLI 50 mg b.i.d. N (%)	FLI 100 mg q.h.s. N (%)
Number of Subjects	1360 (100.0)	733 (100.0)	2072 (100.0)	713 (100.0)	978 (100.0)
Total with SAEs	8 (0.6)	4 (0.5)	13 (0.6)	3 (0.4)	9 (0.9)
Infections and infestations	1 (0.1)	1 (0.1)	5 (0.2)	1 (0.1)	0 (0.0)
Appendicitis	0 (0.0)	1 (0.1)	4 (0.2)	1 (0.1)	0 (0.0)
Erythema infectiosum	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.1)	0 (0.0)	1 (0.0)	1 (0.1)	1 (0.1)
Breast cancer	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer in situ	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Metastases to lymph nodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 3.2.7.1: 1 (continued) Frequency [N (%)] of subjects with serious adverse events by treatment at onset, primary system organ class and preferred term − Phase III placebo−controlled HSDD trials (Page 2 of 3)

System organ class Preferred Term	Placebo N (%)	FLI 25 mg b.i.d. N (%)	FLI 50 mg q.h.s. N (%)	FLI 50 mg b.i.d. N (%)	FLI 100 mg q.h.s. N (%)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Gliosis	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Phlebitis superficial	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Circulatory collapse	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	3 (0.3)
Crohn’s disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Large intestine perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Subileus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Abdominal pain	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	2 (0.1)	0 (0.0)	1 (0.0)	1 (0.1)	0 (0.0)
Biliary colic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cholelithiasis	2 (0.1)	0 (0.0)	1 (0.0)	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	2 (0.2)
Intervertebral disc degeneration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Intervertebral disc protrusion	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	1 (0.1)
Renal and urinary disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 3.2.7.1: 1 (continued) Frequency [N (%)] of subjects with serious adverse events by treatment at onset, primary system organ class and preferred term − Phase III placebo−controlled HSDD trials (Page 3 of 3)

System organ class Preferred Term	Placebo N (%)	FLI 25 mg b.i.d. N (%)	FLI 50 mg q.h.s. N (%)	FLI 50 mg b.i.d. N (%)	FLI 100 mg q.h.s. N (%)
Reproductive system and breast disorders	2 (0.1)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)
Ovarian cyst	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian cyst ruptured	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parovarian cyst	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)	2 (0.2)
Avulsion fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Concussion	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.1)
Femur fracture	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nerve root injury lumbar	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory fume inhalation disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Road traffic accident	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Skin laceration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Abortion induced	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 11.1
The set of trials used as the basis for this display include 511.70, 511.71, 511.75, 511.77
23 patients randomized to the 100 q.h.s. treatment arm discontinued after taking 50 q.h.s. and did not up titrate to the 100 q.h.s. (15 patients in 511.75 and 8 patients in 511.77)
AE displayed by treatment at onset

3.2.7.2 Phase III randomized withdrawal Trial 511.74

There were no differences in the types or frequencies of SAEs reported in the randomized withdrawal Trial 511.74. SAEs occurred in six subjects during the open-label period: One subject each reported the following AEs: pyelonephritis and bacterial sepsis (Subject 11706); malignant melanoma (Subject 11101); suicidal ideation on Day 128 of treatment (Subject 10506; abdominal pain, a ruptured ovarian cyst, and on the same day cholelithiasis (Subject 10905); cholelithiasis (Subject 12612); tibia fracture (Subject 11800). None of the AEs was considered to be related to study treatment.

Two SAEs occurred in two subjects during the double-blind period: (1) an accidental death in a subject in the placebo group (Subject 14104), and (2) hiatus hernia of moderate severity, which required hospitalization, in a subject in the flibanserin 100 mg q.h.s. group (Subject 14914). Neither of those two events was judged by the investigator to be related to the treatment or relevant to the overall safety profile of flibanserin. A total of 14 subjects were reported to have incurred 22 SAEs during Trial 511.74; this total included 1 subject who had an SAE during the screening period, three subjects who experienced SAEs post-treatment, and two subjects reported SAEs post study (one 3 months and one 5 months after completion of the trial).

3.2.7.3 Open-label, extension Trials 511.84 and 511.118

For the two studies cumulatively a total of 30 (1.4%) subjects had SAEs at the various flibanserin doses to which the 2203 subjects were exposed. Among the 1791 subjects receiving flibanserin 100 mg q.h.s. in the Phase III open-label extension trials, 16 (0.9%) experienced one or more SAEs. In the flibanserin 100 mg q.h.s. group, SOCs with the most subjects having SAEs (3, 0.2%) were gastrointestinal disorders, musculoskeletal and connective tissue disorders, and injury, poisoning, and procedural complications.

3.2.7.4 MDD trials

Among the MDD trials, SAEs occurred in fewer than 1% of subjects in the 50 mg b.i.d. and the 100 mg q.h.s. treatment groups, in 1/68 (1.5%) subjects in the flibanserin 50-mg q.h.s. group, 4/247 (1.6%) in the flibanserin 150 mg total daily dose group, and in 2/161 (1.2%) in the flibanserin 100 mg b.i.d. group. No single type of SAE occurred in ≥1% of subjects, with the exception of cerebrovascular disorder, which occurred in 1/68 (1.5%) subjects in the flibanserin 50-mg q.h.s. group. Serious AEs considered related to study treatment occurred in four subjects: Two (Subjects 3510 and 3930) had SAEs of depression, one subject (Subject 3510) had a SAE of somnolence, and one subject (Subject 3852) had a SAE of maculopapular rash.

3.2.7.5 Phase I trials

Four SAEs (1 depressive episode, on flibanserin; one multiple myeloma, off treatment; one right upper quadrant chest pain and one fainting in same subject, on flibanserin) were reported in Phase I trial.

3.2.7.6 Effects on ability to drive or operate machinery or impairment of mental ability

This section summarizes safety data related to any impairment in the senses or coordination or any other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability. This includes relevant adverse effects reported in safety monitoring (e.g., dizziness, somnolence, fatigue, falls, accidents) and specific cognitive function Trials 511.2, 511.3, 511.10 and 511.28. There was some indication in Phase I studies that flibanserin had mild, dose-dependent sedative properties in healthy volunteers from 1-2.5 hours post-dose, as evidenced by declines in alertness and attention (Trials 511.2, 511.3). Similarly, cognitive tests in Phase II studies revealed mild, transient sedative-type effects that were maximal at 2 hours after the 100-mg dose, but mostly reversed 6 hours post-dose (Trials 511.10, 511.28). These sedative effects generally dissipated during the two weeks of flibanserin treatment.

3.2.7.6.1 Accidental injuries

Among the Phase II/III placebo-controlled HSDD trials, 19/978 (1.9%) subjects receiving flibanserin 100 mg q.h.s. experienced accidental injury (user-defined) on treatment compared with 21/1508 (1.4%) receiving placebo. The accidental injuries occurring among subjects receiving flibanserin 100 mg q.h.s. in the Phase II/III HSDD studies were muscle strain (0.4% versus 0.2% of placebo subjects), contusion (0.4% versus 0.2% of placebo subjects), road traffic accident (0.2% versus 0.1% of placebo subjects), and concussion (0.2% versus 0.0% of placebo subjects).

Injuries possibly related to neurologic function include fall (one, 0.1% of flibanserin 100 mg q.h.s. subjects versus one, 0.1% of placebo subjects), road traffic accident (two, 0.2% of flibanserin subjects versus one, 0.1% of placebo subjects), concussion (two, 0.2% of flibanserin subjects versus none of placebo subjects), and head injury (none occurred in either treatment group).

Accidental injuries were assessed in relation to concurrent AEs of dizziness, somnolence and fatigue in an effort to determine if the injuries may have been related to flibanserin. Table 3.2.7.6.1: 1 displays subjects with accidental injuries for placebo and flibanserin 100 mg qhs occurring concomitantly (within three days) with selected AEs of sedation, somnolence, fatigue, and dizziness. In patients with accidental injuries sedative type of AEs occurred with similar frequency in flibanserin 100 mg and placebo treatment arms.

Table 3.2.7.6.1: 1 Subjects with accidental injuries occurring concomitantly (within 3 days) with selected adverse events in Phase III trials

Subject ID	Study	Treatment at Onset	AE	AE Start/ Stop Days	AE Severity	Serious
17499	511.70	Placebo	Dizziness	2/48	Severe	No
			Bursa injury	47/57	Moderate	No
			Fall	47/47	Moderate	No
19433	511.70	Placebo	Drowsiness	2/74	Mild	No
			Joint ligament rupture	46/217	Moderate	No
20734	511.70	Placebo	Somnolence	17/41	Moderate	No
			Abrasions	35/50	Mild	No
25935	511.71	Flib 100 q.h.s.	Somnolence	1/173	Mild	No
			Bruising	113/141	Mild	No
			Motor vehicle accident	113/141	Mild	No
26707	511.71	Flib 100 mg q.h.s.	Fatigue	1/171	Severe	No
			Pulled muscle	68/83	Moderate	No
31735	511.75	Flib 50 mg q.h.s.	Fatigue	1/47	Mild	No
		Flib 100 mg q.h.s.	Contusion	24/32	Mild	No

Trials 511.70, .71, .75, and .77

3.2.7.6.2 Road traffic accidents

Among all HSDD trials, 13 road traffic accidents occurred (Table 3.2.7.6.2: 1). There were 9 (0.3%) road traffic accidents with flibanserin (any dose), and one (0.1%) with placebo in the Phase III placebo-controlled trials. In addition, two subjects treated with flibanserin reported road traffic accidents in the ongoing, OL trials as of the data cut-off for NDA (13 Feb 2009). One subject reported to be involved in a road traffic accident in the OL Trial 511.118 after the cut-off date for the NDA submission, but reported in the 4-month safety update report. Four of the subjects were not driving at the time of the accidents. In the Phase III placebo-controlled trials using the flibanserin dose 100 mg q.h.s., two (0.2%) subjects receiving flibanserin 100 mg q.h.s. experienced road traffic accidents and none of the placebo subjects had AEs of road accident.

Table 3.2.7.6.2: 1 Subjects in road traffic accidents - All HSDD trials

Total Number of Subjects in Road Traffic Accidents (13)

	Phase III placebo-controlled					Open label		
	Placebo (1)	Flibanserin (9)				Flibanserin (3)		
Dose	Placebo	25 mg bid	50 mg qhs	50 mg bid	100 mg qhs	25 mg bid	50 mg qhs	100 mg qhs
Total Treated	1360	733	969	728	1001	57	2197	1791
Total Accidents	1 (0.1)	3 (0.4)	3 (0.3)	1 (0.1)	2 (0.2)	1 (0.05)	1 (0.05)	1 (0.06)
Passenger (4)								
AE	0	2 (0.3)	1 (0.1)	1 (0.1)	0	0	0	0
SAE	0	0	0	0	0	0	0	0
Driver (9)								
AE	1 (0.1)	0	1 (0.1)	0	1 (0.1)	1 (0.05)	0	1 (0.06)
SAE	0	1 (0.1)	1 (0.1)	0	1 (0.1)	0	1 (0.05)	0

Four of the road traffic accidents were reported as SAEs:

Two subjects in Trial 511.75 were involved in such accidents: one was receiving flibanserin 25 mg b.i.d. and suffered an avulsion fracture due to a road accident. She was driving, but was not considered at fault. The subject had no sedative type AEs at the time of the accident. The investigator and the Sponsor considered the SAE of road accident to be unrelated to flibanserin treatment. Another subject was receiving flibanserin 100 mg q.h.s. when she suffered an SAE of concussion as a result of an SAE of road accident (rollover). The subject had been off-road driving an all-terrain vehicle and was not wearing a helmet at the time of the accident. She also experienced SAEs of nerve root injury and skin laceration due to the accident. The subject had no sedative type AEs at the time of the accident.

One subject in Trial 511.77, receiving flibanserin 50 mg, suffered an SAE of thoracic vertebral fracture as a result of an SAE of road traffic accident. She told the investigator that she was not responsible for the accident. The driver of the car just behind her did not stop in time and was the only guilty party. The subject had no sedative type AEs at the time of the accident.

One subject in Trial 511.118, receiving flibanserin 50 mg q.h.s., experienced SAEs of motorcycle accident and a fractured femur that required hospitalization. The subject lost control of her motorcycle, collided with two other motorbikes, and the reason is unknown. Based on re-check of the source documentation the investigator confirmed that the subject did not suffer from any sedative type AEs and had no concomitant diagnosis and concomitant therapy at the time of the accident. The investigator and the Sponsor did not see any causal relationship between the accident and study medication.

Nonserious AEs of road traffic accidents were reported in 8 subjects receiving flibanserin:

One subject, in Trial 511.84, receiving flibanserin 100 mg q.h.s. was driving the vehicle involved in the accident, but was not at fault. The AE was not considered by the investigator or the Sponsor to be related to flibanserin treatment. The subject had no AEs related to sedative effects at the time of the accident. Three other subjects, receiving flibanserin 25 mg b.i.d., flibanserin 25 mg b.i.d., and flibanserin 50 mg b.i.d., respectively in Trial 511.70 were passengers in motor vehicle accident AEs. Two subjects receiving flibanserin 50 mg q.h.s. and 100 mg q.h.s. in Trial 511.71 were involved in motor vehicle accidents: One was driving in rainy weather when she was hit from behind; the other one was driving when her vehicle was hit by another vehicle on the passenger side; the subject reported AEs somnolence at the time of the accident. One subject in Trial 511.77 receiving flibanserin 50 mg q.h.s. was involved in a road traffic accident, and suffered a painful left knee; the subject was not driving, but was a passenger in the vehicle. In trial 511.118, one subject receiving flibanserin 25 mg b.i.d. was involved in a road traffic accident. The AE was non-serious and of mild severity. No therapy was administered and the AE was considered by the investigator to be not related to treatment. The driving information on this subject is currently not determined.

The information described in this section does not suggest a relationship between flibanserin and accidental injuries.

3.2.8 Overdosage, drug abuse and dependence, withdrawal

3.2.8.1 Overdose

No human overdoses of flibanserin have been reported except for one non-serious AE in a woman with HSDD (Patient 16711 in extension Trial 511.84) who erroneously took two 100 mg tablets at night for 14 consecutive days after up-titration from 50 mg q.h.s.; the only symptom reported was moderate headache. Thus, the risk associated with an overdose of any flibanserin dose larger than 200 mg can only be extrapolated, comparing preclinical toxicology to human dose related AE data.

In the first single rising-dose Phase I tolerability trial (511.009) , after administering 150 mg flibanserin (the highest dose tested in humans) to healthy volunteers, several AEs were observed per subject . The reported AEs were somnolence, fatigue, pallor, slurred speech, and nausea. None of the AEs was serious, and all were transient.

Ingestion of flibanserin at doses over 100 mg may lead to a significantly increased risk of CNS side effects, such as sedation, somnolence, dizziness, nausea, and vomiting. In the event of co-occurrence of somnolence and vomiting, risk of aspiration might exist. Side effects to flibanserin generally develop gradually, so if an overdosed patient is observed and the nature of the ingestion discovered, the gradual onset should allow medical intervention before symptoms progress too far. Prevention of absorption of the compound before 2 hours post ingestion should be attempted by irrigation of the stomach.

Flibanserin has never been used in children. Therefore, the maximum non-toxic dose in children cannot be specified. The effects of the drug might be exaggerated in children. As in adults, irrigation of the stomach should be attempted earlier than 2 hours post intake to prevent absorption of the compound. Flibanserin, like all other drugs, should be kept out of the reach of children.

3.2.8.2 Drug abuse and dependence

Evaluation of abuse potential in flibanserin Phase I, II, and III clinical trials incorporated all currently favored ways to predict abuse liability in routine parallel clinical trials: detailed prospective self-rating of subjective effects; clinician interview-based evaluations of mood effects; prospective evaluation of withdrawal effects after chronic dosing; systematic collection of AE reports for stimulant, mood elevation, sedation, and psychotomimetic events (psychotic events, paranoia, abnormal dreams, etc.); supratherapeutic dosing; and extensive use of psychiatric patients (those with MDD), who have greater vulnerability to abuse liability.

Since no signal of any dependence potential was observed in the animal studies and in available AE data, no human trials to investigate flibanserin abuse have been performed. However, use of >120% of prescribed study medication was pre-specified as overuse in every study. Less than 1% of subjects over-used flibanserin, which was less than or equal to the proportion over-using placebo.

No evidence of drug dependence or abuse with flibanserin has been detected.

3.2.8.3 Withdrawal effects

Phase III Trial 511.74 (randomized, double-blind withdrawal onto placebo or continuation of flibanserin after exposure to the active drug for 24 weeks) also showed no association of flibanserin with withdrawal events. In the whole 24-week-long double-blind withdrawal period, in the first 30 days of that double-blind period, and also independently in the 4-week non-treatment period at the end of treatment at Week 48, the overall incidence of AEs was similar between placebo- and flibanserin-treated patients. Table 3.2.8.3: 1 shows this result for the first 30 days after randomization to placebo compared to continuing flibanserin treatment. In the post-treatment period (Weeks 49-52), no AEs were reported by 2% or more of patients after either treatment. In summary, there was no evidence of withdrawal AEs after abrupt discontinuation of flibanserin after 24 or 48 weeks of use at 50 or 100 mg flibanserin per day.

Table 3.2.8.3: 1 Adverse events reported in randomized withdrawal Trial 511.74 by at least 2% of patients in the placebo group during the first 30 days of the double-blind period

Preferred term	Placebo	Flibanserin
Total treated	170 (100.0)	163 (100.0)
Total with any AE	52 (30.6)	53 (32.5)
Nasopharyngitis	5 (2.9)	7 (4.3)
Nausea	5 (2.9)	2 (1.2)
Headache	5 (2.9)	5 (3.1)
Dizziness	3 (1.8)	1 (0.6)
Irritability	4 (2.4)	1 (0.6)

Sorted by most common to least common in the placebo group

3.2.8.4 Discussion

The AEs reported most frequently, and in higher proportions of subjects with 100 mg flibanserin q.h.s compared to placebo, were dizziness, nausea, fatigue, and somnolence, at approximately 10-12% each, and insomnia, at about 5%. The less frequent AEs that the Sponsor considered drug-related were dry mouth, anxiety, sedation, and constipation, at about 2% each, and sleep disorder, and palpitations, at about 1% each, and hypotension at about 0.4%. The occurrence of the most frequent AEs decreased with the continuation of flibanserin treatment. Most AEs were generally of mild to moderate severity (Table 7.2.2: 3, Appendix 7.2.2), and extremely few were reported as related SAEs (two related SAEs in one women with HSDD).

No observation was made that would raise concern over the use of flibanserin in premenopausal women with HSDD in regard to suicide, depression, abuse potential, hypersexuality, ophthalmologic safety, hormonal changes including indices of fecundity, or pregnancy outcome (observations were limited to women whose treatment was stopped promptly upon discovery of pregnancy). Too few pregnancies were reported, however, to provide clinical guidance.

To further explore the safety and efficacy of flibanserin including postmenopausal women with HSDD, the following five Phase III clinical trials have been initiated after the NDA submission (October 2009); two of those are Phase IIIb trials, two are Phase III primary efficacy trials in a new population, and one is an OL extension trial:

- Trial 511.147: A 24-week, randomized, double-blind, placebo-controlled, safety and efficacy trial of flibanserin (100 milligrams) administered orally once daily in premenopausal women with HSDD in the United States.

- Trial 511.114: A 12-week, randomized, double-blind, placebo-controlled, Phase III safety trial of flibanserin tablets (100 milligrams daily) in women taking a Selective

Serotonin or Serotonin-Norepinephrine Reuptake Inhibitor with decreased sexual desire and distress.

- Trial 511.130: A 24-week, randomized, double-blind, placebo-controlled, safety and efficacy trial of flibanserin (100 milligrams) administered orally once daily in naturally *postmenopausal women* with HSDD in the United States.

- Trial 511.156: A 24-week, randomized, double-blind, placebo-controlled, safety and efficacy trial of flibanserin, with up-titration, 100 milligrams administered orally once daily in naturally *postmenopausal women* with HSDD in North America.

- Trial 511.133: A 28- week, open-label, safety, extension trial of flibanserin 100 milligrams daily in premenopausal and naturally postmenopausal women with HSDD in North America.

No new safety information has emerged from these trials to alter the safety statements in this briefing document.

4. CLINICAL PHARMACOLOGY

The pharmacokinetics of flibanserin were characterized in healthy subjects (men and women) and women with HSDD. Factors, such as age, gender, race, weight, hight, and smoking status, potential drug-drug interactions, and the effect of meals were investigated. The pharmacodynamics of flibanserin with respect to cognitive effects and ECG changes were characterized in healthy subjects and patients with depression.

The results of dedicated Phase I trials evaluating factors potentially affecting drug exposure are summarized in Table 4.2: 1.

4.1 BASIC PHARMACOKINETICS

At chronic oral treatment, flibanserin plasma concentrations rise rapidly, usually within the first hour and decrease biexponentially thereafter ($C_{max,ss}$: 469 ng/mL; t_{max}: 45 to 60 min; $AUC_{\tau,ss}$: 2080 ng·h/mL for 100 mg once daily dose) [U07-1871]. Ninety percent of the dose is absorbed, primarily from the upper intestine, and 33% of flibanserin is available systemically due to first-pass metabolism [U99-1776].

The basic pharmacokinetic properties of flibanserin demonstrate adequate exposure to flibanserin also for once daily administration due to its terminal half-life of approx. 10 h. Flibanserin shows moderate accumulation (accumulation ratio for AUC 1.44 after once daily 100 mg dosing), steady-state is established within three days, and plasma levels do not change afterwards as observed during two weeks of chronic dosing [U07-1871, U97-2256]. Therefore, flibanserin exposure is not likely to increase over a longer time without the possiblility to control for it by dosing. For all doses tested in Phase III, flibanserin exposure is proportional to dose [U07-1871]. As expected for a centrally acting drug, the flibanserin volume of distribution (183 L) and plasma protein binding (98% to albumin) were high. Penetration of flibanserin and related material into blood cells was low [U99-1776].

Flibanserin is nearly completely metabolized with at least 35 metabolites formed in humans; three metabolites showed some affinity to serotonergic receptors. However, based on the receptor binding affinity of flibanserin and its metabolites, human plasma exposure, and brain penetration in rat, flibanserin is the central nervous system active substance at therapeutic doses [U09-1907-01]. Flibanserin metabolites are primarily excreted in urine (44.1%) and feces (50.9%) [U99-1776].

4.2 EFFECT OF IMPAIRED LIVER AND KIDNEY FUNCTION

Consistent with the fact that flibanserin is extensively metabolized, hepatic impairment had a pronounced impact on flibanserin exposure but renal impairment did not (see Table 4.2: 1). Therefore, it is not recommended that flibanserin be administered to patients with impaired liver function as defined by a Child-Pugh score greater than five. No dose adjustment is proposed for renal impairment.

Table 4.2: 1 Factors investigated in dedicated Phase I trials potentially influencing flibanserin exposure or to be affected by flibanserin

Factor investigated in a dedicated study (Sample size)	Flibanserin dose	Reference treatment	Test treatment(s)	AUC geometric mean ratio test:reference (90% CI) [%]	C_{max} geometric mean ratio test:reference (90% CI) [%]
Food (N=24)	50 mg single dose	Fasted	Light meal Normal meal High fat/ caloric meal	118 (107-130) 143 (130-158) 156 (142-172)	99 (81-120) 112 (92-137) 115 (94-140)
Hepatic impairment (N=28)	50 mg single dose	Healthy subjects matched by age, sex, weight	Child-Pugh A (N=10) Child Pugh B (N=4)	452.9 (344.8-595.0) 261.2 (115.9-588.8)	90.6 (62.9-130.5) 36.2 (13.6-96.4)
Renal impairment (N=32)	50 mg single dose	Healthy subjects matched by age, sex, weight	Mild to moderate (GFR 30-80 mL/min, N=7) Severe (GFR < 30 mL/min, N=9)	108.7 (74.5-158.6) 120.3 (94.4-153.3)	92.7 (69.1-124.2) 131.2 (91.4-188.2)
CYP3A4 inhibitiors (N=24)	50 mg single dose	Flibanserin alone	Flibanserin with ketoconazole 400 mg once daily	450.3 (379.1-510.6)	184.5 (165.0-206.2)
CYP3A4 inhibitiors (N=12)	50 mg single dose	Flibanserin alone	Flibanserin with itraconazole 200 mg once daily	257 (214.6-306.4)	169 (141.5-202.3)
CYP3A4 inducers (N=24)	100 mg single dose	Flibanserin alone	Flibanserin after rifampicin 600 mg qd (evening dose) pre-treatment	4.5 (3.8-5.4)	9.7 (7.9-12.0)
CYP2D6 inhibitors (N=17)	50 mg twice daily	Flibanserin alone	Flibanserin with paroxetine 40 mg qd	95.8 (88.8-103.3)	102.5 (90.5-115.9)
CYP3A4 inhibition by flibanserin (N=12)	50 mg twice daily	Simvastatin 40 mg single dose alone	Simvastatin 40 mg single dose with flibanserin	Simvastatin: 132 (108-161) Simvastatin acid: 147 (110-197)	Simvastatin: 115 (95.0-139) Simvastatin acid: 137 (117-159)
CYP2B6 inhibition by flibanserin (N=28)	100 mg single dose	Bupropion 150 mg twice daily alone	Bupropion 150 mg twice daily with flibanserin	Bupropion: 102.7 (97.2.108.5) Hydroxybupropion: 92.4 (83.3-102.4)	Bupropion: 102.5 (94.1-111.6) Hydroxybupropion: 90.6 (81.7-100.5)
Oral contraceptives (N=24)	100 mg once daily at bedtime for 2 weeks	Ethinylestradiol 30 µg / levonorgestrel 150 µg single dose alone	Ethinylestradiol 30 µg/ levonorgestrel 150 µg single dose after pre-treatment with flibanserin	Ethinylestradiol: 109.0 (101.2-117.5) Levonorgestrel: 99.9 (94.1-106.2)	Ethinylestradiol: 106.3 (98.8-114.3) Levonorgestrel: 98.3 (92.7-104.3)

4.3 DRUG-DRUG AND DRUG-FOOD INTERACTIONS

With respect to metabolic drug drug interactions, flibanserin exposure can be affected by alterations in cytochrome P450 (CYP) 3A4 activity, which is the major, albeit not the only isoform involved in the metabolism of flibanserin. With the strong CYP3A4 inhibitors ketoconazole and itraconazole, flibanserin total and maximum exposure, AUC and C_{max}, were increased by 2.57-4.50-fold and 1.69-1.85-fold, respectively (see Table 4.2: 1). Based on these data and the observed steady-state exposure at 100 mg q.d. in HSDD patients, a flibanserin AUC in the range of approx. 5400-9400 ng·h/mL and C_{max} in the range of approx. 800-870 ng/mL can be expected when flibanserin is taken concomitantly with strong CYP3A4 inhibitors. Although this expected exposure is close to the daily exposure observed at the highest dose in the multiple rising dose Trial 511.2 (see Table 4.4: 1), which was still considered safe (see Section 3.2.2.1.5), taking flibanserin together with strong CYP3A4 inhibitors is not recommended.

In an interaction trial with the strong inducer CYP3A4 rifampicin, significantly lower flibanserin exposure was seen (Table 4.2: 1). As this could affect flibanserin efficacy, the concomitant use of flibanserin with strong CYP3A4 inducers is not recommended. Flibanserin exposure was not altered by impaired CYP2D6 function by paroxetine, as CYP2D6 plays only a minor role in flibanserin metabolism (see Table 4.2: 1). No clinically relevant effect of flibanserin was observed on the pharmacokinetics of the CYP3A4 substrate simvastatin, the CYP2B6 substrate bupropion, or a combination of levonorgestrel and ethinyl estradiol (see Table 4.2: 1).

Flibanserin can be given with or without food. Food increased flibanserin systemic exposure by up to 1.56-fold (with a high-fat and high-caloric meal containing 64 gram fat and 1184 Kcal), but had only a minimal effect on the maximum plasma concentrations and thereby on the typical flibanserin side effects.

4.4 MAXIMUM TESTED HUMAN EXPOSURE

The flibanserin maximal and total exposure in HSDD patients at the proposed therapeutic dose of 100 mg given once daily is compared to the exposure at higher doses tested in Phase I in Table 4.4: 1. The highest daily exposure was seen in the multiple rising dose study 511.2 at a chronic dose of 100 mg t.i.d., where the geometric mean $C_{max,ss}$ was 1.5-fold higher and the estimated daily exposure was 4.5-fold higher than the observed exposure in HSDD patients at a dose of 100 mg q.d.

Table 4.4: 1 Geometric mean and range or geometric coefficient of variation (gCV) of flibanserin exposure observed at doses higher than 100 mg qd in Phase I trials

Study No	511.1	511.9	511.2	511.90	511.105
Study type	Single rising dose	Single rising dose	Multiple rising dose	QT Study	PK in target population
Study population	6 healthy volunteers	6 healthy volunteers	12 healthy volunteers	53 healthy volunteers	29 HSDD patients
Dosing	Single dose	Single dose	Steady state	Steady state	Steady state
Dose	150 mg	150 mg	100 mg t.i.d.	100 mg t.i.d.	100 mg q.d.
Cmax [ng/mL]	510 (379 - 688)	424 (246 - 731)	729 (469 - 1134)	565 (gCV 41.6%)	469 (gCV 42.7%)
AUC[1] [ng·h/mL]	2309 (1429 - 3730)	2071 (1361 - 3173)	3148 (2055 - 4825)	2670(gCV 49.1%)	2080 (gCV 46.6%)
Estimated mean daily AUC_{ss} [ng·h/mL]			9444	8010	2080

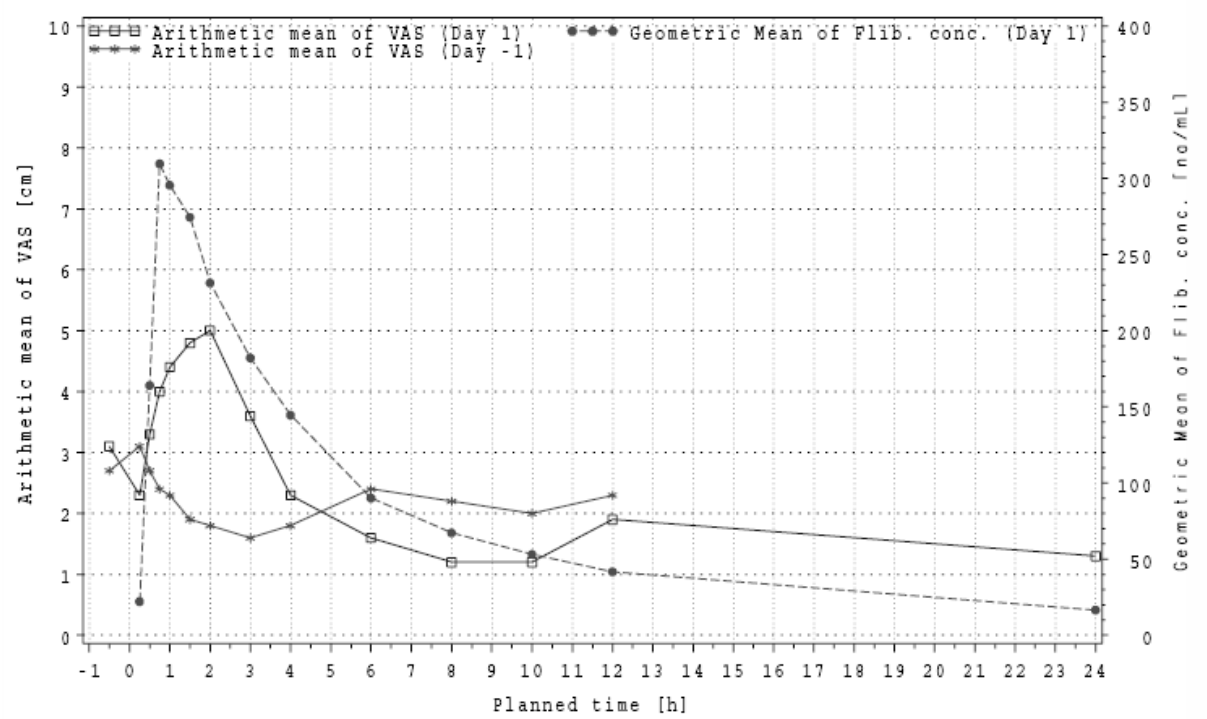
[1] AUC_{0-24} after single dose; AUC over the dosing interval ($AUC_{\tau,ss}$) at steady state

4.5 PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIP

No clinically relevant increases in the individually heart rate corrected QT interval were observed for flibanserin when compared with placebo up to the maximum tested dose of 100 mg t.i.d. These findings were supported by the evaluation of centrally-read ECGs in the Phase III trials, where no clinically relevant findings were observed.

Trials in healthy volunteers and young and elderly (>65 years) depressed patients utilized cognitive testing and self-scored visual analog scales to study the sedating or vigilance-enhancing properties of the compound. Overall, these trials provide supportive evidence for flibanserin having dose-dependent but mild sedative properties (decline in alertness and attention). After an initial daytime dose of 50 or 100 mg in both the young and the elderly, small but statistically significant declines in alertness and attention occurred after 1-2.5 hours but not at the next testing point, 3.5 hours post dose in healthy subjects or 6 hours in depressed patients, whether younger or older. Suggestive evidence of improved alertness or cognitive function 6 hours or later after an initial dose was seen in two trials. Testing for cognitive effects after b.i.d. dosing with flibanserin for 7 or 14 days showed an absence of effects.

The sedative adverse effects are closely related to max. flibanserin plasma concentrations being most prominent 1-4 hours after dosing (see Figure 4.5: 1 below). This supports bedtime dosing.



Solid lines: Mean VAS "drowsiness at baseline day (*) and under flibanserin treatment (□)
Dashed line: Geometric mean flibanserin plasma concentration (•)

Figure 4.5: 1 Arithmetic means OF VAS "drowsiness" and geometric means of flibanserin plasma concentrations after treatment with a single 100 mg flibanserin film-coated tablet versus time after dose (Study 511.110, U07-1821)

4.6 ADVERSE EVENTS WITH DAILY DOSES HIGHER THAN 100 MG

4.6.1 Phase I trials

In the Phase I trials, the most common AEs were fatigue (31.0% vs. 6.2% for placebo), dizziness (26.0% vs. 4.3% for placebo), headache (22.5% vs. 7.4% for placebo), somnolence (22.4% vs. 1.8% for placebo), and nausea (17.6% vs. 4.3% for placebo). It should be emphasized that those subjects took medication primarily in the morning and that doses up to 100 mg t.i.d. were used, leading to numerically higher AE rates compared to the rates being seen with flibanserin 100 mg q.h.s. in the Phase III HSDD trials. However, qualitatively the AEs were the same. In addition, this display combines different trial designs, pooling the AEs occurring in open-label Phase I trials with those in double-blind placebo-controlled Phase I trials which overestimate the frequency of AEs in total flibanserin vs. placebo.

For the flibanserin maximal and total exposure in HSDD patients at the proposed therapeutic dose of 100 mg q.d. compared to the exposure at higher doses tested in Phase I please refer to Section 4.4 of this briefing document.

Clinical tolerability of flibanserin after single oral doses was evaluated in two studies in healthy male subjects, Trials 511.1 and 511.9.

In the first trial, 511.1, flibanserin was reasonably well-tolerated over the entire dose range investigated up to 150 mg q.d. At the 150 mg q.d. dose of flibanserin where flibanserin maximum plasma concentrations (C_{max}) of 510 ng/mL were measured, all reported adverse events were mild to moderate in severity, transient and all subjects completed the trial without any need for drug therapy.

In the second trial, 511.9, all of the six subjects exposed to flibanserin 150 mg q.d. reported transient fatigue; five of them also experienced somnolence. Nausea and pallor were reported by 3/6 subjects, and 3/6 subjects experienced transient slurred speech. One subject each reported restlessness, hot flushes, dysphagia, lack of concentration, and weakness. The vital parameters, e.g., systolic and diastolic blood pressure, pulse and respiratory rate in the supine position as well as body temperature were not affected by the trial medication. Two subjects could not perform postural manoeuvres due to nausea, somnolence and decrease of blood pressure. Another subject experienced a 20 mmHg drop in systolic blood pressure and could not perform the postural manoeuvre due to asthenia. None of these events were reported by the two subjects used as placebo control.

The mean flibanserin C_{max} in this trial was 424 ng/mL. None of the AEs was classified as being serious and none of the subjects required therapy. In summary, a single oral dose of 150 mg flibanserin was still tolerated; however, the study did not proceed to higher flibanserin doses because of the number of AEs, as well as their severity.

Adverse events experienced with a single dose of flibanserin 150 mg q.d. were more pronounced in Trial 511.9 than in Trial 511.1. Retrospectively, it was found that the subjects in Trial 511.1 started with a low dose and were then exposed to higher doses in this single-dose rising-dose safety/tolerability study, whereas the subjects in Trial 511.9 were first exposed to the 150 mg dose without any prior exposure to flibanserin. Tolerance to flibanserin upon repeated exposure was suggested as a possible explanation for the discrepancy.

In Trial 511.2, the clinical tolerability of increasing doses flibanserin was evaluated in healthy male and female subjects. Flibanserin was considered safe after multiple oral dosages up to 100 mg t.i.d. for 14 days. Dose dependent increase of adverse events was observed, mainly for fatigue and dizziness. At the 100 mg t.i.d. dose of flibanserin, where the mean flibanserin $C_{max,ss}$ was 729 ng/mL, the most frequent AEs were fatigue (8/13 subjects), dizziness and/or headache (7/13), polyuria (7/13), nausea (3/13) insomnia (3/13), and myasthenia, chest pain, constipation, and/or hiccups, 2/13 (none of these last six types of AE was reported with placebo, N=20). Most of the AEs were mild or moderate in severity. A total of three events with flibanserin 100 mg t.i.d. was classified as severe (somnolence, fatigue, and tremor). No clinically relevant changes were observed in vital signs, ECG, EEG or laboratory safety parameters during the trial, as well as when pre-and post-study examinations were compared. Under steady state conditions sedative adverse events tended to show a development of tolerance. No AE of hypotension, orthostasis, or syncope were reported.

In the thorough QT Trial 511.90, flibanserin 100 mg t.i.d. was administered orally for 5 days to 56 healthy female and male subjects. Flibanserin given over four days was mainly well to satisfactorily tolerated at this high dose where a mean $C_{max,ss}$ of 565ng/mL was determined. Among the 56 subjects, fatigue (19, 33.9% vs. 11.1% for placebo), dizziness (15, 26.8% vs. 5.6% for placebo), nausea (14, 25.0% vs. 3.7% for placebo), headache (13, 23.2% vs. 13.0% for placebo), somnolence (3, 5.4% vs. none for placebo), stomach discomfort, and palpitations (3 each, 5.4% vs. none for placebo) were the most prevalent AEs. The AEs were mainly mild or moderate in severity. Syncope was reported by one subject; no cases of hypotension or orthostasis were reported with flibanserin 100 mg t.i.d. At the end of the trial all subjects with AEs recovered without sequelae. No clinically relevant changes in ECG parameters, laboratory values or vital signs were observed.

No serious adverse event occurred during the Phase I trials. Tables 7.2.6: 1 and 7.2.6: 2 (Appendix 7.2.6) display AEs occurring in the Phase I single and multiple dose trials.

4.6.2 Phase II trials in Major Depressive Disorder

Within the subset of female subjects in MDD trials, the mean exposure was 38.4 days (range: 1 to 85 days), and the total exposure was 73.8 subject-years. Exposure to more than 100 mg/day (in Phase II) was also substantial: 434 patients were exposed to 200 mg/day (as 100 mg b.i.d.) for a total of 63 exposure years, and 251 patients were exposed to 150 mg per day for a total of 46.8 exposure years. The mean exposure to flibanserin 150 mg/day was 68.1 days (approximately 9 weeks), and the mean exposure to flibanserin 200 mg/day was 53.0 days (approximately 7 weeks).

Pooled data from 9 placebo-controlled Phase II trials (511.10, 511.11, 511.12, 511.18, 511.28, 511.41, 511.42, 511.43, and 511.49) in male and female patients with MDD showed that 84.8% of subjects receiving higher total daily dosage than flibanserin 100 mg (211 subjects used >100 mg q.d.) reported AEs compared to 72.4% of subjects receiving placebo. Somnolence, fatigue, headache, dizziness, dry mouth, and nausea were the most prevalent events, each reported in 9.5% to 39.8% of the subjects in the flibanserin group. One AE of hypotension (0.9%), but no AE of orthostasis, orthostatic hypotension, or syncope were reported with flibanserin 100 mg b.i.d. No such AE were reported for the three patients given 150 mg q.d. Table 7.2.6: 3 (Appendix 7.2.6) displays AEs occuring with frequency >=1% in Phase II placebo-controlled MDD trials.

The open-label extension trials were included in an overall AE analysis of the MDD trials. In those exposed to more than 100 mg per day, i.e., 150-200 mg/day, one AE of hypotension (1/274, 0.4%), and no AE of orthostasis, or syncope were reported. SAEs occurred in 4/247 (1.6%) subjects in the flibanserin 150 mg total daily dosage group, and in 2/161 (1.2%) in the flibanserin 100 mg b.i.d. group.

4.6.3 Phase II trials in HSDD

In the Phase II trials in 297 women with HSDD, somnolence (19.4% vs. 2.8% for placebo), dizziness (12.5% vs. 2.6% for placebo), sedation (12.5% vs. 0.4% for placebo), and nausea (11.1% vs. 4.7% for placebo) were the most common AEs reported by patients exposed to

flibanserin 100 mg b.i.d. No serious adverse event occurred during the course of the Phase II trials in women with HSDD. No cases of hypotension, orthostasis or syncope were reported with flibanserin 100 mg b.i.d. Table 7.2.6: 4 (Appendix 7.2.6) displays AEs occuring in >=1% and twice that of placebo in Phase II placebo-controlled HSDD trials.

Conclusion:

In summary, flibanserin is tolerated up to a single dose of 150 mg q.d. and a repeated dose of 100 mg t.i.d. Common AEs occurred dose dependently and with higher frequency and severity in subjects exposed to doses higher than 100 mg q.h.s. Under steady state conditions sedative adverse events tended to show a development of tolerance. In rare cases subjects being exposed to a first dose of 150 mg flibanserin showed signs of hypotension or syncope.

5. BENEFIT AND RISK CONCLUSIONS

As evident by the evolving literature in the field, the Draft Guidance provided by the FDA on FSD, and the ongoing dialog over the last years between the Sponsor and the Division on the flibanserin development program, the science of female sexuality in general and HSDD and its treatment specifically has been constantly evolving. This evolution has led to significantly better understanding of the condition from the patient's perspective, which in turn has led to a more appropriate understanding of the results of clinical trials with flibanserin. This section summarizes the large and complex dataset reported in the previous section, focusing on the three North American primary efficacy trials.

HSDD is by definition a condition characterized by the distressing absence or loss of previously adequate sexual desire; however the symptomatology and patient experience of HSDD is not limited to desire alone, necessitating assessments of multiple components of the condition in order to best characterize the potential benefits of a treatment.

Sexual desire is inherently challenging to measure as it is a complex, multifaceted phenomenological experience involving biological, cognitive and emotional aspects. Although it is recognized that sexual desire has both global qualities (i.e., an overall sense of general readiness and openness and interest in sexual activity) and more episodic qualities (i.e., specific moments of higher sexual motivation and urges for sexual release), the etiology of these different phenomenological experiences of desire is not known. The degree to which a particular woman is more or less bothered by the infrequency of her desires versus the low intensity of her desires is likely to vary, and importantly, we have no basis to presume that frequency and intensity are affected in the same way by the imbalance of neurotransmitters thought to influence HSDD. Hence, there is no *a priori* basis on which to presume that flibanserin will work equally on frequency and intensity of sexual desire, and therefore it is important to assess both. It is known from qualitative studies of women with HSDD that both the lack of "acute" experiences of desire and the global sense of having "no desire" seem to be important in women's reports of the distress that they experience as a result of HSDD.

Regarding individual studies, the co-primary endpoint of SSE was found to be both statistically positive as well as clinically meaningful, as defined by the anchoring to the Patient's Global Impression of Improvement.

Second, the co-primary Diary desire score was formally positive in one of the 3 trials (511.74) while showing consistent positive trends in the other 2.

Although the initial choice of a daily measure of sexual desire assessing episodic intensity was a standard agreed upon by the Sponsor and the FDA, our research has shown that it does not completely capture all relevant measures of desire in women with HSDD. Increases in the intensity of desire experienced episodically on a day-to-day basis as well as increases in women's overall sense of having a satisfactory frequency and level of desire in her life are both relevant to women suffering from HSDD

Improvement in the continuous global measure of sexual desire as assessed by the FSFI desire items was found to be nominally statistically significant in favor of flibanserin in all 3 North American studies.

These findings demonstrate replication of the effect that flibanserin has on increasing sexual desire in women with HSDD and elucidate that flibanserin 100 mg q.h.s. is more consistently effective in increasing women's global experiences of desire than in increasing the intensity of their acute episodes of desire.

Sexually related distress, as assessed by both the FSDS-R total score and the individual FSDS-R Item 13 (relating to distress related to low desire) was found to be nominally statistically significant in favor of flibanserin in all 3 North American studies. Women taking flibanserin reported reductions in all aspects of the distress they experienced; shame, guilt, unhappiness, regret, worry and anger were all reduced in women taking flibanserin.

Recognizing that statistical significance alone for results may not adequately capture the potential benefit to the patient, *a priori* (responder) analyses and post hoc (remitter) analyses were also performed to better characterize these potential benefits. The methodology for these responder analyses were agreed with the Agency to be anchored to an individual woman's assessment of her improvement. This anchor-based assessment of response may in fact be the most clinically relevant endpoint, because a result that is statistically significant may or may not represent what is truly meaningful to an individual woman taking flibanserin. As well, a woman's individual assessment of her treatment is based on her impression of all aspects of her treatment experience, some of which may be more or less important to her than to another woman, but ultimately allows all women in the clinical program to give voice to their personal experience with treatment.

Remitter analyses, while post hoc and exploratory in nature, demonstrated that the proportion of women who took 100 mg of flibanserin who remitted (scores indicative of no longer being in the range of clinical disorder) was statistically significantly greater on the FSFI desire and FSDS-R Q 13 than in women who took placebo.

In the North American trials, the flibanserin 100 mg q.h.s. group consistently showed a clinically meaningful difference from placebo for all of the displayed endpoints (SSE, FSFI desire items, FSFI total, FSDS-R total, FSDS-R Q13), with the exception of the responder endpoints based on the eDiary sexual desire score.

In order to better characterize and more confidently assess the overall effect of flibanserin, as well as to assess subgroups and the effect of flibanserin over time, pooled analyses were pre-planned for those clinical trials that were similar with respect to patient characteristics, data collection, dose of flibanserin and endpoints prior to unblinding, as documented in the briefing package sent to the FDA as part of the Pre-NDA meeting. These pooled analyses in addition to the individual trial results, form the most integrative evidence of the overall effect of flibanserin.

Table 5: 1 illustrates the consistent effect of flibanserin across individual studies and the pooled analyss for a range of endpoints relevant to women with HSDD. The hallmark

symptoms of HSDD, low desire and related distress, are improved, leading to a subsequent increase in the behavioural endpoint of SSEs. These observations are confirmed by women in their own assessments of benefit.

Table 5: 1 Summary of results, Trials 511.71, 511.75 and 511.74 (FAS, LOCF)

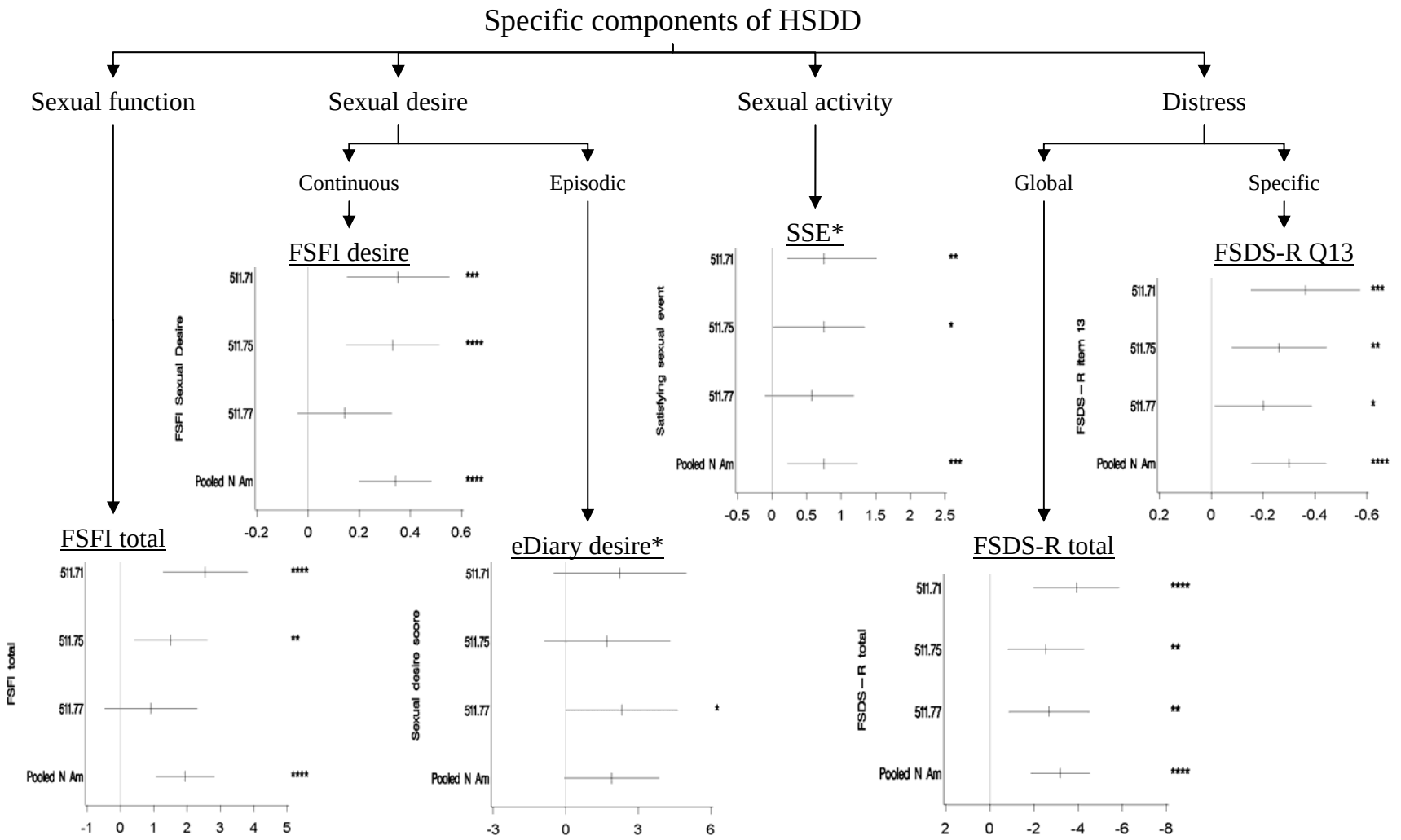
	North America			
	511.74[2]	511.71	511.75	Pooled 511.71/.75
Primary endpoints				
SSE	**	**	*	**
eDiary sexual desire score	*	–	–	*
Key secondary endpoints[1]				
FSFI desire items	##	##	##	##
FSDS-R total	##	##	##	##
Other secondary endpoints				
FSDS-R Item 13	##	##	##	##
FSFI total	##	##	##	##
PGI-I	##	##	##	##
SSE (count)	#	##	#	##
PGI-I anchored responder endpoints				
SSE	N/A	##	#	##
eDiary sexual desire score	N/A	–	–	–
FSFI desire items	N/A	##	##	##
FSFI total	N/A	##	##	##
FSDS-R Q13	N/A	##	#	##
FSDS-R total	N/A	#	##	##
Remitter endpoints				
FSFI desire items remitter (>3.0)	N/A	##	##	##
FSDS-R total remitter (<15)	N/A	##	–	##
Other responder endpoints				
PGI-I (very much/much improved)	N/A	##	##	##
PGI-I (very much/much/minimally improved)	N/A	##	##	##
Patient Benefit Evaluation	N/A	#	##	##

NOTE: Adjusted p-values: – p > 0.05; * p <0.05; ** p <0.01; # nominal p<0.05 ; ## nominal p<0.01

1 Since both primary endpoints were not statistically significant in Trials 511.71 and 511.75, the interpretation of the key secondary endpoints should be interpreted as nominal significance.

2 For Trial 511.74, the endpoints listed under key secondary endpoints were not specifically denoted as key secondary endpoints, but rather as secondary endpoints. Furthermore, the responder/remitter endpoints were Not Applicable (N/A) since these responder/remitter endpoints were not defined as secondary endpoints.

The totality of evidence supports that flibanserin 100 mg q.h.s. improves desire and related distress in women with HSDD. Flibanserin's effect on HSDD is supported by a comprehensive dataset including the SSEs, eDiary desire, FSFI desire items, the FSDS-R total and FSDS-R Q13, and the Patient's Global Impression of Improvement (Figure 5:1). These data coupled with a series of sensitivity analyses all demonstrate that flibanserin 100 mg q.h.s. improves the clinical symptomatology of women suffering from HSDD.



NOTE: Mean and adjusted 95% CI are displayed. Adjusted p-values: * p<0.05; ** p<0.01; *** p<0.001; ****p<0.0001

Figure 5: 1 Mapping of specific HSDD components to clinical endpoints / results

The AEs reported most frequently, and in higher proportions of subjects with 100 mg flibanserin q.h.s compared to placebo, were dizziness, nausea, fatigue, and somnolence, at approximately 10-12% each, and insomnia, at about 5%. The less frequent AEs that the Sponsor considered drug-related were dry mouth, anxiety, sedation, and constipation, at about 2% each, and sleep disorder, and palpitations, at about 1% each, plus hypotension at about 0.4%. The occurrence of the most frequent AEs decreased with the continuation of flibanserin treatment. Most AEs were generally of mild to moderate intensity, and extremely few were reported as related SAEs (no related SAEs in women with HSDD).

No observation was made that would raise concern over the use of flibanserin in premenopausal women with HSDD in regard to suicide, depression, abuse potential, hypersexuality, ophthalmologic safety, hormonal changes including indices of fecundity, or pregnancy outcome (observations were limited to women whose treatment was stopped promptly upon discovery of pregnancy). Too few pregnancies were reported, however, to provide clinical guidance.

In conclusion, the consistent therapeutic effect in well-controlled trials of the flibanserin 100 mg dose regimen, and its use by most patients in the one-year randomized withdrawal (efficacy maintenance) trial, support the claim to treat premenopausal women with flibanserin. Flibanserin 100 mg q.h.s. has been shown to be safe and well-tolerated, with no evidence of a withdrawal effect. The overall risk/benefit ratio was considered to be positive for flibanserin tablets as a treatment of Hypoactive Sexual Desire Disorder in premenopausal women.

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7. APPENDIX

7.1 ADDITIONAL INFORMATION TO SUPPORT THE OVERVIEW OF CLINICAL EFFICACY

7.1.1 Details of the statistical inference strategy

The following sections describe the details of the statistical inference strategy clearly defining what was originally prespecified in the trial protocol and any changes that occurred via trial protocol amendment and/or the TSAP.

7.1.1.1 Trial 511.74 statistical inference

Trial 511.74 tested flibanserin (flexible dosing) versus placebo in a randomized withdrawal trial design. In this trial, patients first entered a 24-week open-label period where patients who met the pre-specified responder criteria at Week 24 were subsequently entered into a 24-week double-blind randomized period. During the open-label period, patients received a flexible dosing regimen of flibanserin until Week 16 after which the patient remained on a stable regimen. The double-blind period used a randomized withdrawal trial design where patients were randomized to flibanserin (the same dose that the patient was on at the end of the open-label period) or placebo. The trial had two primary endpoints (SSE and eDiary sexual desire score) and no key secondary endpoints. The statistical inference strategy is explained in detail below followed by details of each step of the testing procedure.

General inference strategy

Multiple testing of endpoints was addressed by requiring both primary endpoints to be positive. There were no key secondary endpoints defined in the trial.

Multiple testing of doses was not an issue since the testing was performed for flibanserin (flexible dosing) vs. placebo.

Change from the original protocol defined analysis: None

Primary endpoints

SSE: If $p \leq 0.05$, then reject the null hypotheses

eDiary sexual desire score: If $p \leq 0.05$, then reject the null hypotheses

Primary endpoint 1: SSE

For the primary endpoint of SSE, the comparison of flibanserin vs. placebo was statistically significant with a p-value of 0.0064.

Primary endpoint 2: eDiary sexual desire score

For the primary endpoint of eDiary sexual desire score, the comparison of flibanserin vs. placebo was statistically significant with a p-value of 0.0283.

7.1.1.2 Trial 511.75 statistical inference

Trial 511.75 tested three doses of flibanserin (25 mg b.i.d., 50 b.i.d. and 100 mg q.h.s.) versus placebo. The trial had two primary endpoints (SSE and eDiary sexual desire score) and one key secondary endpoint (FSDS-R total). Table 3.2: 2 shows the results of the trial. The

statistical inference strategy is explained in detail below followed by details of each step of the testing procedure.

General inference strategy

Multiple testing of doses was addressed using the Hochberg procedure.

Multiple testing of endpoints was addressed by requiring both primary endpoints to be positive before testing the key secondary endpoint.

Change from the original protocol defined analysis: None

Primary endpoints

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

- Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.
- Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.
- Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

For dose(s) that was positive on SSE, proceed to test the eDiary sexual desire score. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

- Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.
- Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.
- Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If both primary endpoints are positive for the same dose, then proceed to testing the key secondary endpoint

Key secondary endpoint

For dose(s) that was positive on both primary endpoints, proceed to test the FSDS-R total score. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

FSDS-R total score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

- Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.
- Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.
- Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

Primary endpoint 1: SSE

Under the Hochberg procedure, p-values of each dose of flibanserin vs placebo are ordered from largest to the smallest p-values ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$). Thus, the p-value corresponding to the comparison of flibanserin 25 mg b.i.d. vs placebo (p = 0.2896) will be designed as $p_{(3)}$, the p-value corresponding to the comparison of flibanserin 50 mg b.i.d. vs placebo (p = 0.1990) will be designated as $p_{(2)}$, and the p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo (unadjusted p = 0.0081) will be designated as $p_{(1)}$. Since $p_{(3)}$ is greater than 0.05, the null hypotheses is not rejected and proceed to Step 2. Since the adjusted $p_{(2)}$ (unadjusted $p_{(2)}$ times 2) is greater than 0.05, the null hypotheses is not rejected and proceed to Step 3. Since the adjusted $p_{(1)}$ is (unadjusted $p_{(2)}$ times 3) less than 0.05, the null hypotheses is rejected. The comparison of flibanserin 100 mg q.h.s. vs. placebo is statistically significant.

Primary endpoint 2: eDiary sexual desire score

Since only one dose was positive on SSE, the procedure tests the eDiary sexual desire score starting with Step 3. At Step 3, the comparison of flibanserin 100 mg q.h.s. vs. placebo is required to be significant at an unadjusted alpha level of 0.0167 which is equivalent to adjusted p-value (unadjusted times 3) at a level of 0.05. The adjusted p-value of this comparison was greater than 0.05. Therefore, the comparison of flibanserin 100 mg q.h.s. vs. placebo was not statistically significant for eDiary sexual desire score.

Since both primary endpoints were not significant, the p-values of the flibanserin vs. placebo comparisons on the key secondary endpoints must be interpreted as exploratory p-values. The results of the testing procedure are summarized for the key secondary endpoints understanding that the results are interpreted as exploratory significance.

Key secondary endpoint: FSDS-R total score

Since none of the doses were significant for both of the co-primary endpoints, the subsequent p-values will be adjusted by a factor of 3 using the final Hochberg threshold level. For FSDS-R total score, the adjusted p-value corresponding to the comparison of flibanserin 25 mg b.i.d. vs placebo was 0.1315. The adjusted p-value corresponding to the comparison of flibanserin 50 mg b.i.d. vs placebo was 0.0225. The adjusted p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo was 0.0012. The comparisons of the 50 mg b.i.d. and 100 mg q.h.s. flibanserin doses vs. placebo for FSDS-R total score are nominally significant.

7.1.1.3 Trial 511.71 statistical inference

Trial 511.71 tested two doses of flibanserin (50 mg q.h.s. and 100 mg q.h.s.) versus placebo. The trial had two primary endpoints (SSE and eDiary sexual desire score) and two key secondary endpoints (FSDS-R total as originally specified in the trial protocol and FSFI desire items as added in the TSAP before unblinding). The statistical inference strategy is explained in detail below followed by details of each step of the testing procedure.

General inference strategy

Multiple testing of doses was addressed using the Hochberg procedure.
Multiple testing of endpoints was addressed by requiring both primary endpoints to be positive before testing the key secondary endpoints.

Change from the original protocol defined planned analysis

FSFI desire items was added as a key secondary endpoint (originally, this endpoint was specified as other secondary endpoint). The protocol specified only the FSDS-R total score as a key secondary endpoint, but the FSFI desire items was elevated to key secondary in the TSAP before unblinding.

Primary endpoints

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.
Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

For dose(s) that was positive on SSE, proceed to test the eDiary sexual desire score. If both doses were positive, then start the testing at Step 1. If one dose was positive, then start the testing for that dose at Step 2; furthermore, $p_{(2)}$ will be multiplied by 2.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.
Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If both primary endpoints are positive for the same dose, then proceed to testing the key secondary endpoints.

Key secondary endpoints

For dose(s) that was positive on both primary endpoints, proceed to test the key secondary endpoints. If both doses were positive, then start the testing at Step 1. If one dose was positive, start the testing for that dose at Step 2; furthermore, $p_{(2)}$ will be multiplied by 2.

FSDS-R total score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.
Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else that no dose comparisons to placebo are statistically significant.

FSFI desire items - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.
Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

Primary endpoint 1: SSE

Under the Hochberg procedure, p-values of each dose of flibanserin vs placebo are ordered from largest to the smallest p-values ($p_{(1)} \leq p_{(2)}$). Thus, the p-value corresponding to the comparison of flibanserin 50 mg q.h.s. vs placebo (p = 0.0454) will be designed as $p_{(2)}$, and the p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo (p = 0.0024) will be designated as $p_{(1)}$. Since $p_{(2)}$ is less than 0.05, the null hypotheses of both dose comparisons are rejected and conclude that there was a statistically significant difference from placebo for both doses. Since both doses were statistically significant, an adjustment is not necessary.

Primary endpoint 2: eDiary sexual desire score

Since both doses were positive on SSE, the procedure tests the eDiary sexual desire score starting with Step 1. However, neither doses were statistically significantly different from placebo for the eDiary sexual desire score.

Since both primary endpoints were not significant, the p-values of the flibanserin vs. placebo comparisons on the key secondary endpoints must be interpreted as nominal p-values. The results of the testing procedure are summarized for the key secondary endpoints understanding that the results are interpreted as nominal significance.

Key secondary endpoints: FSDS-R total score

Since neither of the doses were significant for both of the co-primary endpoints, the subsequent p-values will be adjusted by a factor of 2 using the final Hochberg threshold level to control for multiple dose testing. For FSDS-R total score, the adjusted p-value corresponding to the comparison of flibanserin 50 mg q.h.s. vs placebo was 0.3202. The adjusted p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo was <0.0001. The comparison of flibanserin 100 mg q.h.s. vs. placebo for FSDS-R total score is nominally significant.

Key secondary endpoints: FSFI desire items

Since neither of the doses were significant for both of the co-primary endpoints, the subsequent p-values will be adjusted by a factor of 2 using the final Hochberg threshold level to control for multiple dose testing. For FSFI desire items, the adjusted p-value corresponding to the comparison of flibanserin 50 mg q.h.s. vs placebo was 0.0345. The adjusted p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo was 0.0002. The comparison of both flibanserin 50 mg q.h.s. and 100 mg q.h.s. vs. placebo for FSFI desire items are nominally significant.

7.1.1.4 Trial 511.77 statistical inference

Trial 511.77 tested two doses of flibanserin (50 q.h.s. and 100 mg q.h.s.) versus placebo. The trial had one primary endpoint (SSE) and two key secondary endpoints (FSFI desire items and FSDS-R total); the original trial protocol had the eDiary sexual desire score instead of the FSFI desire items. Both the original protocol specified statistical inference strategy and the

modified inference strategy defined by the Trial Protocol Amendment 2 are explained in detail below followed by details of each step of the testing procedure.

Original protocol defined inference strategy

General inference strategy

Multiple testing of doses was addressed using the Hochberg procedure.

Multiple testing of endpoints was addressed by requiring the primary endpoint to be positive before testing the key secondary endpoints.

Change from the original protocol defined planned analysis (modified strategy presented on the following page)

Two changes were made to inferences strategy as part of Protocol Amendment 2 while the trial was still on-going:

1) FSFI desire items replaced eDiary sexual desire score as a key secondary endpoint
2) Hierarchical testing strategy with an *a priori* ordered hierarchy was used to control for multiple testing.

Primary endpoints (Defined in the original protocol)

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If the primary endpoint is positive, then proceed to testing the key secondary endpoints.

Key secondary endpoints (Defined in the original protocol)

For dose(s) that was positive on the primary endpoint, proceed to test the key secondary endpoints. If both doses were positive, then start the testing at Step 1. If one dose was positive, start the testing for that dose at Step 2; furthermore, $p_{(2)}$ will be multiplied by 2.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

FSFI desire items - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)}$) and proceed with the following steps

Step 1: If $p_{(2)} \leq 0.05$, then reject the null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

Primary endpoint (based on original plan): SSE

Under the original protocol defined inference strategy, neither of the doses were statistically significant from placebo for SSE, the primary endpoint.

Since the primary endpoint was not significant, the p-values of the flibanserin vs. placebo comparisons on the key secondary endpoints must be interpreted as nominal p-values. The results of the testing procedure are summarized for the key secondary endpoints understanding that the results are interpreted as nominal significance.

Key secondary endpoint (based on original plan): eDiary sexual desire score

Since neither of the doses were significant for the primary endpoint, the subsequent p-values will be adjusted by a factor of 2 using the final Hochberg threshold level to control for multiple dose testing. For eDiary sexual desire score, the adjusted p-value corresponding to the comparison of flibanserin 50 mg q.h.s. vs placebo was 1.0000. The adjusted p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo was 0.0481. The comparison of flibanserin 100 mg q.h.s. vs. placebo for eDiary sexual desire score is nominally statistically significant.

Key secondary endpoint (based on original plan): FSDS-R total score

Since neither of the doses were significant for the primary endpoint, the subsequent p-values will be adjusted by a factor of 2 using the final Hochberg threshold level to control for multiple dose testing. For FSDS-R total score, the adjusted p-value corresponding to the comparison of flibanserin 50 mg q.h.s. vs placebo was 0.3925. The adjusted p-value corresponding to the comparison of flibanserin 100 mg q.h.s. vs placebo was 0.0020. The comparison of flibanserin 100 mg q.h.s. vs. placebo for FSDS-R total score is nominally statistically significant.

Amended inference strategy in Trial Protocol Amendment 2

Change from the original protocol defined planned analysis (Defined in Trial Protocol Amendment 2)

Two changes were made to the inferences strategy as part of Protocol Amendment 2 while the trial was still on-going:

3) FSFI desire items replaced eDiary sexual desire score as a key secondary endpoint
4) Hierarchical testing strategy using an *a priori* ordered hierarchy was used to control for multiple testing of both dose and endpoints.

General inference strategy (Defined in Trial Protocol Amendment 2)

Multiple testing of doses was addressed by requiring the test of Flibanserin 100 mg q.h.s. vs. placebo for SSE to be positive before testing Flibanserin 50 mg q.h.s. vs. placebo

Multiple testing of endpoints was addressed the use of an *a priori* ordered hierarchical testing procedure.

Inference strategy defined in Trial Protocol Amendment 2

Primary endpoints (Defined in Trial Protocol Amendment 2)

SSE

Step 1: If flibanserin 100 mg q.h.s. vs placebo is statistically significant with $p \leq 0.05$, then reject the null hypothesis and proceed to Step 2

Step 2: If flibanserin 50 mg q.h.s. vs placebo is statistically significant with $p \leq 0.05$, then reject the null hypothesis

Key secondary endpoints (Defined in Trial Protocol Amendment 2)

Flibanserin 100 mg q.h.s. vs placebo

Before proceeding to test the key secondary endpoints, flibanserin 100 mg q.h.s. vs placebo must be significant for the primary endpoint

Step 1: FSFI desire items – if statistically significant with $p \leq 0.05$, then reject the null hypothesis and proceed to Step 2

Step 2: FSDS-R total score – if statistically significant with $p \leq 0.05$, then reject the null hypothesis

Flibanserin 50 mg q.h.s. vs placebo

Before proceeding to test the key secondary endpoints, flibanserin 50 mg q.h.s. vs placebo for SSE must be significant for the primary endpoint

Step 1: FSFI desire items – if statistically significant with $p \leq 0.05$, then reject the null hypothesis and proceed to Step 2

Step 2: FSDS-R total score – if statistically significant with $p \leq 0.05$, then reject the null hypothesis

Primary endpoint (based on amended plan): SSE

Under the inference strategy defined in Trial Protocol Amendment 2, an *a priori* hierarchical testing strategy was implemented. The first test in the hierarchy was the comparison of flibanserin 100 mg q.h.s. vs placebo for SSE for which the p-value was 0.1403. Since this was greater that 0.05, the null hypothesis is not rejected, and the testing procedure stops at that step in terms of inference. The results of subsequent tests are provided and are viewed as nominal p-values.

The next step is the test of flibanserin 50 mg q.h.s. vs placebo for which the unadjusted p-value was 0.5413 which is equivalent to an adjusted p-value of 1.000. Since this was greater than 0.05, the null hypothesis is not rejected.

The results for the key secondary endpoints are provided with the understanding that the results are interpreted as exploratory and of nominal significance.

Key secondary endpoint for the comparison of flibanserin 100 mg q.h.s. vs. placebo (based on amended plan)

Following the primary endpoint testing, the next step in the hierarchy for flibanserin 100 mg q.h.s. was the comparison for the FSFI desire items for which the unadjusted p-value was 0.0816 which is equivalent to an adjusted p-value of 0.1633. This was to then be followed by the comparison of flibanserin 100 mg q.h.s. vs. placebo for FSDS-R total score for which the unadjusted p-value was 0.0010 which is equivalent to an adjusted p-value of 0.0020.

Key secondary endpoint for the comparison of flibanserin 50 mg q.h.s. vs. placebo (based on amended plan)

Following the primary endpoint testing, the next step in the hierarchy for flibanserin 50 mg q.h.s. was the comparison for the FSFI desire items for which the unadjusted p-value was 0.9409 which is equivalent to an adjusted p-value of 1.0000. This was to then be followed by the comparison of flibanserin 50 mg q.h.s. vs. placebo for FSDS-R total score for which the p-value was 0.1963 which is equivalent to an adjusted p-value of 0.3925.

7.1.1.5 Trial 511.70 statistical inference

Trial 511.70 tested three doses of flibanserin (25 mg b.i.d., 50 mg q.h.s. and 50 mg b.i.d.) versus placebo. The trial had two primary endpoints (SSE and eDiary sexual desire score) and two key secondary endpoints (FSDS-R total as originally specified in the trial protocol and FSFI desire items as added in the TSAP before unblinding). Table 3.2: 2 shows the results of the trial. The statistical inference strategy is explained in detail below. None of the comparisons of flibanserin vs placebo was statistically significant for the primary endpoints in this trial. As such, the p-values for the key secondary are provided but should be interpreted as nominal p-values.

General inference strategy

Multiple testing of doses was addressed using the Hochberg procedure.
Multiple testing of endpoints was addressed by requiring both primary endpoints to be positive before testing the key secondary endpoints.

Change from the original protocol defined planned analysis

FSFI desire items was added as a key secondary endpoint (originally, this endpoint was specified as other secondary endpoint). The protocol specified only the FSDS-R total score as a key secondary endpoint, but the FSFI desire items was elevated to key secondary in the TSAP before unblinding.

Primary endpoints

SSE - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

- Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.
- Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.
- Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

For dose(s) that was positive on SSE, proceed to test the eDiary sexual desire score. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

eDiary sexual desire score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

- Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.
- Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.
- Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

If both primary endpoints are positive for the same dose, then proceed to testing the key secondary endpoints.

Key secondary endpoints

For dose(s) that was positive on both primary endpoints, proceed to test the key secondary endpoints. If all 3 doses were positive, then start the testing at Step 1. If 2 doses were positive, the start the testing for those doses at Step 2; furthermore, $p_{(3)}$ will be multiplied by 2. If one dose was positive, start the testing for that dose at Step 3; furthermore, $p_{(2)}$ and $p_{(1)}$ will be multiplied by 3.

FSDS-R total score - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

- Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else if $p_{(3)} > 0.05$, proceed to Step 2.
- Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.
- Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

FSFI desire items - Order p-values of each dose of flibanserin vs placebo ($p_{(1)} \leq p_{(2)} \leq p_{(3)}$) and proceed with the following steps

Step 1: If $p_{(3)} \leq 0.05$, then reject all null hypotheses and no adjustments are necessary, else proceed to Step 2.

Step 2: Calculate adjusted p-values for $p_{(2)}$ and $p_{(1)}$ by multiplying the p-value by 2. If the adjusted $p_{(2)} \leq 0.05$, then reject the null hypotheses corresponding to p-values $p_{(1)}$ and $p_{(2)}$, else proceed to Step 3.

Step 3: Calculate adjusted p-value for $p_{(1)}$ by multiplying the p-value by 3. If the adjusted $p_{(1)} \leq 0.05$, then reject the null hypotheses corresponding to p-value $p_{(1)}$, else conclude that no dose comparisons to placebo are statistically significant.

7.1.2 Additional displays

7.1.2.1 Discriminant validity

Table 7.1.2.1: 1 Discriminant validity of SSE, eDiary desire, FSDS-R total, FSDS-R Item 13, FSFI total, and FSFI desire items – Pooled (511.73, 511.106) (FAS, Day 28)

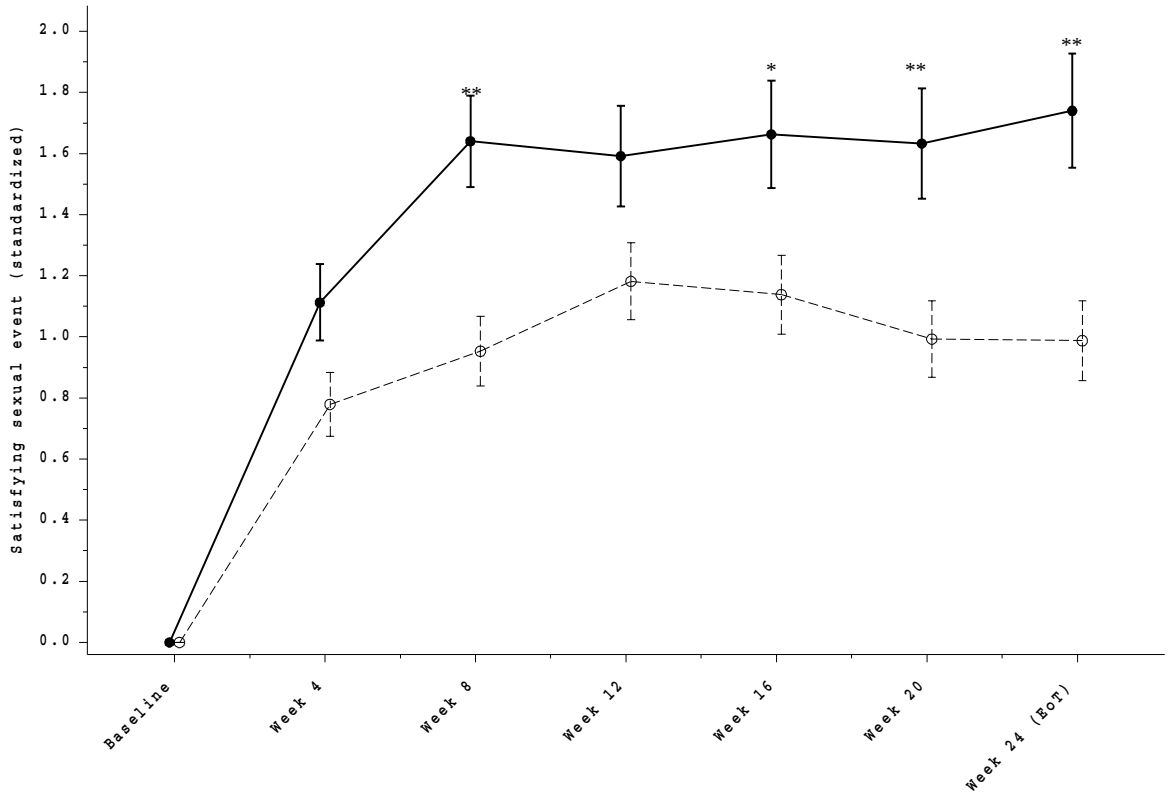
Diagnosis	Statistic	SSE	eDiary desire score*	FSDS-R Total*	FSDS-R Item 13*	FSFI total	FSFI desire items
HSDD	N	244	137	136	136	247	247
	Mean	3.5	17.7	25.6	2.8	21.9	2.2
	SD	4.1	13.3	12.5	1.1	6.9	0.8
FSAD	N	44	N/A*	N/A*	N/A*	49	49
	Mean	4.6				21.1	3.3
	SD	4.8				6.3	1.3
Other FSD	N	46	46	45	45	45	45
	Mean	4.8	23.3	25.8	2.6	19.6	2.8
	SD	5.5	13.9	11.8	1.2	6.2	1.1
No FSD	N	134	75	72	72	133	133
	Mean	12.4	49.1	2.6	0.3	32.4	4.6
	SD	10.4	18.6	4.8	0.7	3.9	1.0
HSDD - No FSD	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
FSAD - No FSD	P-value	< 0.0001				< 0.0001	< 0.0001
Other FSD - NoFSD	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
HSDD - No FSD	95% CI	(-10.3,-7.4)	(-35.7,-27.2)	(19.9, 26.1)	(2.2, 2.8)	(-11.8,-9.2)	(-2.6,-2.2)
FSAD - No FSD	95% CI	(-10.1,-5.5)				(-13.3,-9.3)	(-1.6,-0.9)
Other FSD - NoFSD	95% CI	(-5.3,-9.9)	(-20.2,-31.4)	(27.2, 19.2)	(2.6, 1.9)	(-10.8,-14.9)	(-1.5,-2.1)

* Note: The eDiary desire question (same version used in the Phase III trials) and the FSDS-R were only tested in 511.106 which did not include the FSAD population; therefore, the results are marked as Not Applicable (N/A).
P-values based on ANOVA model with diagnosis as the main effect.

7.1.2.2 Efficacy

SSE

For the onset of response analyses for SSE, the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 1). At Week 4, the flibanserin 100 mg q.h.s. group had a mean change from baseline SSE value of 1.1 which then increases to 1.6 at Week 8 after which the value was relatively stable at SSE of 1.6 to 1.7 through the end of the trial. In comparison, at Week 4, patients on placebo had a mean change from baseline value of 0.8 that increased to 1.2 at Week 12 after which the values were between 1.0 to 1.1 through the end of the trial.



P-value based on comparison using Wilcoxon rank sum test controlling for pooled centre: * $p < 0.05$; ** $p < 0.01$

Placebo (N=679) FLI 100qhs (N=660)

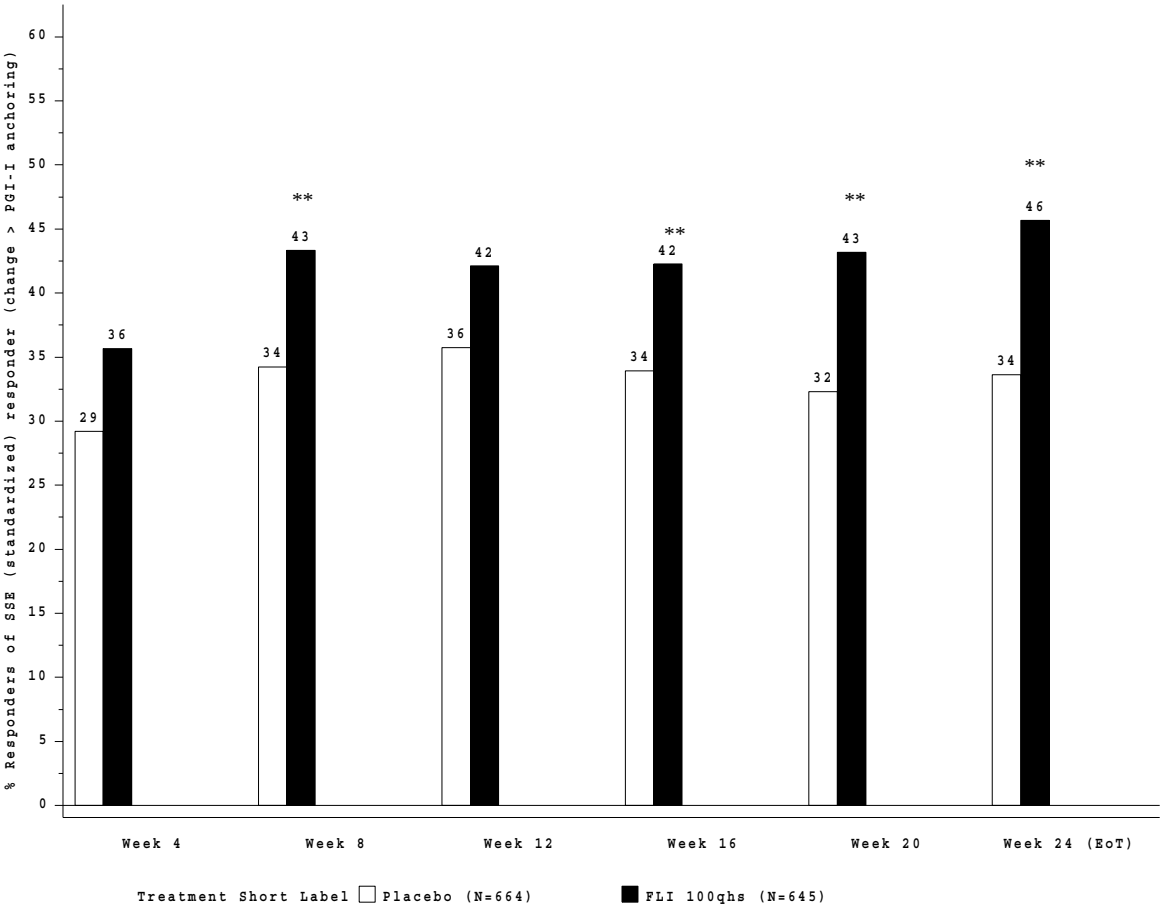
Note: Change from baseline Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 1 Satisfying sexual event change from baseline by treatment – Pooled (511.71, 511.75) (FAS, LOCF)

The responder analysis of SSE using the PGI-I anchoring demonstrated flibanserin 100 mg q.h.s. showing statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 2). At Week 4, the flibanserin 100 mg q.h.s. group had 35.7% responders which increased to 43.3% at Week 8 after which the percent of

responders was relatively stable through Week 20 (42.1%-43.2%) and increased slightly at Week 24 to 45.7%. In comparison, at Week 4, the placebo group had 29.2% responders which increased to 35.7% at Week 12 after which the percent of responders was relatively stable between 32.3% to 33.9% through the end of the trial.

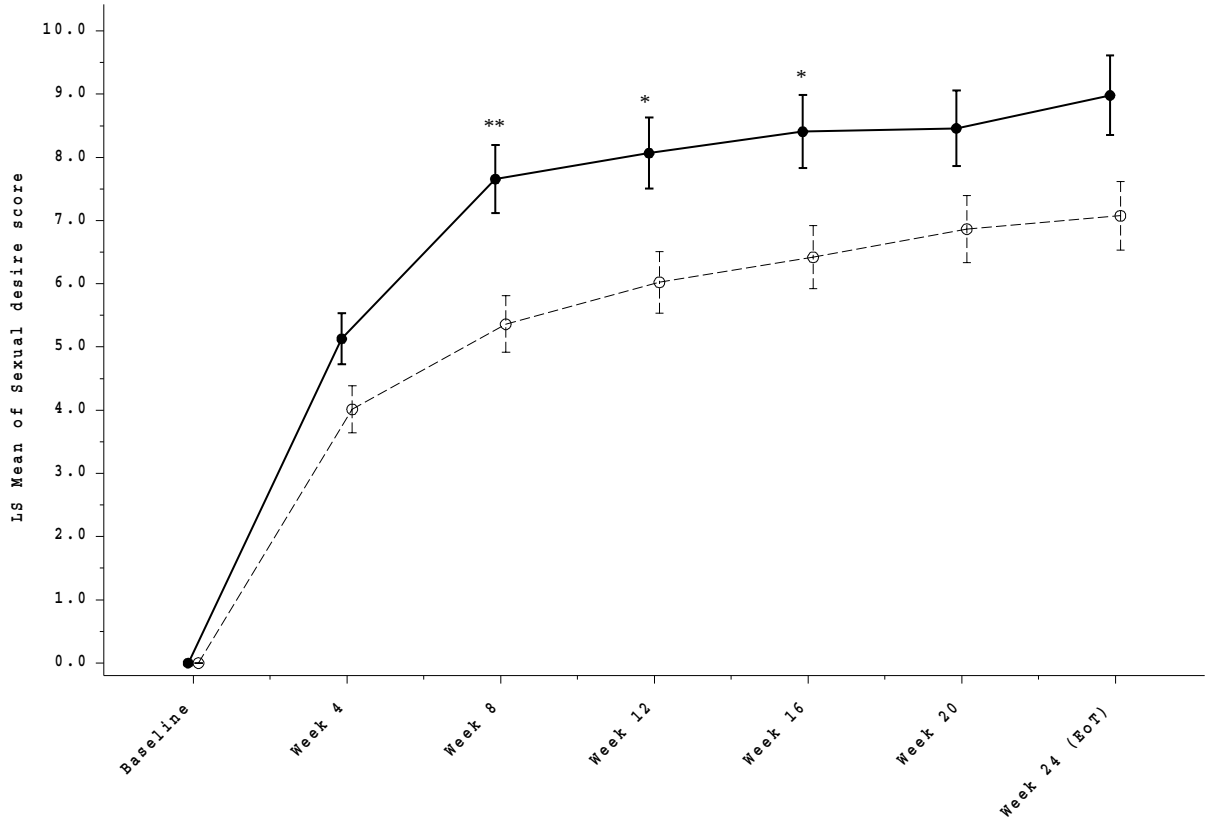


P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre.
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 2 SSE responders – Pooled (511.71, 511.75) (FAS, LOCF)

eDiary sexual desire score

For the eDiary sexual desire score, the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 3). At Week 4, the flibanserin 100 mg q.h.s. group had a mean eDiary sexual desire score change from baseline value of 5.1 which continued to increase to 9.0 at Week 24. In comparison, at Week 4, patients on placebo had a mean change from baseline value of 4.0 that increased 7.1 at Week 24.



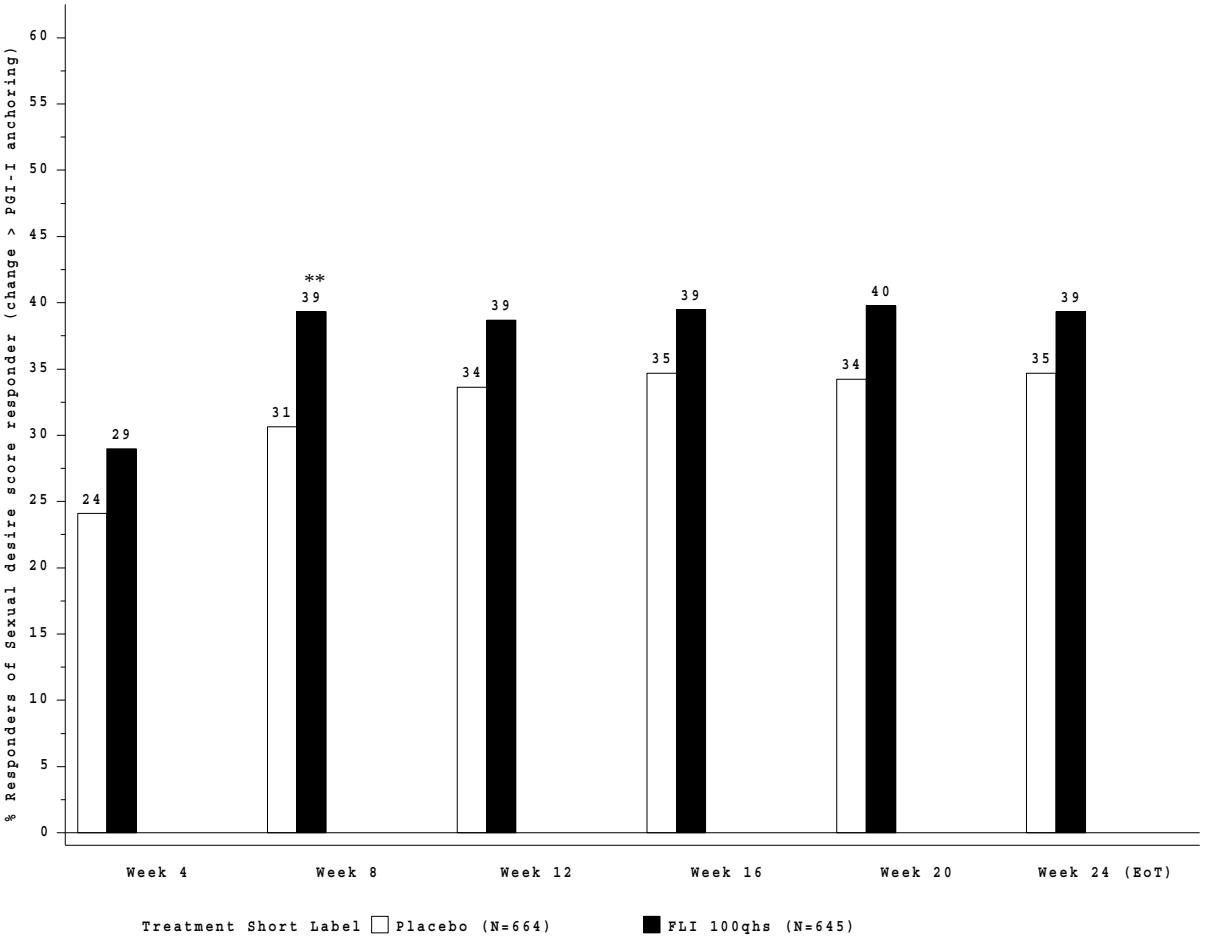
P-value based on ANCOVA model using baseline as a covariate with main effect terms treatment, study and pooled center nested in study
* p < 0.05; ** p < 0.01

Note: Change from baseline Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 3 eDiary sexual desire score change from baseline by treatment – Pooled (511.71, 511.75) (FAS, LOCF)

The responder analyses of the eDiary sexual desire score using the PGI-I anchor based responder criterion showed that the flibanserin 100 mg q.h.s. group did not show statistical separation from placebo (p = 0.0653) at Week 24 (Figure 7.1.2.2: 4). While the comparisons of the flibanserin 100 mg q.h.s. group compared to placebo were below p = 0.05 at most visits starting at Week 4, at Weeks 16 and 24 the flibanserin 100 mg q.h.s. comparison to placebo had p-values of 0.0560 and 0.0653, respectively. The flibanserin 100 mg q.h.s. group consistently had more responders compared to placebo with 29.0% at Week 4 which increased to 39.3% at Week 24. In comparison, at Week 4, there were 24.1% responders on placebo which increased to 34.7% at Week 24.

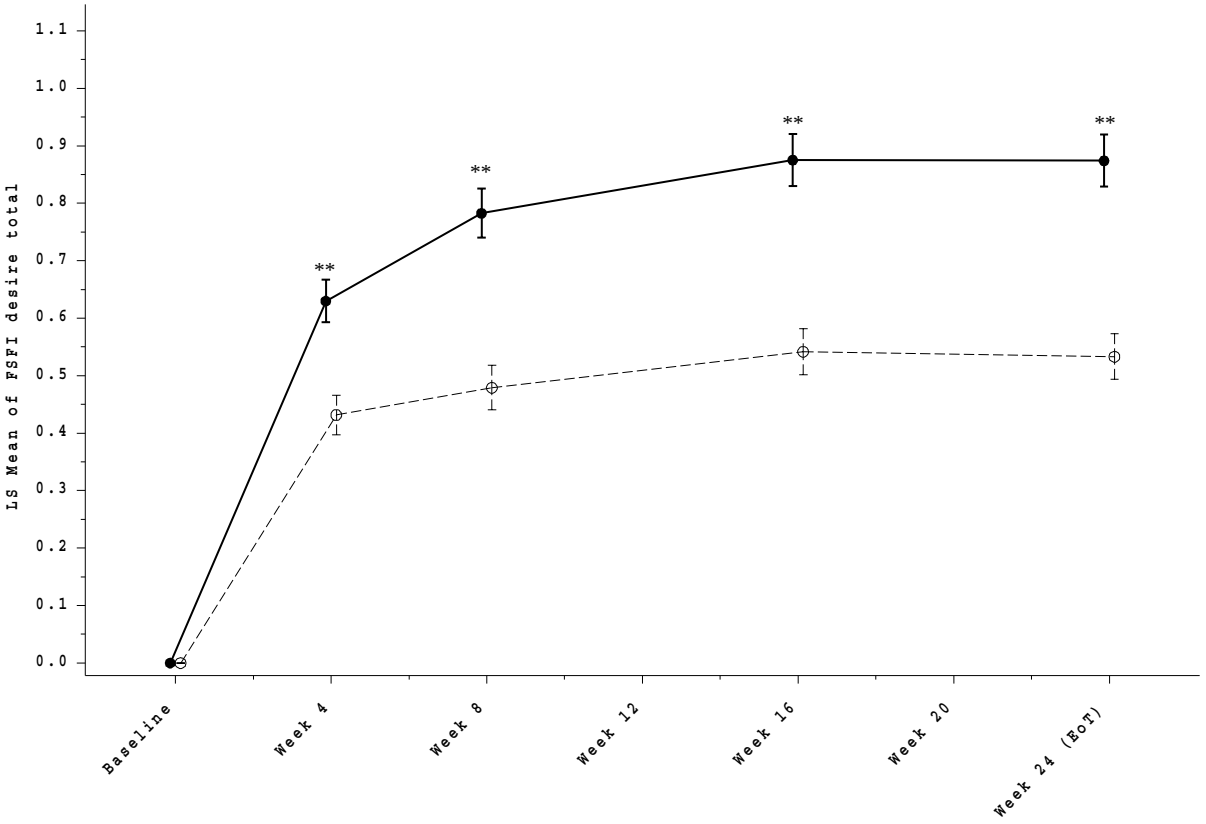


P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre: * $p < 0.05$; ** $p < 0.01$
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 4 eDiary sexual desire score responders – Pooled (511.71, 511.75) (FAS, LOCF)

FSFI desire items

For the FSFI desire items, the flibanserin 100 mg q.h.s. group began to show statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 5). At Week 4, the flibanserin 100 mg q.h.s. group had a mean FSFI desire items change from baseline value of 0.6 which then increased to 0.8 at Week 8 and further increased to 0.9 at Weeks 16 and 24. In comparison, at Week 4, patients on placebo had a mean change from baseline value of 0.4 that increased to 0.5 at Week 8 after which the value was stable at 0.5 through the end of the trial.



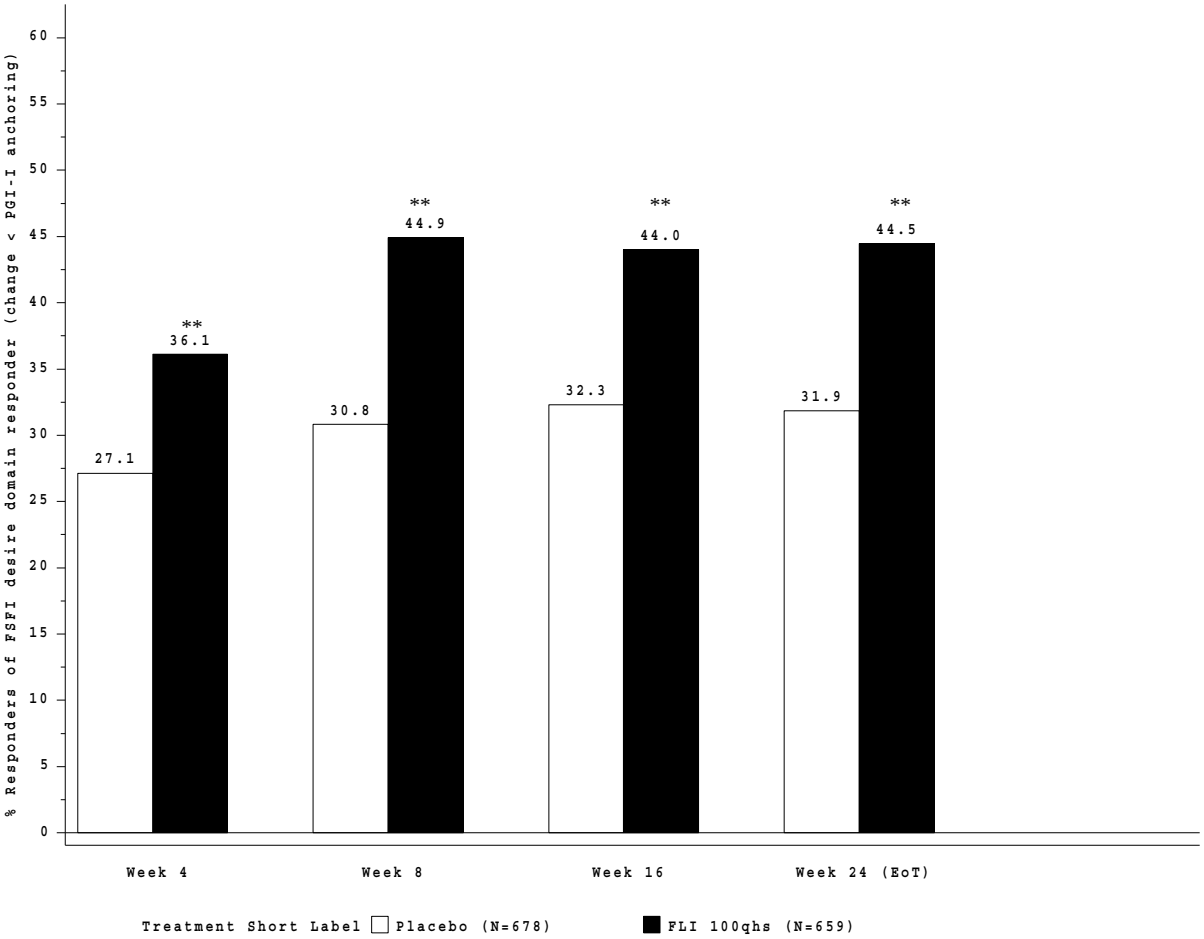
P-value based on ANCOVA model with main effect terms treatment and pooled center and using baseline as a covariate: * $p < 0.05$; ** $p < 0.01$

Note: Change from baseline Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 5 FSFI desire items change from baseline by treatment – Pooled (511.71, 511.75) (FAS, LOCF)

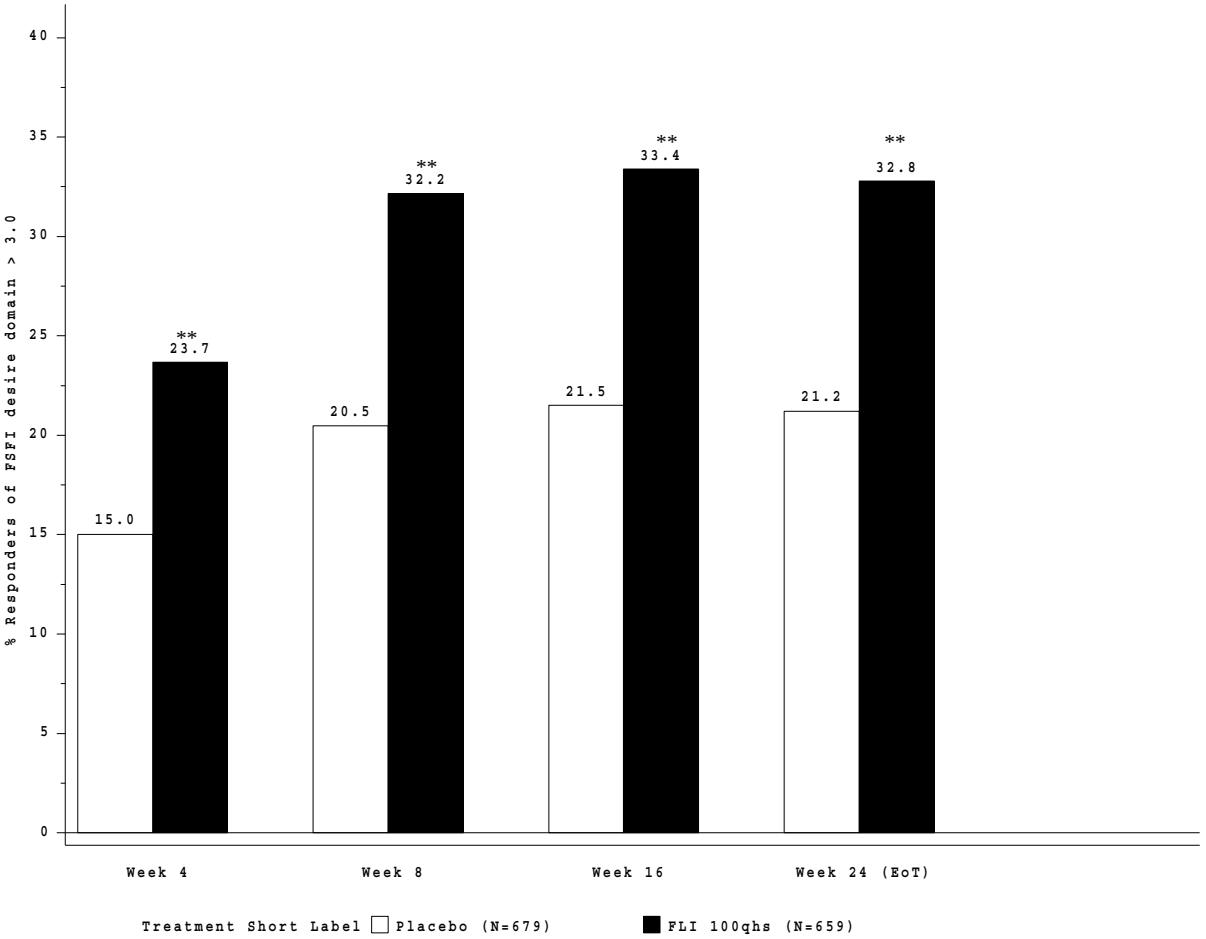
The FSFI desire items using the PGI-I anchor based criterion demonstrated the flibanserin 100 mg q.h.s. group showing statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 6). At Week 4, the flibanserin 100 mg q.h.s. group had 36.1% responders which increased to 44.9% at Week 8 after which the percent of responders was relatively stable through the end of the trial with 44.5% responders at Week 24. In comparison, at Week 4, the placebo group had 27.1% responders which increased to 30.8% at Week 8 after which the percent of responders was relatively stable through the end of the trial with 31.9% responders at Week 24.



P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre.
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 6 FSFI desire items responders – Pooled (511.71, 511.75) (FAS, LOCF)

For the FSFI desire items remitter endpoint (defined as a cut-off value of greater than 3.0), the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 7). At Week 4, the flibanserin 100 mg q.h.s. group had 23.7% responders which increased to 32.2% at Week 8 after which the percent of responders was relatively stable through the end of the trial with 32.8% responders at Week 24. In comparison, at Week 4, the placebo group had 15.0% responders which increased to 20.5% at Week 8 after which the percent of responders was relatively stable through the end of the trial with 21.2% responders at Week 24.

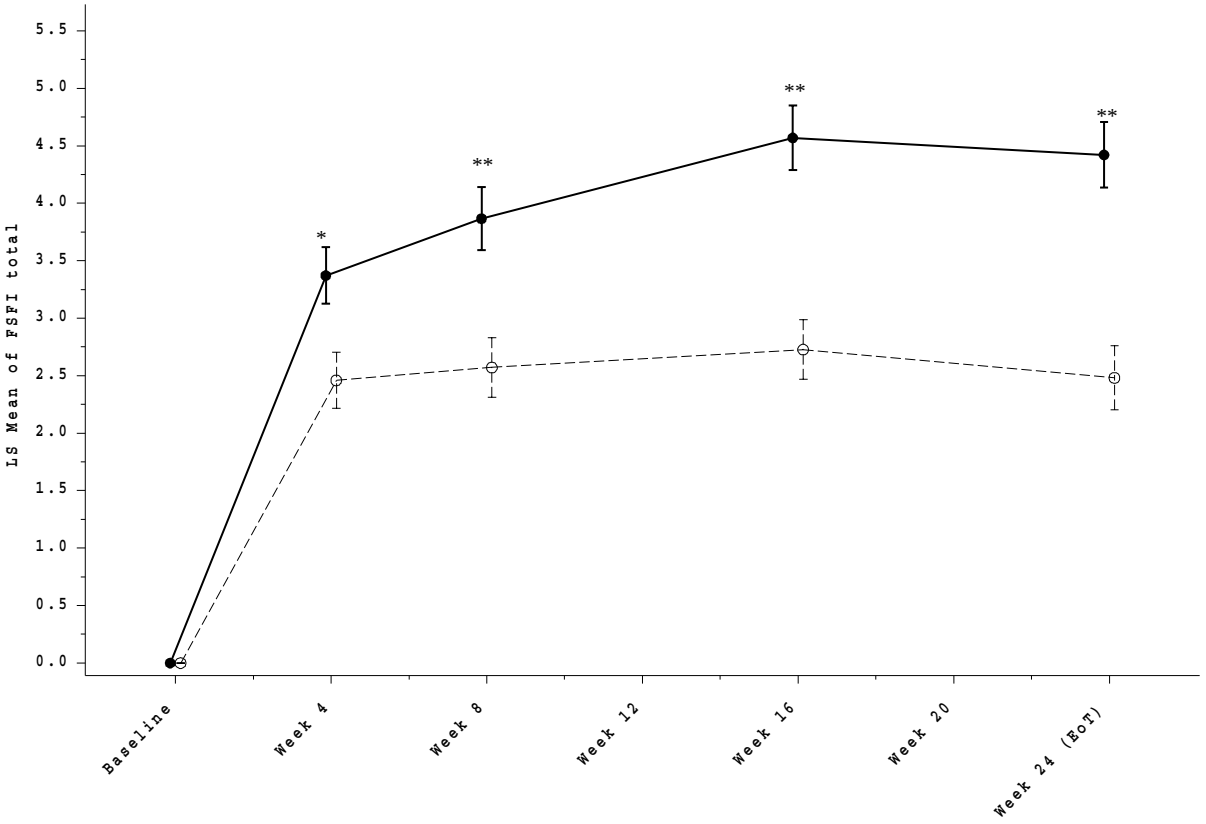


P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre.
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 7 FSFI desire items remitter (>3.0) – Pooled (511.71, 511.75) (FAS, LOCF)

FSFI total score

For the FSFI total score, the flibanserin 100 mg q.h.s. group began to show statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 8). At Week 4, the flibanserin 100 mg q.h.s. group had a mean FSFI total score change from baseline value of 3.4 which then increased to 3.9 at Week 8 and further increased to 4.6 and 4.4 at Weeks 16 and 24, respectively. In comparison, at Week 4, patients on placebo had a mean change from baseline value of 2.5 that increased to 2.6 at Week 8 after which the value was relatively stable with a value of 2.5 at the end of the trial.



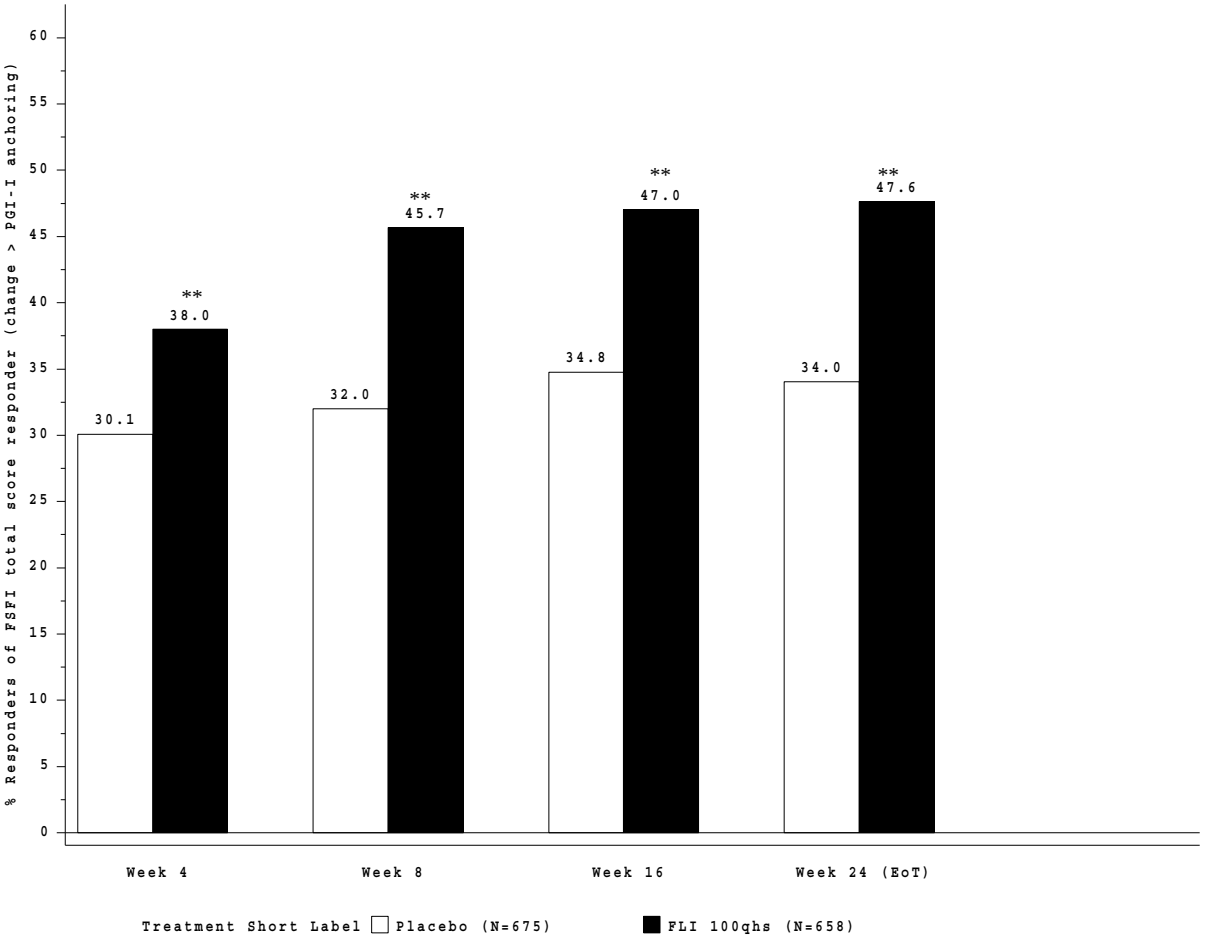
P-value based on ANCOVA model using baseline as a covariate with main effect terms treatment, study and pooled center nested in study
* p < 0.05; ** p < 0.01

Note: Change from baseline Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 8 FSFI total score change from baseline by treatment – Pooled (511.71, 511.75) (FAS, LOCF)

The FSFI total score responders using the PGI-I anchor based criterion demonstrated the flibanserin 100 mg q.h.s. group showing statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 9). At Week 4, the flibanserin 100 mg q.h.s. group had 38.0% responders which increased to 45.7% at Week 8 after which the percent of responders was relatively stable through the end of the trial with 47.6% responders at Week 24. In comparison, at Week 4, the placebo group had 30.1% responders which increased to 32.0% at Week 8 after which the percent of responders was relatively stable through the end of the trial with 34.0% responders at Week 24.

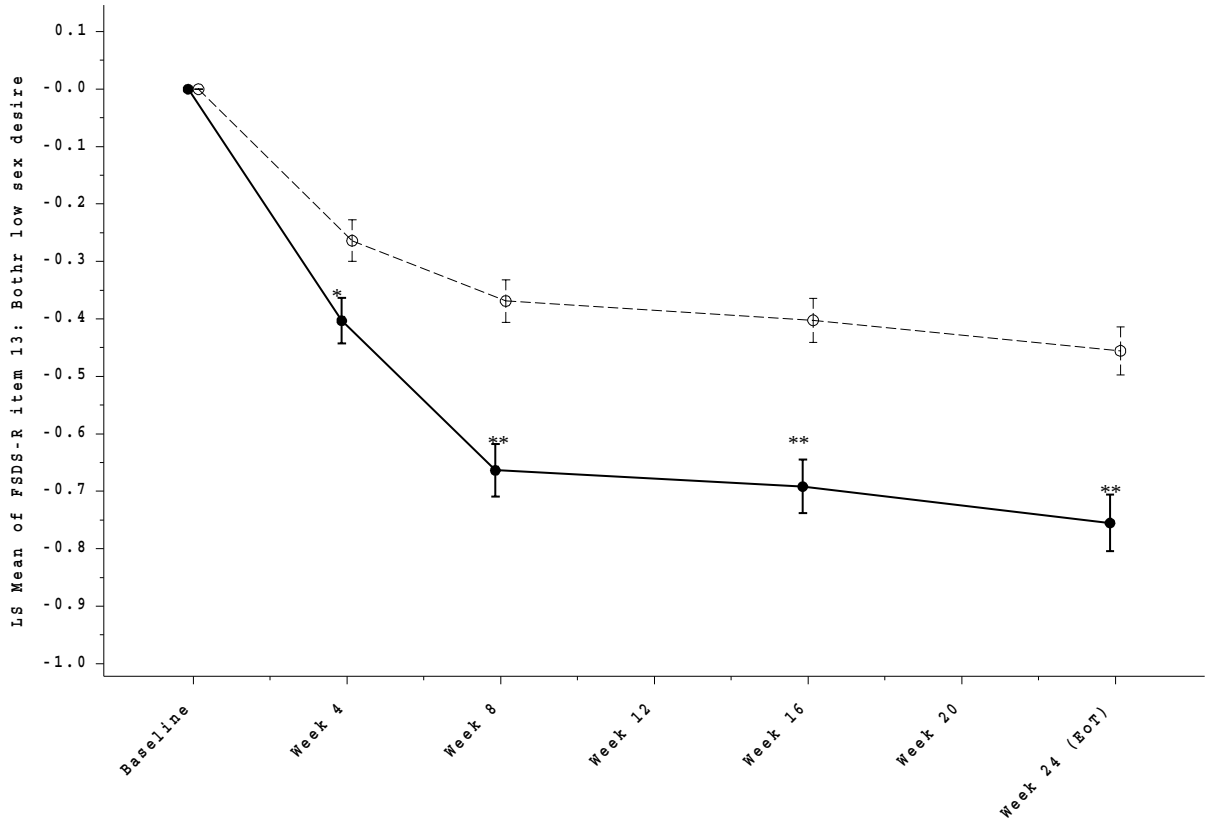


P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre.
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 9 FSFI total score responders – Pooled (511.71, 511.75) (FAS, LOCF)

FSDS-R Item 13

For the FSDS-R Item 13 analysis, the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 10). At Week 4, the flibanserin 100 mg q.h.s. group had a mean FSDS-R Item 13 change from baseline value of -0.4 which decreased to -0.8 at Week 24. In comparison, at Week 4, patients on placebo had a mean value of -0.3 that decreased to -0.5 at Week 24.



P-value based on ANCOVA model using baseline as a covariate with main effect terms treatment, study and pooled center nested in study. Lower values indicate improvement.

Placebo (N=679) FLI 100qhs (N=660)

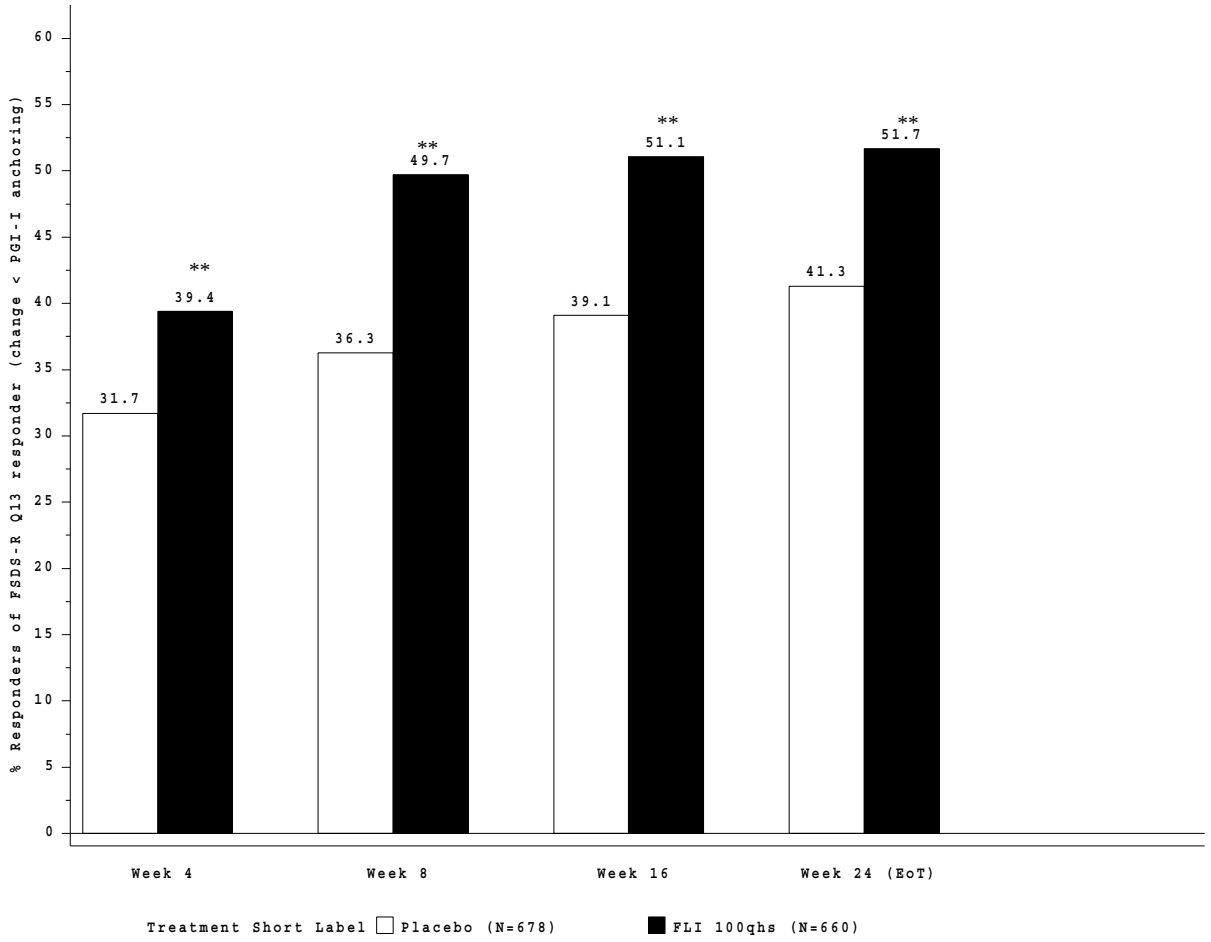
Note: Change from baseline Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 10 FSDS-R Item 13 change from baseline by treatment – Pooled (511.71, 511.75) (FAS, LOCF)

In the responder analyses of FSDS-R Item 13 using the PGI-I anchor based responder criterion, the flibanserin 100 mg q.h.s. group began to show statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 11). At Week 4, the flibanserin 100 mg q.h.s. group had 39.4% responders which increased to 49.7% at Week 8 and was relatively stable through the end of the trial

with 51.7% responders at Week 24. In comparison, at Week 4, there were 31.7% responders on placebo which increased to 41.3% at Week 24.

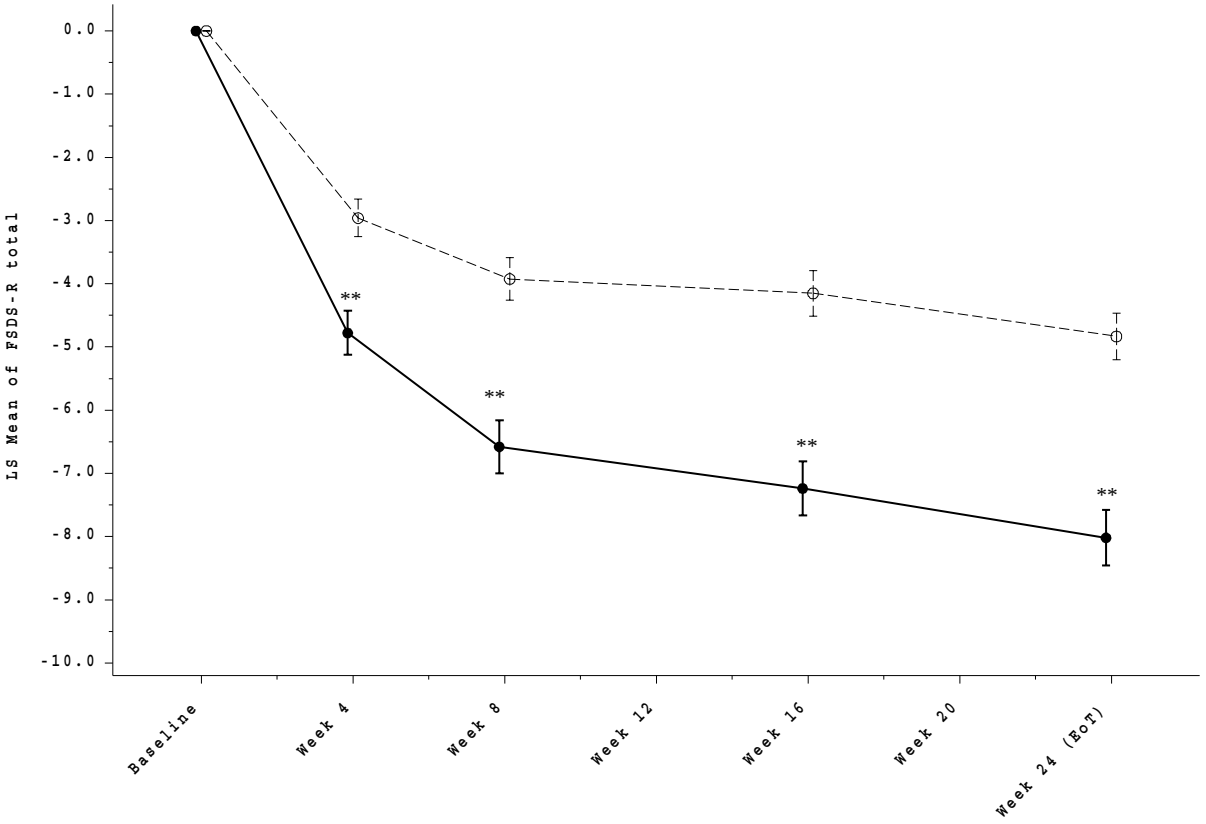


P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre.
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 11 FSDS-R Item 13 responders – Pooled (511.71, 511.75) (FAS, LOCF)

FSDS-R total score

For the FSDS-R total score, the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 12). At Week 4, the flibanserin 100 mg q.h.s. group had a mean change from baseline value of -4.8 which decreased to -8.0 at Week 24. In comparison, at Week 4, patients on placebo had a mean value of -3.0 that decreased to -4.8 at Week 24.



P-value based on ANCOVA model using baseline as a covariate with main effect terms treatment, study and pooled center nested in study. Lower values indicate improvement.

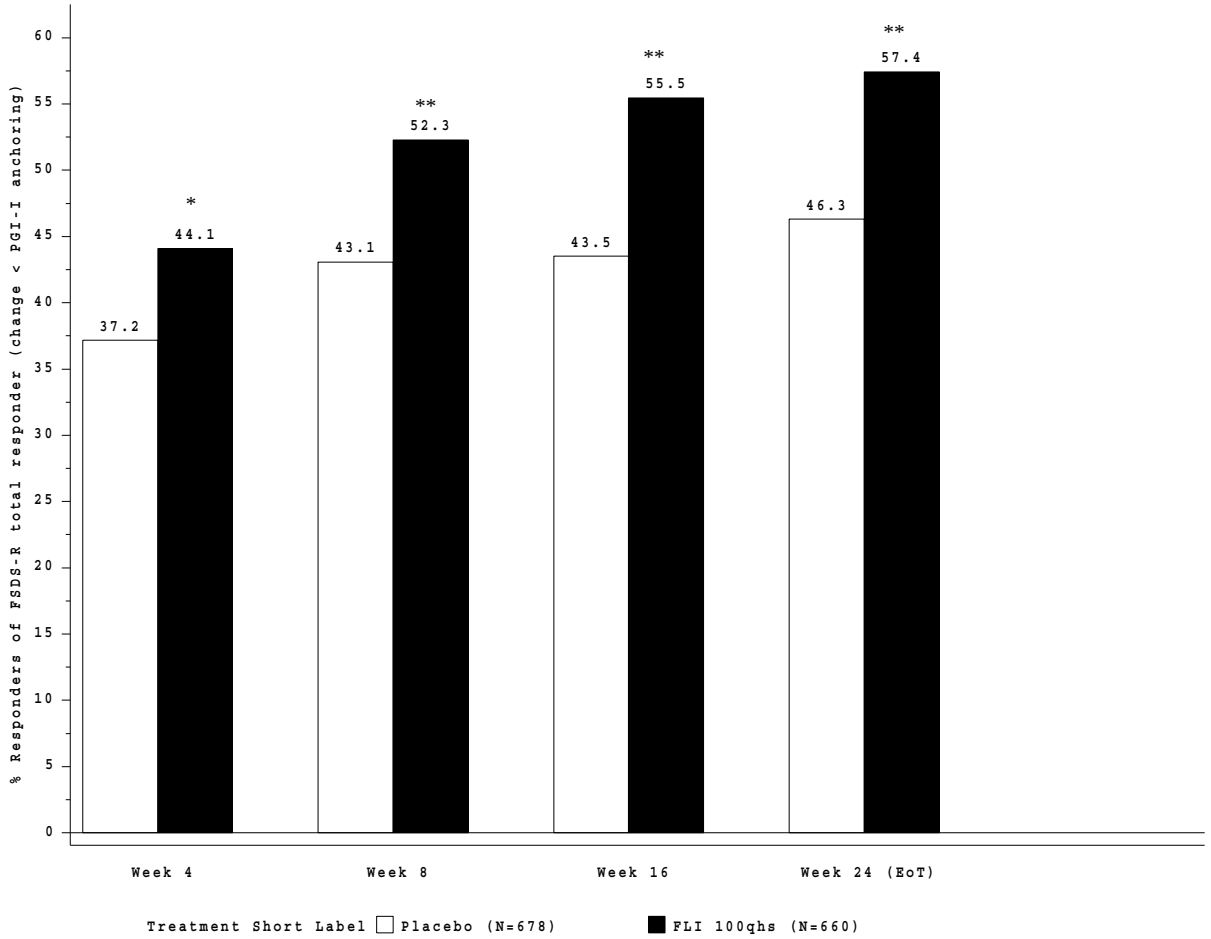
Placebo (N=679) FLI 100qhs (N=660)

Note: Change from baseline Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 12 FSDS-R total score change from baseline by treatment – Pooled (511.71, 511.75) (FAS, LOCF)

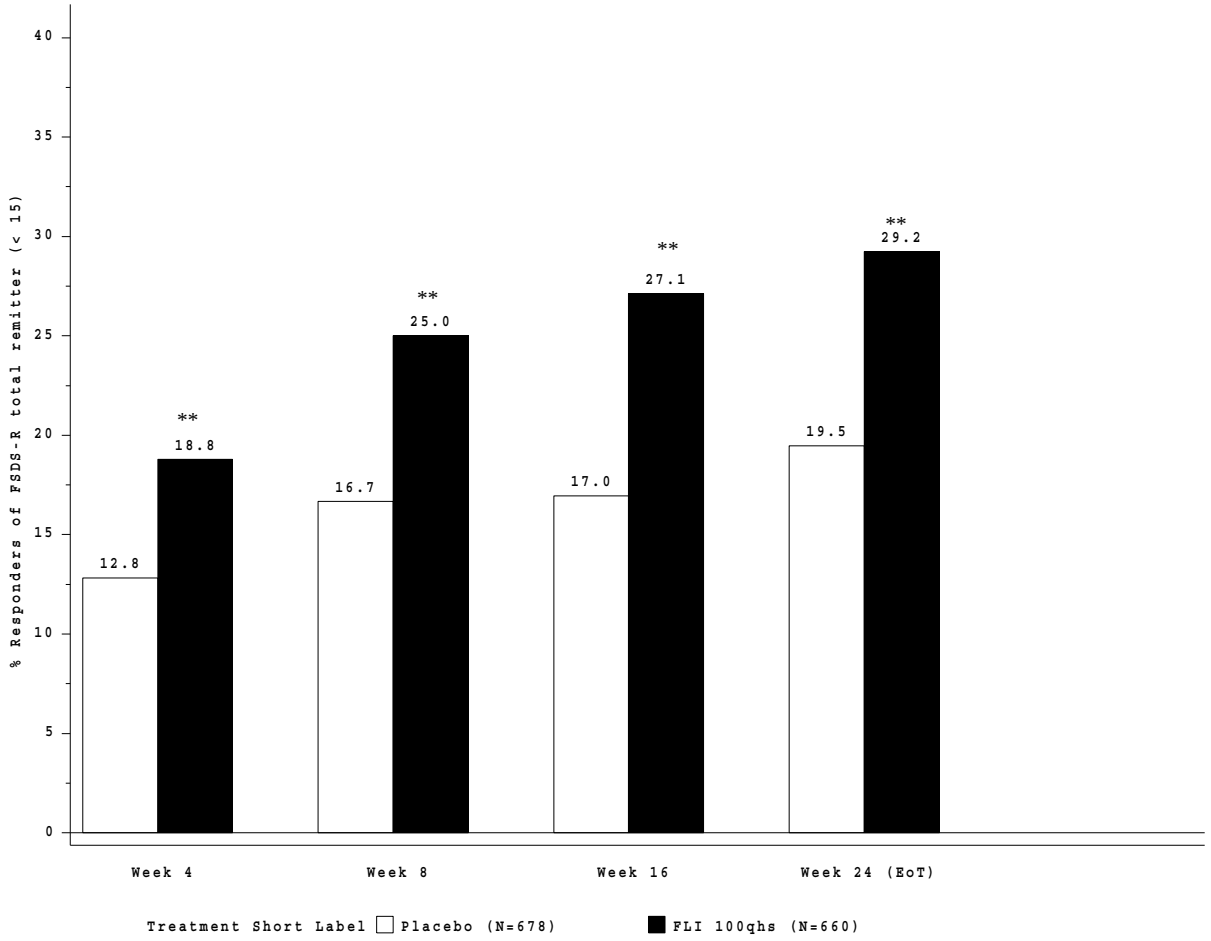
In the FSDS-R total score using the PGI-I anchor based responder criteria, the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 13). At Week 4, the flibanserin 100 mg q.h.s. group had 44.1% responders which increased to 57.4% at Week 24. In comparison, at Week 4, there were 37.2% responders on placebo which increased to 46.3% at Week 24.



P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre.
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 13 FSDS-R total responders – Pooled (511.71, 511.75) (FAS, LOCF)

In the FSDS-R total score remitter (less than 15), the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 14). At Week 4, the flibanserin 100 mg q.h.s. group had 18.8% responders which increased to 29.2% at Week 24. In comparison, at Week 4, there were 12.8% responders on placebo which increased to 19.5% at Week 24.

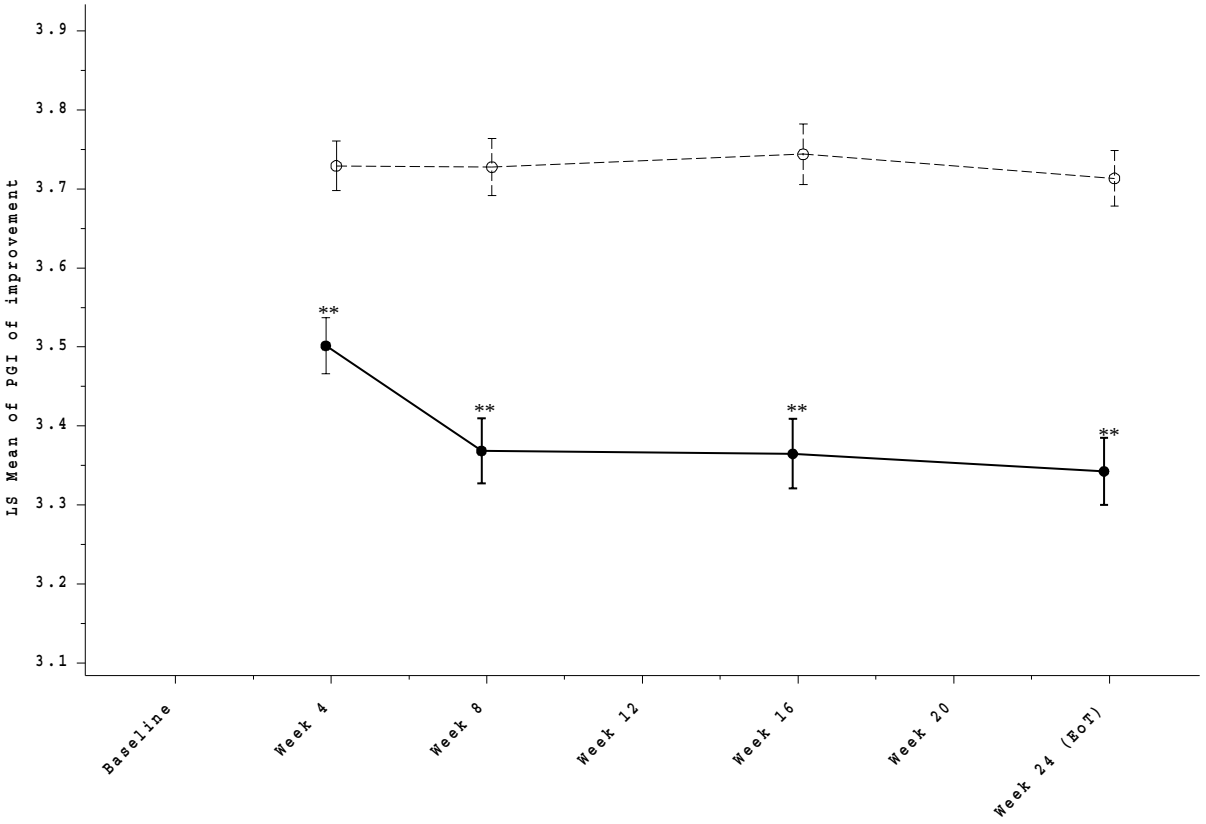


P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled .
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 14 FSDS-R total score remitters (less than 15) – Pooled (511.71, 511.75) (FAS, LOCF)

PGI-I

For the PGI of Improvement, the flibanserin 100 mg q.h.s. group showed statistical separation from placebo starting at Week 4 which was maintained until the end of the trial (Figure 7.1.2.2: 15). At Week 4, the flibanserin 100 mg q.h.s. group had a mean value of 3.5 which decreased to 3.3 at Week 24. In comparison, at Week 4, patients on placebo had a mean value of 3.7 which remained stable at 3.7 through Week 24.



P-value based on ANCOVA model with main effect terms treatment, study and pooled center nested in study. PGI-I is an endpoint with regards to improvement; therefore, this endpoint is not collected at baseline. Lower values indicate improvement.

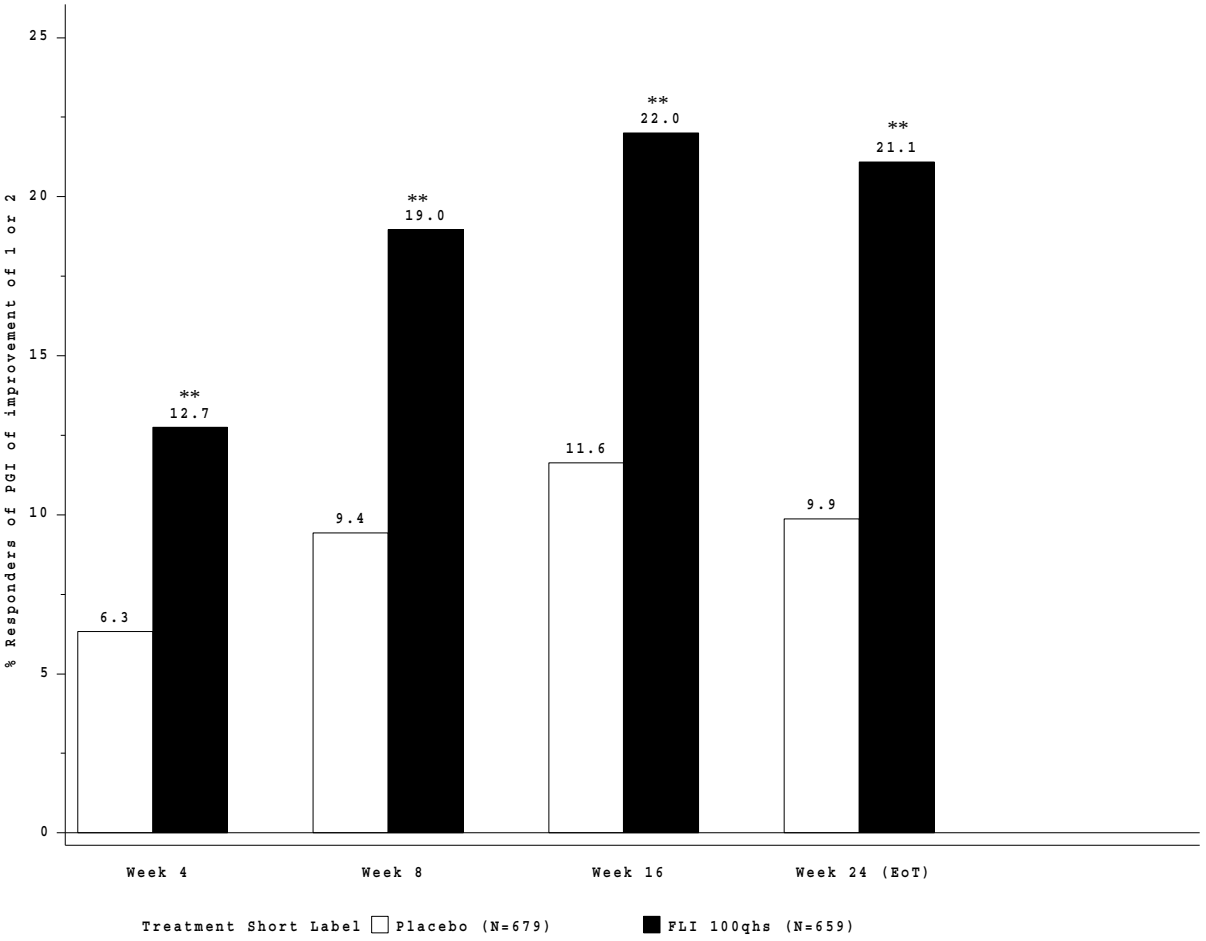
Placebo (N=679) FLI 100qhs (N=660)

Note: Mean (Standard Error) are presented

Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 15 PGI-I by visit – Pooled (511.71, 511.75) (FAS, LOCF)

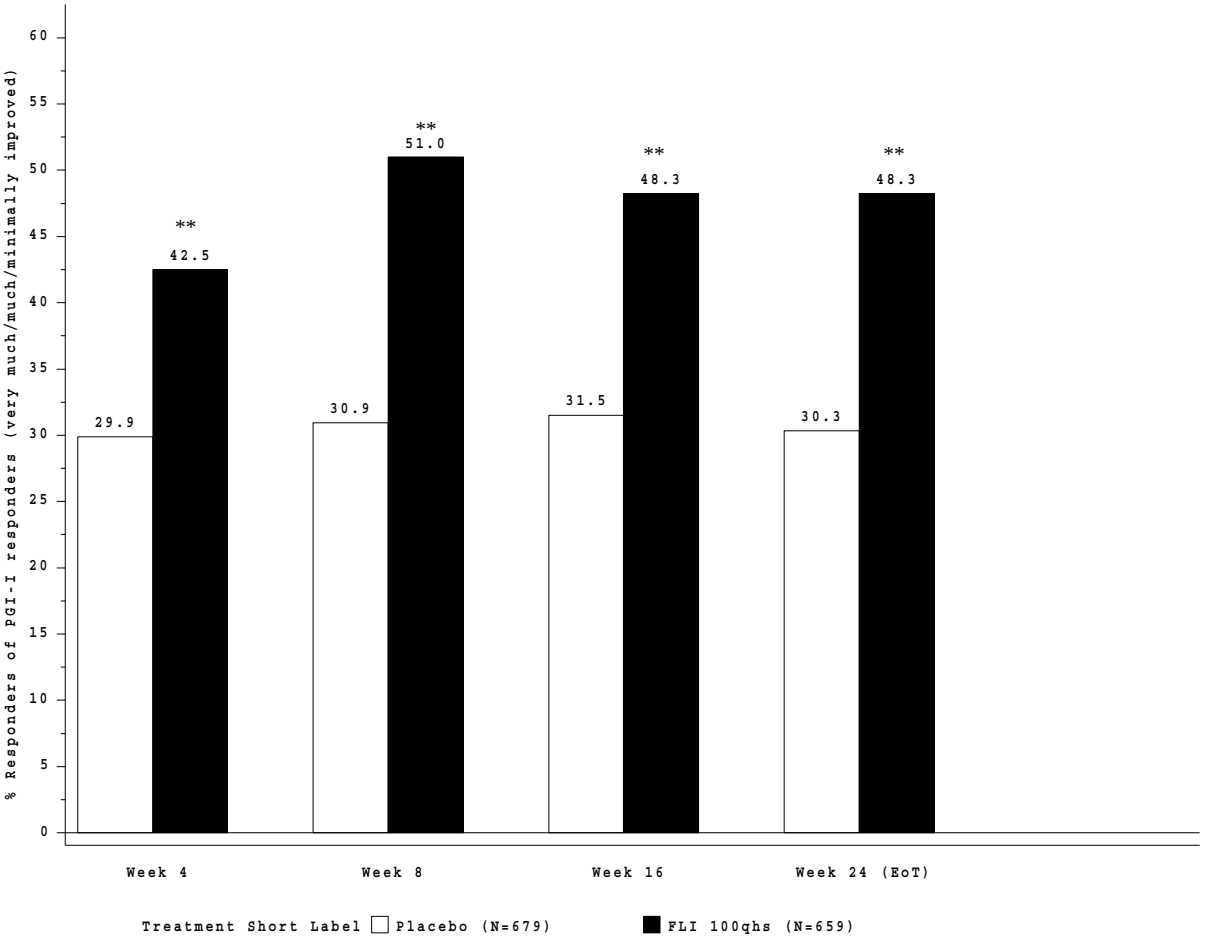
In examining the responder analyses of the PGI-I responder endpoint of 1 or 2 (“very much” or “much improved”), the flibanserin 100 mg q.h.s. group showed statistical separation from placebo at Week 4 which was maintained until Week 24 (Figure 7.1.2.2: 16). At Week 4, the flibanserin 100 mg q.h.s. group had 12.7% responders which increased to 21.1% at Week 24. In comparison, at Week 4, there were 6.3% responders on placebo which increased to 9.9% at Week 24.



P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 16 PGI-I responders of 1 or 2 (“very much” or “much improved”) – Pooled (511.71, 511.75) (FAS, LOCF)

In examining the responder analyses of the PGI-I responder endpoint of 1, 2 or 3 (“very much”, “much improved” or “minimally improved”), the flibanserin 100 mg q.h.s. group showed statistical separation from placebo at Week 4 which was maintained until Week 24 (Figure 7.1.2.2: 17). At Week 4, the flibanserin 100 mg q.h.s. group had 42.5% responders which increased to 48.3% at Week 24. In comparison, at Week 4, there were 29.9% responders on placebo which remained stable through the end of the trial with 30.3% responders at Week 24.



P-value based on comparison vs placebo using Cochran-Mantel-Haenszel stratified by pooled centre
Adjusted p-values: * < 0.05; ** < 0.01

Figure 7.1.2.2: 17 PGI-I responders of 1, 2 or 3 (very much/much/minimally improved) – Pooled (511.71, 511.75) (FAS, LOCF)

Table 7.1.2.2: 1 Responder analysis using additional cutoff thresholds – Trials 511.71, 511.75 and pooled (FAS, LOCF)

				>=1			>=2			>=3			>=4		
			Total	N	%	Adjusted P-value	N	%	Adjusted P-value	N	%	Adjusted P-value	N	%	Adjusted P-value
SSE	511.71	Placebo	285	120	42.1		83	29.1		56	19.6		34	11.9	
		FLI 100qhs	275	157	57.1	0.0008	113	41.1	0.0062	73	26.5	0.1411	46	16.7	0.2868
	511.75	Placebo	381	180	47.2		119	31.2		82	21.5		57	15	
		FLI 100qhs	371	202	54.4	0.1451	150	40.4	0.0318	106	28.6	0.1482	81	21.8	0.0900
	511.71/75	Placebo	666	300	45.0		202	30.3		138	20.7		91	13.7	
		FLI 100qhs	646	359	55.6	0.0004	263	40.7	0.0003	179	27.7	0.0229	127	19.7	0.0271
				> 8			> 10			> 12			> 14		
eDiary desire score	511.71	Placebo	285	102	35.8		89	31.2		75	26.3		69	24.2	
		FLI 100qhs	275	113	41.1	0.3866	99	36.0	0.3548	88	32.0	0.2018	75	27.3	0.6351
	511.75	Placebo	381	120	31.5		112	29.4		105	27.6		97	25.5	
		FLI 100qhs	371	140	37.7	0.1570	128	34.5	0.3757	118	31.8	0.5425	106	28.6	1.0000
	511.71/75	Placebo	666	222	33.3		201	30.2		180	27.0		166	24.9	
		FLI 100qhs	646	253	39.2	0.0618	227	35.1	0.1234	206	31.9	0.1113	181	28.0	0.5087
				< -5			< -8			< -11			< -14		
FSDS-R total	511.71	Placebo	289	127	43.9		94	32.5		75	26		46	15.9	
		FLI 100qhs	280	156	55.7	0.0128	127	45.4	0.0035	106	37.9	0.0051	86	30.7	<0.0001
	511.75	Placebo	389	159	40.9		117	30.1		83	21.3		57	14.7	
		FLI 100qhs	380	198	52.1	0.0030	155	40.8	0.0057	117	30.8	0.0076	81	21.3	0.0353
	511.71/75	Placebo	678	286	42.2		211	31.1		158	23.3		103	15.2	
		FLI 100qhs	660	354	53.6	<0.0001	282	42.7	<0.0001	223	33.8	<0.0001	167	25.3	<0.0001
				<= -1			<= -2			<= -3					
FSDS-R item 13	511.71	Placebo	289	124	42.9		41	14.2		16	5.5				
		FLI 100qhs	280	153	54.6	0.0098	77	27.5	0.0003	34	12.1	0.0134			
	511.75	Placebo	389	156	40.1		57	14.7		19	4.9				
		FLI 100qhs	380	188	49.5	0.0399	81	21.3	0.0489	42	11.1	0.0054			
	511.71/75	Placebo	678	280	41.3		98	14.5		35	5.2				
		FLI 100qhs	660	341	51.7	0.0006	158	23.9	<0.0001	76	11.5	<0.0001			
				>= 0.6			>= 1.2			>= 1.8			>= 2.4		

Table 7.1.2.2: 1 (continued) Responder analysis using additional cutoff thresholds – Trials 511.71, 511.75 and pooled (FAS, LOCF) (Page 2 of 2)

FSFI desire	511.71	Placebo	290	117	40.3		89	30.7		45	15.5		27	-9.3	
		FLI 100qhs	280	155	55.4	0.0013	119	42.5	0.0086	76	27.1	0.0012	44	15.7	0.0322
	511.75	Placebo	388	157	40.5		127	32.7		57	14.7		33	-8.5	
		FLI 100qhs	379	206	54.4	0.0002	173	45.6	0.0005	93	24.5	0.0017	61	16.1	0.0040
	511.71/75	Placebo	678	274	40.4		216	31.9		102	15.0		60	-8.8	
		FLI 100qhs	659	361	54.8	<0.0001	292	44.3	<0.0001	169	25.6	<0.0001	105	15.9	0.0002
				>= 4			>= 6			>= 8			>= 10		
FSFI total	511.71	Placebo	289	100	34.6		67	23.2		46	15.9		37	12.8	
		FLI 100qhs	280	142	50.7	0.0005	108	38.6	0.0002	76	27.1	0.0016	57	20.4	0.0172
	511.75	Placebo	387	135	34.9		95	24.5		65	16.8		48	12.4	
		FLI 100qhs	379	180	47.5	0.0009	134	35.4	0.0031	101	26.6	0.0024	64	16.9	0.2358
	511.71/75	Placebo	676	235	34.8		162	24.0		111	16.4		85	12.6	
		FLI 100qhs	659	322	48.9	<0.0001	242	36.7	<0.0001	177	26.9	<0.0001	121	18.4	0.0066

7.1.2.3 LOCF evaluation

Table 7.1.2.3: 1 Evaluation of data being carried forward via LOCF – Trials 511.71 and 511.75 (FAS)

			511.71				511.75			
			Dropped out		Stayed in		Dropped out		Stayed in	
			N	Mean	N	Mean	N	Mean	N	Mean
Week 4	Placebo	SSE	19	3.2	266	3.4	37	3.9	344	3.5
		eDiary sexual desire score	19	11.0	266	16.0	37	17.9	344	13.7
		FSDS-R total	20	26.8	269	27.0	35	24.5	354	27.5
		FSFI desire items	21	2.4	269	2.3	35	2.4	354	2.2
	FLI 100 q.h.s.	SSE	26	4.3	248	4.2	45	2.7	328	3.8
		eDiary sexual desire score	26	21.1	248	18.4	45	12.5	328	16.7
		FSDS-R total	26	22.7	254	25.2	39	29.8	341	25.8
		FSFI desire items	26	2.5	254	2.6	38	2.1	341	2.4
Week 8	Placebo	SSE	15	3.7	251	3.4	22	4.0	322	3.7
		eDiary sexual desire score	15	20.2	251	17.0	22	16.0	322	15.8
		FSDS-R total	18	23.1	251	26.3	31	26.3	323	26.3
		FSFI desire items	18	2.9	251	2.5	31	2.2	323	2.3
	FLI 100 q.h.s.	SSE	20	3.6	228	5.0	27	3.3	299	4.4
		eDiary sexual desire score	20	16.9	228	22.0	27	15.3	299	19.6
		FSDS-R total	25	21.8	229	22.9	39	27.4	302	23.5
		FSFI desire items	25	2.5	229	2.7	39	2.7	302	2.7
Week 12	Placebo	SSE	10	5.7	237	3.7	14	5.9	305	3.9
		eDiary sexual desire score	10	24.5	237	17.4	14	18.9	305	16.3
	FLI 100 q.h.s.	SSE	9	2.1	212	4.7	18	4.7	281	4.6
		eDiary sexual desire score	9	16.9	212	21.1	18	18.5	281	21.3

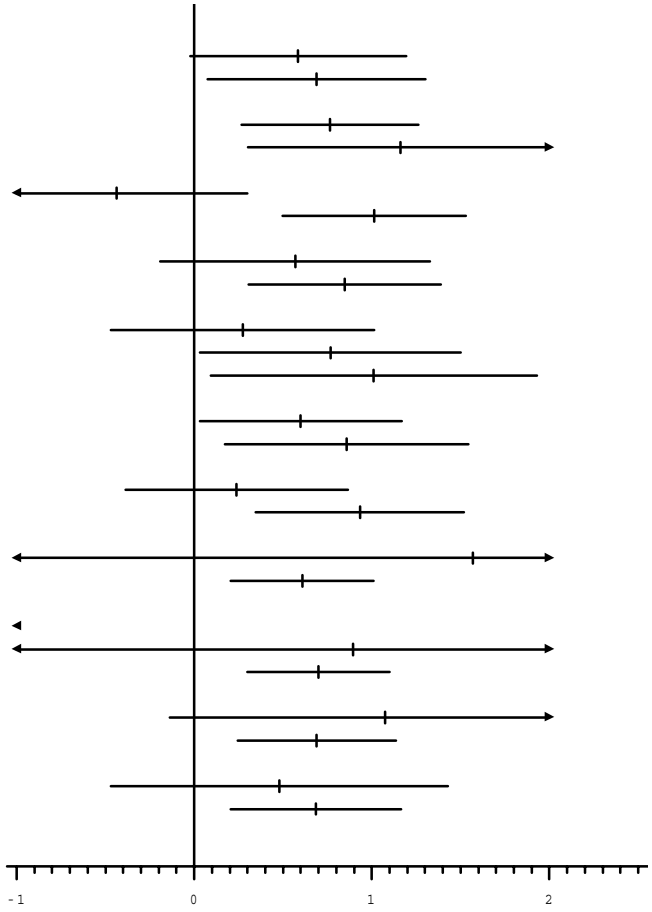
Table 7.1.2.3: 1 (continued) Evaluation of data being carried forward via LOCF – Trials 511.71 and 511.75 (FAS) (Page 2 of 2)

			511.71				511.75			
			Dropped out		Stayed in		Dropped out		Stayed in	
			N	Mean	N	Mean	N	Mean	N	Mean
Week 16	Placebo	SSE	8	4.1	228	3.7	23	4.1	283	3.7
		eDiary sexual desire score	8	21.7	228	17.2	23	16.9	283	16.5
		FSDS-R total	16	29.2	235	25.6	33	26.9	290	26.0
		FSFI desire items	15	2.4	236	2.4	33	2.6	290	2.3
	FLI 100 q.h.s.	SSE	14	3.3	200	4.6	19	5.2	259	4.8
		eDiary sexual desire score	14	24.8	200	21.0	19	19.2	259	21.5
		FSDS-R total	21	23.1	208	22.6	41	25.9	261	21.5
		FSFI desire items	21	3.0	208	2.7	41	2.7	261	2.8
Week 20	Placebo	SSE	15	3.1	210	3.4	8	3.0	275	3.7
		eDiary sexual desire score	15	16.7	210	18.4	8	22.7	275	16.7
	FLI 100 q.h.s.	SSE	10	3.9	186	4.8	18	6.6	241	4.5
		eDiary sexual desire score	10	15.5	186	21.5	18	26.5	241	21.0

NOTE: For non-eDiary endpoints, data are collected only at clinic visits at Weeks 4, 8, 16, and 24 (Week 24 data are not displayed in this table since this table displays results of data being carried forward due to premature discontinuation).

7.1.2.4 Sub-population analyses

Endpoint	Int p-value	Subgroup	Level	N	Mean diff (95% CI)
SSE	0.9339	Base FSDS-R total (>30)	Yes	337	0.6 (-0.0, 1.2)
			No	309	0.7 (0.1, 1.3)
	0.9281	Base FSFI desire (>1.8)	No	402	0.8 (0.3, 1.3)
			Yes	244	1.2 (0.3, 2.0)
	0.0091	Baseline DHEAS (>= 60)	No	182	-0.4 (-1.2, 0.3)
			Yes	460	1.0 (0.5, 1.5)
	0.7638	Baseline Free-T (>=1.1)	No	218	0.6 (-0.2, 1.3)
			Yes	418	0.8 (0.3, 1.4)
	0.8363	Baseline SHBG	>= 150.0	203	0.3 (-0.5, 1.0)
			80.0 - < 150.0	230	0.8 (0.0, 1.5)
			< 80	209	1.0 (0.1, 1.9)
	0.5195	Baseline SSE(>2)	No	359	0.6 (0.0, 1.2)
			Yes	287	0.9 (0.2, 1.5)
	0.1674	HC use	Yes	266	0.2 (-0.4, 0.9)
			No	380	0.9 (0.3, 1.5)
	0.0333	Is the patient Hispanic?	Yes	42	1.6 (-2.7, 5.8)
			No	603	0.6 (0.2, 1.0)
	0.4353	Race	Asian	13	-3.0
			Black	54	0.9 (-1.8, 3.6)
			White	579	0.7 (0.3, 1.1)
	0.9036	Secondary FOD	Yes	104	1.1 (-0.1, 2.3)
			No	531	0.7 (0.2, 1.1)
	0.9851	Secondary FSAD	Yes	166	0.5 (-0.5, 1.4)
			No	469	0.7 (0.2, 1.2)



Note: For the purposes of these analyses, SSE and SSE (count) were analyzed using ANCOVA to calculate the LS Means and 95% confidence intervals.

Figure 7.1.2.4: 1 Subgroup analysis for SSE – Pooled (511.71, 511.75) (FAS, LOCF)

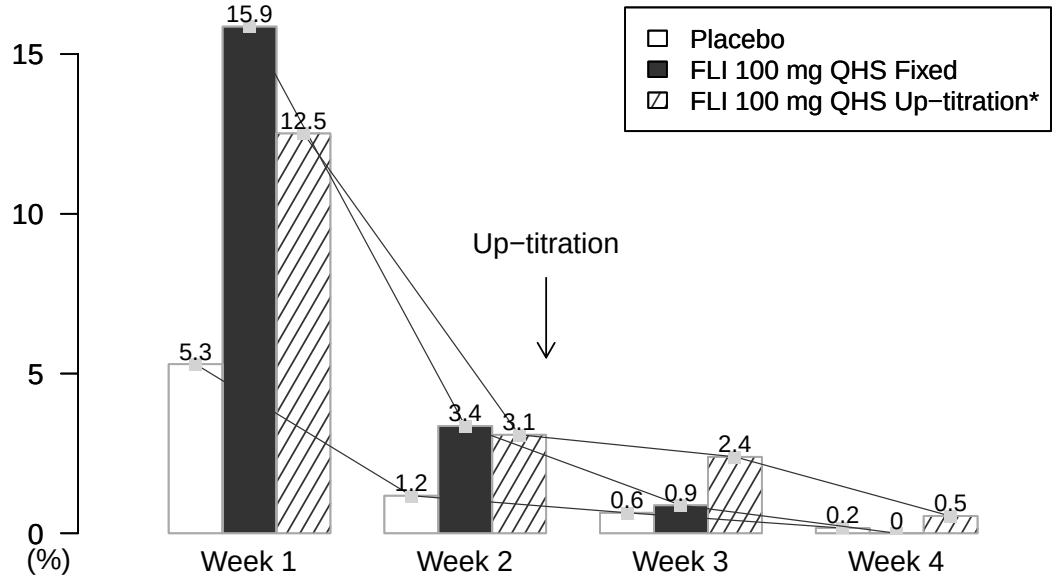
7.2 SAFETY DISPLAYS

7.2.1 Summary of patients in Phase I and dose selection in Phase III

Table 7.2.1: 1 Phase I clinical trials with flibanserin

Female Subjects with HSDD		Male and Female Subjects with MDD			
511.105	N = 67	511.5	N = 43		
Healthy Female Subjects		Healthy Male Subjects		Healthy Male and Female Subjects	
511.86	511.11	511.19	511.33	511.37	511.87
511.88	511.93	511.1	511.14	511.108	511.2
511.97	511.117	511.9	511.3	511.90	511.110
		511.26	511.17	511.103	511.115
		511.15			
Total Healthy Male and Female Subjects treated with flibanserin = 629					
Healthy & Hepatically Impaired Male and Female Subjects		Healthy & Renally Impaired Male and Female Subjects			
511.67	N = 28	511.96	N = 36		

7.2.2 Adverse events



* The up−titration treatment regimen reflects 50 mg QHS for the first two weeks after which subjects uptitrate to 100 mg QHS.

Figure 7.2.2: 1 Rate of first onset of somnolence, fatigue, or sedation by fixed versus up-titration (flibanserin 100 mg q.h.s.) - Placebo-controlled trials 511.71, 511.75 and 511.77

Table 7.2.2: 1 Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1% by treatment, primary system organ class and preferred term - Phase III open-label, uncontrolled extension HSDD trials

System organ class Preferred term	Flibanserin N (%)
Number of subjects	2203 (100.0)
Total with adverse events	1617 (73.4)
Infections and infestations	758 (34.4)
Nasopharyngitis	176 (8.0)
Upper respiratory tract infection	131 (5.9)
Sinusitis	101 (4.6)
Urinary tract infection	90 (4.1)
Influenza	87 (3.9)
Bronchitis	53 (2.4)
Gastroenteritis viral	35 (1.6)
Pharyngitis streptococcal	34 (1.5)
Vulvovaginal mycotic infection	31 (1.4)
Cystitis	21 (1.0)
Gastritis	21 (1.0)
Psychiatric disorders	331 (15.0)
Insomnia	97 (4.4)
Depression	46 (2.1)
Anxiety	39 (1.8)
Abnormal dreams	38 (1.7)
Sleep disorder	25 (1.1)
Nervous system disorders	651 (29.6)
Somnolence	302 (13.7)
Headache	164 (7.4)
Dizziness	159 (7.2)
Migraine	30 (1.4)
Sedation	29 (1.3)
Ear and labyrinth disorders	38 (1.7)
Vertigo	26 (1.2)
Respiratory, thoracic and mediastinal disorders	135 (6.1)
Cough	36 (1.6)
Oropharyngeal pain	26 (1.2)
Nasal congestion	23 (1.0)
Sinus congestion	23 (1.0)

Table 7.2.2: 1 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1% by treatment, primary system organ class and preferred term - Phase III open-label, uncontrolled extension HSDD trials (Page 2 of 2)

System organ class Preferred term	Flibanserin N (%)
Gastrointestinal disorders	348 (15.8)
Nausea	150 (6.8)
Diarrhoea	36 (1.6)
Vomiting	34 (1.5)
Dry mouth	26 (1.2)
Skin and subcutaneous tissue disorders	156 (7.1)
Rash	31 (1.4)
Acne	22 (1.0)
Musculoskeletal and connective tissue disorders	190 (8.6)
Back pain	48 (2.2)
Musculoskeletal pain	23 (1.0)
Arthralgia	22 (1.0)
Reproductive system and breast disorders	282 (12.8)
Menorrhagia	62 (2.8)
Metrorrhagia	38 (1.7)
Dysmenorrhoea	27 (1.2)
General disorders and administration site conditions	325 (14.8)
Fatigue	200 (9.1)
Irritability	43 (2.0)
Pyrexia	21 (1.0)

Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 12.1.
Includes all data from Trials 511.84 and .118 in the project database as of 17 Nov 2009.

Table 7.2.2: 2 Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1% by treatment, primary system organ class and preferred term - Phase III open-label, uncontrolled extension HSDD trials

System organ classa Preferred term	FLI 25 bid N (%)	FLI 50 qhs N (%)	FLI 50 bid N (%)	FLI 100 qhs N (%)
Number of subjects	57 (100.0)	2197 (100.0)	305 (100.0)	1791 (100.0)
Total with adverse events	27 (47.4)	1001 (45.6)	163 (53.4)	1098 (61.3)
Infections and infestations	15 (26.3)	324 (14.7)	46 (15.1)	473 (26.4)
Upper respiratory tract infection	4 (7.0)	49 (2.2)	7 (2.3)	75 (4.2)
Nasopharyngitis	3 (5.3)	78 (3.6)	7 (2.3)	96 (5.4)
Influenza	2 (3.5)	29 (1.3)	5 (1.6)	52 (2.9)
Sinusitis	2 (3.5)	39 (1.8)	7 (2.3)	56 (3.1)
Urinary tract infection	2 (3.5)	28 (1.3)	5 (1.6)	58 (3.2)
Bronchitis	1 (1.8)	13 (0.6)	3 (1.0)	36 (2.0)
Cystitis	1 (1.8)	6 (0.3)	3 (1.0)	11 (0.6)
Gastroenteritis viral	1 (1.8)	12 (0.5)	1 (0.3)	21 (1.2)
Viral upper respiratory tract infection	1 (1.8)	0 (0.0)	1 (0.3)	4 (0.2)
Pharyngitis streptococcal	0 (0.0)	8 (0.4)	1 (0.3)	26 (1.5)
Vulvovaginal mycotic infection	0 (0.0)	7 (0.3)	3 (1.0)	22 (1.2)
Vulvovaginal candidiasis	0 (0.0)	7 (0.3)	3 (1.0)	7 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.8)	11 (0.5)	2 (0.7)	13 (0.7)
Breast cancer in situ	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	1 (1.8)	8 (0.4)	0 (0.0)	12 (0.7)
Anaemia	1 (1.8)	2 (0.1)	0 (0.0)	10 (0.6)
Immune system disorders	1 (1.8)	5 (0.2)	4 (1.3)	19 (1.1)
Seasonal allergy	1 (1.8)	1 (0.0)	2 (0.7)	7 (0.4)
Psychiatric disorders	5 (8.8)	157 (7.1)	14 (4.6)	183 (10.2)
Anxiety	3 (5.3)	18 (0.8)	0 (0.0)	19 (1.1)
Insomnia	0 (0.0)	49 (2.2)	3 (1.0)	49 (2.7)
Abnormal dreams	1 (1.8)	26 (1.2)	1 (0.3)	12 (0.7)
Stress	1 (1.8)	2 (0.1)	1 (0.3)	14 (0.8)
Depression	0 (0.0)	16 (0.7)	3 (1.0)	28 (1.6)
Sleep disorder	0 (0.0)	12 (0.5)	3 (1.0)	13 (0.7)

Table 7.2.2: 2 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term - Phase III open-label, uncontrolled extension HSDD trials (Page 2 of 3)

System organ classa Preferred term	FLI 25 bid N (%)	FLI 50 qhs N (%)	FLI 50 bid N (%)	FLI 100 qhs N (%)
Nervous system disorders	4 (7.0)	361 (16.4)	77 (25.2)	320 (17.9)
Somnolence	3 (5.3)	170 (7.7)	42 (13.8)	113 (6.3)
Dizziness	1 (1.8)	64 (2.9)	18 (5.9)	87 (4.9)
Headache	1 (1.8)	99 (4.5)	7 (2.3)	74 (4.1)
Dysgeusia	1 (1.8)	3 (0.1)	0 (0.0)	0 (0.0)
Sedation	0 (0.0)	16 (0.7)	4 (1.3)	11 (0.6)
Migraine	0 (0.0)	15 (0.7)	0 (0.0)	19 (1.1)
Ear and labyrinth disorders	0 (0.0)	13 (0.6)	3 (1.0)	24 (1.3)
Vertigo	0 (0.0)	9 (0.4)	3 (1.0)	16 (0.9)
Respiratory, thoracic and mediastinal disorders	3 (5.3)	55 (2.5)	8 (2.6)	75 (4.2)
Cough	1 (1.8)	19 (0.9)	1 (0.3)	17 (0.9)
Oropharyngeal pain	1 (1.8)	9 (0.4)	2 (0.7)	14 (0.8)
Rhinitis seasonal	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (7.0)	163 (7.4)	21 (6.9)	188 (10.5)
Nausea	1 (1.8)	77 (3.5)	10 (3.3)	75 (4.2)
Diarrhoea	1 (1.8)	13 (0.6)	4 (1.3)	18 (1.0)
Tooth impacted	1 (1.8)	1 (0.0)	0 (0.0)	2 (0.1)
Vomiting	1 (1.8)	9 (0.4)	2 (0.7)	23 (1.3)
Skin and subcutaneous tissue	2 (3.5)	74 (3.4)	11 (3.6)	80 (4.5)
Cutaneous lupus erythematosus	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	1 (1.8)	13 (0.6)	2 (0.7)	16 (0.9)
Musculoskeletal and connective tissue disorders	2 (3.5)	76 (3.5)	9 (3.0)	110 (6.1)
Back pain	0 (0.0)	17 (0.8)	1 (0.3)	32 (1.8)
Muscle twitching	1 (1.8)	0 (0.0)	0 (0.0)	2 (0.1)
Musculoskeletal discomfort	1 (1.8)	0 (0.0)	0 (0.0)	2 (0.1)
Myalgia	1 (1.8)	8 (0.4)	3 (1.0)	6 (0.3)
Musculoskeletal pain	0 (0.0)	6 (0.3)	4 (1.3)	13 (0.7)

Table 7.2.2: 2 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term - Phase III open-label, uncontrolled extension HSDD trials (Page 3 of 3)

System organ class[a] Preferred term	FLI 25 bid N (%)	FLI 50 qhs N (%)	FLI 50 bid N (%)	FLI 100 qhs N (%)
Reproductive system and breast disorders	3 (5.3)	113 (5.1)	11 (3.6)	173 (9.7)
Cystocele	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dysmenorrhoea	1 (1.8)	8 (0.4)	1 (0.3)	17 (0.9)
Menorrhagia	0 (0.0)	28 (1.3)	3 (1.0)	35 (2.0)
Pelvic pain	1 (1.8)	4 (0.2)	0 (0.0)	6 (0.3)
Perineal fistula	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Metrorrhagia	0 (0.0)	15 (0.7)	0 (0.0)	25 (1.4)
General disorders and administration site conditions	5 (8.8)	175 (8.0)	26 (8.5)	144 (8.0)
Fatigue	3 (5.3)	128 (5.8)	14 (4.6)	68 (3.8)
Malaise	2 (3.5)	3 (0.1)	1 (0.3)	6 (0.3)
Irritability	0 (0.0)	19 (0.9)	4 (1.3)	21 (1.2)
Asthenia	0 (0.0)	4 (0.2)	3 (1.0)	3 (0.2)
Investigations	2 (3.5)	32 (1.5)	3 (1.0)	53 (3.0)
Intraocular pressure increased	1 (1.8)	1 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	1 (1.8)	2 (0.1)	1 (0.3)	4 (0.2)
Injury, poisoning and procedural complications	1 (1.8)	37 (1.7)	12 (3.9)	79 (4.4)
Road traffic accident	1 (1.8)	1 (0.0)	0 (0.0)	1 (0.1)
Surgical and medical procedures	2 (3.5)	2 (0.1)	2 (0.7)	11 (0.6)
Nasal operation	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Septoplasty	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth extraction	1 (1.8)	1 (0.0)	0 (0.0)	0 (0.0)

a Subjects may appear in more than one column. Percentages are calculated using total number of subjects per treatment as the denominator.

FLI = flibanserin

MedDRA version used for reporting: 12.1.

Includes all data from Trials 511.84 and.118 in the project database as of 17 Nov 2009.

AE displayed by treatment at onset.

Table 7.2.2: 3 Severity of most common Adverse Events - Phase III placebo-controlled HSDD Trials 511.70, 511.71, 511.75 and 511.77

AE [N(%)]	Placebo N=1360	FLI 100 qhs N=1001
Dizziness		
Mild	24 (1.8)	76 (7.6)
Moderate	8 (0.6)	37 (3.7)
Severe	2 (0.1)	7 (0.7)
Nausea		
Mild	38 (2.8)	72 (7.2)
Moderate	20 (1.5)	40 (4.0)
Severe	0 (0.0)	7 (0.7)
Fatigue		
Mild	55 (4.0)	69 (6.9)
Moderate	20 (1.5)	33 (3.3)
Severe	2 (0.1)	8 (0.8)
Somnolence		
Mild	31 (2.3)	65 (6.5)
Moderate	8 (0.6)	27 (2.7)
Severe	1 (0.1)	3 (0.3)
Insomnia		
Mild	20 (1.5)	21 (2.1)
Moderate	12 (0.9)	29 (2.9)
Severe	0 (0.0)	1 (0.1)
Dry Mouth		
Mild	8 (0.6)	20 (2.0)
Moderate	1 (0.1)	2 (0.2)
Severe	0 (0.0)	1 (0.1)
Anxiety		
Mild	5 (0.4)	8 (0.8)
Moderate	4 (0.3)	11 (1.1)
Severe	0 (0.0)	1 (0.1)

Table 7.2.2: 4 Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a]

System organ class/ Preferred term	Placebo N (%)	<50 tdd N (%)	FLI 50_100 N (%)	FLI > 100 N (%)
Number of subjects	**718 (100.0)**	**408 (100.0)**	**687(100.0)**	**211 (100.0)**
Total with adverse events	**520(72.4)**	**310 (76.0)**	**562(81.8)**	**179 (84.8)**
Infections and infestations	101(14.1)	74 (18.1)	101(14.7)	26 (12.3)
Upper respiratory tract infection	55 (7.7)	33 (8.1)	56 (8.2)	13 (6.2)
Sinusitis	11 (1.5)	10 (2.5)	14 (2.0)	5 (2.4)
Rhinitis	6 (0.8)	9 (2.2)	8 (1.2)	5 (2.4)
Pharyngitis	12 (1.7)	9 (2.2)	11 (1.6)	4 (1.9)
Blood and lymphatic system disorders	5 (0.7)	4 (1.0)	1 (0.1)	0 (0.0)
Lymphadenopathy	3 (0.4)	4 (1.0)	0 (0.0)	0 (0.0)
Immune system disorders	2 (0.3)	0 (0.0)	3 (0.4)	3 (1.4)
Hypersensitivity	2 (0.3)	0 (0.0)	3 (0.4)	3 (1.4)
Metabolism and nutrition disorders	19 (2.6)	13 (3.2)	23 (3.3)	8 (3.8)
Anorexia	11 (1.5)	10 (2.5)	13 (1.9)	6 (2.8)
Increased appetite	3 (0.4)	3 (0.7)	7 (1.0)	2 (0.9)
Psychiatric disorders	114 (15.9)	70 (17.2)	140 (20.4)	42(19.9)
Insomnia	43 (6.0)	30 (7.4)	55 (8.0)	15 (7.1)
Anxiety	11 (1.5)	8 (2.0)	12 (1.7)	9 (4.3)
Abnormal dreams	17 (2.4)	12 (2.9)	22 (3.2)	2 (0.9)
Agitation	12 (1.7)	7 (1.7)	21 (3.1)	2 (0.9)
Confusional state	3 (0.4)	8 (2.0)	6 (0.9)	6 (2.8)
Nervousness	19 (2.6)	9 (2.2)	16 (2.3)	6 (2.8)
Libido decreased	4 (0.6)	3 (0.7)	12 (1.7)	3 (1.4)
Depression	6 (0.8)	3 (0.7)	11 (1.6)	3 (1.4)
Nightmare	8 (1.1)	2 (0.5)	7 (1.0)	1 (0.5)
Nervous system disorders	236(32.9)	160 (39.2)	336 (48.9)	129(61.1)
Somnolence	63 (8.8)	45 (11.0)	154 (22.4)	84(39.8)
Dizziness	34(4.7)	23 (5.6)	114 (16.6)	59(28.0)
Headache	131(18.2)	89 (21.8)	124 (18.0)	23(10.9)
Paraesthesia	4 (0.6)	8 (2.0)	10 (1.5)	3 (1.4)
Hypertonia	5 (0.7)	7 (1.7)	9 (1.3)	1 (0.5)
Hypoaesthesia	1 (0.1)	7 (1.7)	4 (0.6)	1 (0.5)
Muscle contractions involuntary	5 (0.7)	7 (1.7)	8 (1.2)	1 (0.5)
Disturbance in attention	7 (1.0)	4 (1.0)	9 (1.3)	3 (1.4)
Tremor	10 (1.4)	3 (0.7)	9 (1.3)	2 (0.9)
Amnesia	7 (1.0)	4 (1.0)	7 (1.0)	2 (0.9)
Dysgeusia	4 (0.6)	4 (1.0)	2 (0.3)	0 (0.0)
Migraine	7 (1.0)	4 (1.0)	5 (0.7)	0 (0.0)

Table 7.2.2:4 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a] (Page 2 of 3)

Eye disorders	30 (4.2)	23 (5.6)	30 (4.4)	11 (5.2)
Visual impairment	10 (1.4)	11 (2.7)	11 (1.6)	6 (2.8)
Xerophthalmia	8 (1.1)	1 (0.2)	4 (0.6)	1 (0.5)
Ear and labyrinth disorders	11 (1.5)	9 (2.2)	8 (1.2)	4 (1.9)
Tinnitus	5 (0.7)	5 (1.2)	0 (0.0)	1 (0.5)
Cardiac disorders	40 (5.6)	15 (3.7)	24 (3.5)	8 (3.8)
Palpitations	20 (2.8)	9 (2.2)	15 (2.2)	5 (2.4)
Tachycardia	11 (1.5)	4 (1.0)	5 (0.7)	2 (0.9)
Vascular disorders	19 (2.6)	9 (2.2)	13 (1.9)	1 (0.5)
Hypertension	9 (1.3)	1 (0.2)	3 (0.4)	0 (0.0)
Flushing	5 (0.7)	4 (1.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	11 (1.5)	17 (4.2)	24 (3.5)	5 (2.4)
Dyspnoea	5 (0.7)	6 (1.5)	8 (1.2)	2 (0.9)
Cough	2 (0.3)	5 (1.2)	3 (0.4)	0 (0.0)
Epistaxis	1 (0.1)	4 (1.0)	5 (0.7)	1 (0.5)
Gastrointestinal disorders	227 (31.6)	134 (32.8)	265(38.6)	87(41.2)
Nausea	68 (9.5)	34 (8.3)	124(18.0)	46(21.8)
Dry mouth	52 (7.2)	32 (7.8)	54 (7.9)	22 (10.4)
Diarrhoea	50 (7.0)	28 (6.9)	36 (5.2)	8 (3.8)
Abdominal pain	40 (5.6)	19 (4.7)	38 (5.5)	6 (2.8)
Constipation	20 (2.8)	18 (4.4)	29 (4.2)	10 (4.7)
Flatulence	22 (3.1)	19 (4.7)	11 (1.6)	4 (1.9)
Vomiting	9 (1.3)	9 (2.2)	18 (2.6)	10 (4.7)
Dyspepsia	27 (3.8)	14 (3.4)	27 (3.9)	8 (3.8)
Gastrointestinal disorder	4 (0.6)	1 (0.2)	7 (1.0)	0 (0.0)
Skin and subcutaneous tissue disorders	55 (7.7)	31 (7.6)	41 (6.0)	6 (2.8)
Hyperhidrosis	22 (3.1)	6 (1.5)	13 (1.9)	2 (0.9)
Pruritus	11 (1.5)	2 (0.5)	2 (0.3)	0 (0.0)
Rash	9 (1.3)	4 (1.0)	6 (0.9)	1 (0.5)
Photosensitivity reaction	2 (0.3)	5 (1.2)	4 (0.6)	1 (0.5)
Acne	2 (0.3)	4 (1.0)	3 (0.4)	1 (0.5)

Table 7.2.2:4 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a] (Page 3 of 3)

Musculoskeletal and connective tissue disorders	48 (6.7)	36 (8.8)	53 (7.7)	15 (7.1)
Back pain	23 (3.2)	17 (4.2)	22 (3.2)	5 (2.4)
Myalgia	13 (1.8)	12 (2.9)	15 (2.2)	6 (2.8)
Arthralgia	5 (0.7)	3 (0.7)	2 (0.3)	3 (1.4)
Renal and urinary disorders	35 (4.9)	22 (5.4)	35 (5.1)	11 (5.2)
Pollakiuria	29 (4.0)	14 (3.4)	26 (3.8)	8 (3.8)
Polyuria	5 (0.7)	6 (1.5)	4 (0.6)	0 (0.0)
Reproductive system and breast disorders	17 (2.4)	14 (3.4)	20 (2.9)	7 (3.3)
Dysmenorrhoea	5 (0.7)	8 (2.0)	8 (1.2)	1 (0.5)
Erectile dysfunction	2 (0.3)	1 (0.2)	1 (0.1)	3 (1.4)
General disorders and administration site conditions	114 (15.9)	71 (17.4)	171(24.9)	43 (20.4)
Fatigue	34 (4.7)	20 (4.9)	81 (11.8)	20 (9.5)
Asthenia	19 (2.6)	5 (1.2)	41 (6.0)	8 (3.8)
Influenza like illness	30 (4.2)	20 (4.9)	25 (3.6)	6 (2.8)
Pain	14 (1.9)	11 (2.7)	13 (1.9)	5 (2.4)
Pyrexia	5 (0.7)	8 (2.0)	4 (0.6)	0 (0.0)
Chest pain	14 (1.9)	5 (1.2)	6 (0.9)	1 (0.5)
Oedema peripheral	0 (0.0)	5 (1.2)	5 (0.7)	1 (0.5)
Injury, poisoning and procedural complications	16 (2.2)	9 (2.2)	13 (1.9)	8 (3.8)
Accident at home	11 (1.5)	7 (1.7)	9 (1.3)	7 (3.3)

The set of trials used as the basis for this display include − 0511_0010, 0511_0011, 0511_0012, 0511_0018, 0511_0028, 0511_0041, 0511_0042, 0511_0043, 0511_0049

Table 7.2.2: 5 Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a]

System organ class/	Placebo		<50 tdd		FLI 50 qhs		FLI 50 bid		FLI 100 qhs		FLI 150 tdd		FLI 100 bid	
Preferred term	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Number of subjects	**417**	**(100.0)**	**240**	**(100.0)**	**33**	**(100.0)**	**313**	**(100.0)**	**65**	**(100.0)**	**4**	**(100.0)**	**113**	**(100.0)**
Total with adverse events	**303**	**(72.7)**	**180**	**(75.0)**	**30**	**(90.9)**	**259**	**(82.7)**	**54**	**(83.1)**	**2**	**(50.0)**	**95**	**(84.1)**
Infections and infestations	65	(15.6)	41	(17.1)	5	(15.2)	45	(14.4)	7	(10.8)	0	(0.0)	14	(12.4)
Upper respiratory tract infection	38	(9.1)	18	(7.5)	2	(6.1)	27	(8.6)	2	(3.1)	0	(0.0)	6	(5.3)
Herpes simplex	3	(0.7)	1	(0.4)	2	(6.1)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Sinusitis	6	(1.4)	7	(2.9)	0	(0.0)	6	(1.9)	2	(3.1)	0	(0.0)	4	(3.5)
Rhinitis	4	(1.0)	5	(2.1)	1	(3.0)	1	(0.3)	1	(1.5)	0	(0.0)	2	(1.8)
Pharyngitis	6	(1.4)	4	(1.7)	0	(0.0)	5	(1.6)	0	(0.0)	0	(0.0)	2	(1.8)
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Urinary tract infection	3	(0.7)	2	(0.8)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	0	(0.0)
Immune system disorders	1	(0.2)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	1	(0.9)
Hypersensitivity	1	(0.2)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	1	(0.9)
Metabolism and nutrition disorders	16	(3.8)	10	(4.2)	1	(3.0)	5	(1.6)	5	(7.7)	0	(0.0)	3	(2.7)
Anorexia	10	(2.4)	8	(3.3)	0	(0.0)	3	(1.0)	3	(4.6)	0	(0.0)	2	(1.8)
Increased appetite	3	(0.7)	2	(0.8)	1	(3.0)	2	(0.6)	1	(1.5)	0	(0.0)	1	(0.9)
Food craving	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Psychiatric disorders	77	(18.5)	42	(17.5)	13	(39.4)	53	(16.9)	14	(21.5)	1	(25.0)	22	(19.5)
Depression	5	(1.2)	1	(0.4)	0	(0.0)	7	(2.2)	1	(1.5)	1	(25.0)	2	(1.8)
Abnormal dreams	12	(2.9)	7	(2.9)	4	(12.1)	5	(1.6)	1	(1.5)	0	(0.0)	1	(0.9)
Nervousness	11	(2.6)	5	(2.1)	4	(12.1	4	(1.3)	3	(4.6)	0	(0.0)	2	(1.8)
Insomnia	30	(7.2)	19	(7.9)	3	(9.1)	19	(6.1)	7	(10.8)	0	(0.0)	6	(5.3)
Anxiety	6	(1.4)	7	(2.9)	3	(9.1)	2	(0.6)	1	(1.5)	0	(0.0)	5	(4.4)
Confusional state	3	(0.7)	4	(1.7)	2	(6.1)	1	(0.3)	2	(3.1)	0	(0.0)	5	(4.4)
Agitation	10	(2.4)	5	(2.1)	1	(3.0)	10	(3.2)	2	(3.1)	0	(0.0)	2	(1.8)
Anorgasmia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)	1	(1.5)	0	(0.0)	1	(0.9)

Table 7.2.2: 5 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a] (Page 2 of 5)

Suicide attempt	3	(0.7)	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Libido decreased	2	(0.5)	0	(0.0)	0	(0.0)	5	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
Affect lability	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(1.5)	0	(0.0)	0	(0.0)
Nightmare	6	(1.4)	1	(0.4)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	1	(0.9)
Psychotic disorder	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	0	(0.0)
Nervous system disorders	140	(33.6)	93	(38.8)	14	(42.4)	167	(53.4)	29	(44.6)	1	(25.0)	70	(61.9)
Somnolence	35	(8.4)	31	(12.9)	6	(18.2)	90	(28.8)	10	(15.4)	1	(25.0)	47	(41.6)
Dizziness	19	(4.6)	16	(6.7)	6	(18.2)	53	(16.9)	11	(16.9)	0	(0.0)	35	(31.0)
Headache	80	(19.2)	50	(20.8)	8	(24.2)	54	(17.3)	15	(23.1)	0	(0.0)	12	(10.6)
Hypertonia	3	(0.7)	4	(1.7)	1	(3.0)	3	(1.0)	2	(3.1)	0	(0.0)	0	(0.0)
Hypoaesthesia	0	(0.0)	4	(1.7)	1	(3.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Paraesthesia	3	(0.7)	4	(1.7)	1	(3.0)	5	(1.6)	1	(1.5)	0	(0.0)	2	(1.8)
Parosmia	0	(0.0)	0	(0.0)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tremor	9	(2.2)	1	(0.4)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	2	(1.8)
Coordination abnormal	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	2	(1.8)
Disturbance in attention	4	(1.0)	4	(1.7)	0	(0.0)	4	(1.3)	0	(0.0)	0	(0.0)	2	(1.8)
Amnesia	3	(0.7)	4	(1.7)	0	(0.0)	4	(1.3)	1	(1.5)	0	(0.0)	1	(0.9)
Migraine	7	(1.7)	4	(1.7)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperkinesia	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Muscle contractions involuntary	3	(0.7)	3	(1.3)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	1	(0.9)
Speech disorder	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	0	(0.0)
Dysgeusia	3	(0.7)	3	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ataxia	1	(0.2)	1	(0.4)	0	(0.0)	3	(91.0)	0	(0.0)	0	(0.0)	1	(0.9)
Eye disorders	18	(4.3)	13	(5.4)	1	(3.0)	15	(4.8)	5	(7.7)	0	(0.0)	7	(6.2)
Visual impairment	8	(1.9)	4	(1.7)	0	(0.0)	6	(1.9)	2	(3.1)	0	(0.0)	3	(2.7)
Cataract	1	(0.2)	1	(0.4)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis	6	(1.4)	2	(0.8)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	2	(1.8)
Eye disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Eye pain	1	(0.2)	2	(0.8)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	1	(0.9)
Lacrimal disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(1.5)	0	(0.0)	0	(0.0)
Miosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Vision blurred	1	(0.2)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 7.2.2: 5 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a] (Page 3 of 5)

Ear and labyrinth disorders	6	(1.4)	6	(2.5)	1	(3.0)	5	(1.6)	1	(1.5)	0	(0.0)	4	(3.5)
Vertigo	3	(0.7)	0	(0.0)	1	(3.0)	3	(1.0)	0	(0.0)	0	(0.0)	2	(1.8)
Tinnitus	2	(0.5)	4	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
Ear pain	1	(0.2)	1	(0.4)	0	(0.0)	1	(0.3)	1	(1.5)	0	(0.0)	0	(0.0)
Cardiac disorders	23	(5.5)	7	(2.9)	0	(0.0)	14	(4.5)	3	(4.6)	0	(0.0)	5	(4.4)
Palpitations	13	(3.1)	4	(1.7)	0	(0.0)	10	(3.2)	2	(3.1)	0	(0.0)	3	(2.7)
Tachycardia	5	(1.2)	2	(0.8)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	1	(0.9)
Vascular disorders	7	(1.7)	5	(2.1)	0	(0.0)	9	(2.9)	2	(3.1)	0	(0.0)	1	(0.9)
Orthostatic hypotension	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	2	(3.1)	0	(0.0)	0	(0.0)
Flushing	3	(0.7)	3	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypotension	1	(0.2)	0	(0.0)	0	(0.0)	4	(1.3)	0	(0.0)	0	(0.0)	1	(0.9)
Respiratory, thoracic and mediastinal disorders	10	(2.4)	12	(5.0)	2	(6.1)	13	(4.2)	1	(1.5)	0	(0.0)	1	(0.9)
Dyspnoea	4	(1.0)	5	(2.1)	2	(6.1)	2	(0.6)	1	(1.5)	0	(0.0)	1	(0.9)
Cough	2	(0.5)	5	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Epistaxis	1	(0.2)	1	(0.4)	0	(0.0)	5	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
Asthma	1	(0.2)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Yawning	3	(0.7)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	135	(32.4)	83	(34.6)	13	(39.4)	131	(41.9)	28	(43.1)	1	(25.0)	53	(46.9)
Nausea	50	(12.0)	23	(9.6)	6	(18.2)	64	(20.4)	17	(26.2)	1	(25.0)	30	(26.5)
Dry mouth	24	(5.8)	14	(5.8)	3	(9.1)	27	(8.6)	6	(9.2)	0	(0.0)	14	(12.4)
Diarrhoea	27	(6.5)	14	(5.8)	1	(3.0)	12	(3.8)	5	(7.7)	0	(0.0)	4	(3.5)
Abdominal pain	25	(6.0)	12	(5.0)	2	(6.1)	18	(5.8)	4	(6.2)	0	(0.0)	3	(2.7)
Constipation	13	(3.1)	14	(5.8)	2	(6.1)	16	(5.1)	2	(3.1)	0	(0.0)	3	(2.7)
Vomiting	6	(1.4)	6	(2.5)	2	(6.1)	9	(2.9)	3	(4.6)	0	(0.0)	6	(5.3)
Dyspepsia	17	(4.1)	8	(3.3)	1	(3.0)	10	(3.2)	3	(4.6)	0	(0.0)	5	(4.4)
Flatulence	16	(3.8)	11	(4.6)	0	(0.0)	5	(1.6)	0	(0.0)	0	(0.0)	3	(2.7)

Table 7.2.2: 5 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a] (Page 4 of 5)

Gastrooesophageal reflux disease	1	(0.2)	1	(0.4)	1	(3.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorder	2	(0.5)	1	(0.4)	0	(0.0)	5	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal distension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Tooth disorder	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Toothache	3	(0.7)	1	(0.4)	0	(0.0)	4	(1.3)	0	(0.0)	0	(0.0)	1	(0.9)
Skin and subcutaneous tissue disorders	36	(8.6)	22	(9.2)	2	(6.1)	15	(4.8)	8	(12.3)	0	(0.0)	3	(2.7)
Hyperhidrosis	17	(4.1)	4	(1.7)	1	(3.0)	3	(1.0)	4	(6.2)	0	(0.0)	1	(0.9)
Rash	5	(1.2)	4	(1.7)	1	(3.0)	1	(0.3)	2	(3.1)	0	(0.0)	1	(0.9)
Pruritus	7	(1.7)	0	(0.0)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Photosensitivity reaction	1	(0.2)	3	(1.3)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Skin odour abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Acne	1	(0.2)	3	(1.3)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	25	(6.0)	24	(10.0)	3	(9.1)	18	(5.8)	10	(15.4)	0	(0.0)	10	(0.8)
Back pain	11	(2.6)	12	(5.0)	0	(0.0)	8	(2.6)	4	(6.2)	0	(0.0)	4	(3.5)
Myalgia	7	(1.7)	8	(3.3)	2	(6.1)	4	(1.3)	3	(4.6)	0	(0.0)	3	(2.7)
Muscle spasms	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	3	(4.6)	0	(0.0)	1	(0.9)
Pain in extremity	2	(0.5)	1	(0.4)	1	(3.0)	2	(0.6)	0	(0.0)	0	(0.0)	1	(0.9)
Arthralgia	3	(0.7)	1	(0.4)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	2	(1.8)
Muscular weakness	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal and urinary disorders	19	(4.6)	14	(5.8)	4	(12.1)	7	(2.2)	7	(10.8)	0	(0.0)	4	(3.5)
Pollakiuria	16	(3.8)	9	(3.8)	2	6.1)	6	(1.9)	6	(9.2)	0	(0.0)	3	(2.7)
Dysuria	0	(0.0)	1	(0.4)	1	3.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Polyuria	3	(0.7)	4	(1.7)	1	3.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Micturition urgency	0	(0.0)	0	(0.0)	0	0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)

Table 7.2.2: 5 (continued) Frequency [N (%)] of subjects with adverse events occurring with incidence in preferred term greater than or equal to 1 % by treatment, primary system organ class and preferred term − Phase II placebo−controlled MDD trials[a] (Page 5 of 5)

Reproductive system and breast disorders	12	(2.9)	13	(5.4)	2	(6.1)	14	(4.5)	1	(1.5)	0	(0.0)	2	(1.8)
Dysmenorrhoea	5	(1.2)	8	(3.3)	2	(6.1)	6	(1.9)	0	0.0)	0	(0.0)	1	(0.9)
Menorrhagia	1	(0.2)	1	(0.4)	0	(0.0)	3	(1.0)	1	1.5)	0	(0.0)	1	(0.9)
Menstrual disorder	3	(0.7)	3	(1.3)	0	(0.0)	1	(0.3)	0	0.0)	0	(0.0)	0	(0.0)
General disorders and Administration site conditions	71	(17.0)	49	(20.4)	15	(45.5)	74	(23.6)	11	(16.9)	0	(0.0)	22	(19.5)
Fatigue	21	(5.0)	12	(5.0)	7	(21.2)	41	(13.1)	4	(6.2)	0	(0.0)	12	(10.6)
Asthenia	10	(2.4)	2	(0.8)	5	(15.2)	15	(4.8)	0	(0.0)	0	(0.0)	4	(3.5)
Influenza like illness	18	(4.3)	14	(5.8)	2	(6.1)	9	(2.9)	2	(3.1)	0	(0.0)	4	(3.5)
Pain	11	(2.6)	9	(3.8)	0	(0.0)	4	(1.3)	1	(1.5)	0	(0.0)	1	(0.9)
Generalised oedema	1	(0.2)	2	(0.8)	1	(3.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
Thirst	3	(0.7)	1	(0.4)	1	(3.0)	1	(0.3)	1	(1.5)	0	(0.0)	0	(0.0)
Pyrexia	3	(0.7)	5	(2.1)	0	(0.0)	2	(0.6)	1	(1.5)	0	(0.0)	0	(0.0)
Chest pain	7	(1.7)	3	(1.3)	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Oedema peripheral	0	(0.0)	4	(1.7)	0	(0.0)	4	(1.3)	1	(1.5)	0	(0.0)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(1.5)	0	(0.0)	0	(0.0)
Gravitational oedema	1	(0.2)	3	(1.3)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Investigations	8	(1.9)	2	(0.8)	0	(0.0)	4	(1.3)	1	(1.5)	0	(0.0)	2	(1.8)
Urine analysis abnormal	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	0	(0.0)
Weight increased	3	(0.7)	1	(0.4)	0	(0.0)	3	(1.0)	0	(0.0)	0	(0.0)	1	(0.9)
Injury, poisoning and procedural complications	11	(2.6)	4	(1.7)	1	(3.0)	6	(1.9)	1	(1.5)	0	(0.0)	4	(3.5)
Accident at home	7	(1.7)	2	(0.8)	1	(3.0)	5	(1.6)	0	(0.0)	0	(0.0)	3	(2.7)
Road traffic accident	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.5)	0	(0.0)	1	(0.9)

Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 11.1
The set of trials used as the basis for this display include − 0511_0010, 0511_0011, 0511_0012, 0511_0018, 0511_0028, 0511_0041, 0511_0042, 0511_0043, 0511_0049

Table 7.2.2: 6 Subjects with adverse events leading to treatment discontinuation in ≥1% of subjects in any treatment group by preferred term and randomized treatment - Phase III placebo-controlled HSDD Trials 511.70, 511.71, 511.75, and 511.77

System organ class/ Preferred term	Placebo N (%)	FLI 25 b.i.d. N (%)	FLI 50 q.h.s. N (%)	FLI 50 b.i.da. N (%)	FLI 100 q.h.s.b N (%)	Flibanserin (all doses) N (%)
Number of subjects	1360 (100.0)	733 (100.0)	969 (100.0)	728 (100.0)	1001 (100.0)	3431 (100.0)
Total with AEs leading to treatment discontinuation	92 (6.8)	50 (6.8)	99 (10.2)	148 (20.3)	146 (14.6)	443 (12.9)
Fatigue	7 (0.5)	7 (1.0)	7 (0.7)	37 (5.1)	11 (1.1)	62 (1.8)
Dizziness	1 (0.1)	2 (0.3)	9 (0.9)	29 (4.0)	18 (1.8)	58 (1.7)
Somnolence	7 (0.5)	3 (0.4)	4 (0.4)	29 (4.0)	8 (0.8)	44 (1.3)
Nausea	3 (0.2)	2 (0.3)	5 (0.5)	18 (2.5)	16 (1.6)	41 (1.2)
Headache	9 (0.7)	6 (0.8)	11 (1.1)	13 (1.8)	6 (0.6)	36 (1.0)
Anxiety	4 (0.3)	3 (0.4)	10 (1.0)	4 (0.5)	13 (1.3)	30 (0.9)
Insomnia	3 (0.2)	1 (0.1)	3 (0.3)	6 (0.8)	13 (1.3)	23 (0.7)

a Subjects in 511.75 start on flibanserin 50 mg q.h.s. for the first 2 weeks, then up-titrate to 50 mg b.i.d.
b Subjects in 511.75 start on flibanserin 50 mg q.h.s. for the first 2 weeks, then up-titrate to 100 mg q.h.s.

7.2.3 Laboratory parameters

Table 7.2.3: 1 Descriptive statistics for normalized values of female hormones by randomized treatment: Last value on treatment - Phase III placebo-controlled HSDD trials

	Last Value on Treatment			Difference from Baseline		
Treatment/Visit	N	Mean (SD)	Min - Max	N	Mean (SD)	Min - Max
Total testosterone (normal range: 10 - 55 ng/dL)						
Placebo	961	26.4 (14.5)	6.2 - 210.6	956	0.5 (13.5)	-57.9 - 188.4
Flibanserin 100 mg q.h.s.	621	25.0 (10.6)	6.2 - 97.0	618	-1.4 (9.8)	-48.8 - 52.5
Free testosterone (normal range: 1.1 - 6.3 pg/mL)						
Placebo	928	1.7 (1.7)	-0.1 - 38.0	911	0.1 (1.7)	-12.8 - 35.6
Flibanserin 100 mg q.h.s.	615	1.5 (1.1)	0.1 - 7.4	607	-0.1 (1.0)	-9.2 - 4.9
Percent free testosterone (normal range: 0.8 - 1.4%)						
Placebo	929	0.7 (0.4)	0.1 - 3.1	915	0.0 (0.3)	-2.0 - 2.6
Flibanserin 100 mg q.h.s.	617	0.7 (0.4)	0.1 - 2.7	612	0.0 (0.3)	-1.4 - 1.5
Sex hormone binding protein (normal range: 40 - 120 nmol/L)						
Placebo	937	150.9 (118.5)	15.0 - 632.0	930	-6.2 (67.7)	-509.0 - 326.0
Flibanserin 100 mg q.h.s.	621	159.9 (120.3)	16.0 - 757.0	620	-4.1 (76.2)	-402.0 - 638.0
Prolactin (normal range: 3 - 30 ng/dL)						
Placebo	936	13.7 (8.8)	1.6 - 101.0	925	-0.7 (9.4)	-93.4 - 64.0
Flibanserin 100 mg q.h.s.	626	15.2 (15.1)	3.2 - 293.0	626	0.2 (11.1)	-158.0 - 52.0
Progesterone (normal range: 0 - 3750 ng/dL)						
Placebo	930	362.4 (666.2)	-0.0 - 4672.5	915	-35.1 (772.2)	-3050 - 4572.2
Flibanserin 100 mg q.h.s.	612	303.8 (614.5)	0.0 - 3272.6	606	-11.8 (776.6)	-3820 - 2799.8

Table 7.2.3: 1 (continued) Descriptive statistics for normalized values of female hormones by randomized treatment: Last value on treatment - Phase III placebo-controlled HSDD trials (Page 2 of 2)

	Last Value on Treatment			Difference from Baseline		
Treatment/Visit	N	Mean (SD)	Min - Max	N	Mean (SD)	Min - Max
Estradiol (normal range: 110 - 1101 pmol/L)						
Placebo	866	333.3 (339.8)	61.3 - 2874.4	814	24.4 (378.2)	-1436 - 2781.8
Flibanserin 100 mg q.h.s.	584	324.1 (317.6)	61.3 - 3256.9	558	-13.5 (372.6)	-1773 - 2747.0
FSH (normal range: 1.5 - 33.4 mIU/mL)						
Placebo	933	3.0 (2.1)	1.5 - 31.2	922	0.1 (2.0)	-17.8 - 29.6
Flibanserin 100 mg q.h.s.	626	3.0 (2.2)	1.5 - 23.3	625	0.1 (2.2)	-18.5 - 20.1
DHEA (normal range: 160 - 800 ng/dL)						
Placebo	954	457.7 (244.0)	23.0 - 1759.0	950	-183.9 (1721.3)	-24780 - 887.0
Flibanserin 100 mg q.h.s.	614	466.5 (256.8)	22.2 - 2136.0	607	-230.2 (2142.8)	-25504 - 1418.0
DHEAS (normal range: 19 - 255 µg/dL)						
Placebo	959	77.0 (47.5)	10.0 - 424.0	958	-63.9 (510.0)	-7687 - 101.0
Flibanserin 100 mg q.h.s.	621	80.3 (50.3)	10.0 - 296.0	620	-60.9 (482.8)	-5939 - 129.0
Lutenizing hormone (normal range: 0.5 - 76.3 IU/L)						
Placebo	934	6.8 (8.4)	0.5 - 87.9	923	0.6 (9.3)	-64.5 - 84.9
Flibanserin 100 mg q.h.s.	626	7.1 (9.4)	0.5 - 68.0	625	0.6 (10.9)	-62.7 - 64.1

Normal ranges are displayed in Appendix 7, Table 7.1.1.

Table 7.2.3: 2 Frequency of subjects [N (%)] with transitions from baseline to last value on treatment relative to the reference range - treated set - Phase III placebo-controlled HSDD trials

		Baseline Low			Baseline Normal			Baseline High		
Parameter/ Treatment	N	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Hematocrit										
Placebo	868	2 (0.2)	9 (1.0)	0	16 (1.8)	837 (96.4)	3 (0.3)	0	1 (0.1)	0
FLI 100 q.h.s	600	6 (1.0)	4 (0.7)	0	10 (1.7)	579 (96.5)	0	0	1 (0.2)	0
Hemoglobin										
Placebo	878	20 (2.3)	12 (1.4)	0	18 (2.1)	828 (94.3)	0	0	0	0
FLI 100 q.h.s.	608	22 (3.6)	12 (2.0)	0	15 (2.5)	559 (91.9)	0	0	0	0
WBC										
Placebo	878	4 (0.5)	20 (2.3)	0	27 (3.1)	784 (89.3)	20 (2.3)	0	17 (1.9)	6 (0.7)
FLI 100 q.h.s.	608	10 (1.6)	11 (1.8)	0	8 (1.3)	545 (89.6)	17 (2.8)	0	11 (1.8)	6 (1.0)
RBC morphology (qual)										
Placebo	666	0	0	0	0	646 (97.0)	14 (2.1)	0	6 (0.9)	0
FLI 100 q.h.s.	416	0	0	0	0	403 (96.9)	9 (2.2)	0	3 (0.7)	1 (0.2)
Lymphocytes (absolute)										
Placebo	878	1 (0.1)	3 (0.3)	0	5 (0.6)	863 (98.3)	2 (0.2)	0	4 (0.5)	0
FLI 100 q.h.s.	608	0	2 (0.3)	0	6 (1.0)	596 (98.0)	3 (0.5)	0	0	1 (0.2)
Monocytes (absolute)										
Placebo	878	0	5 (0.6)	0	3 (0.3)	863 (98.3)	6 (0.7)	0	1 (0.1)	0
FLI 100 q.h.s.	608	0	2 (0.3)	0	0	602 (99.0)	2 (0.3)	0	2 (0.3)	0

Table 7.2.3: 2 (continued) Frequency of subjects [N (%)] with transitions from baseline to last value on treatment relative to the reference range - treated set - Phase III placebo-controlled HSDD trials (Page 2 of 5)

		Baseline Low			Baseline Normal			Baseline High		
Parameter/ Treatment	N	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Eosinophils (absolute)										
Placebo	878	0	0	0	0	869 (99.0)	2 (0.2)	0	3 (0.3)	4 (0.5)
FLI 100 q.h.s.	608	0	0	0	0	603 (99.2)	2 (0.3)	0	2 (0.3)	1 (0.2)
Basophils (absolute)										
Placebo	878	0	0	0	0	877 (99.9)	1 (0.1)	0	0	0
FLI 100 q.h.s.	608	0	0	0	0	606 (99.7)	2 (0.3)	0	0	0
Platelets										
Placebo	868	2 (0.2)	2 (0.2)	0	2 (0.2)	827 (95.3)	15 (1.7)	0	9 (1.0)	11 (1.3)
FLI 100 q.h.s.	603	1 (0.2)	2 (0.3)	0	2 (0.3)	565 (93.7)	4 (0.7)	0	13 (2.2)	16 (2.7)
Neutrophils (absolute)										
Placebo	878	7 (0.8)	24 (2.7)	0	22 (2.5)	779 (88.7)	19 (2.2)	0	19 (2.2)	8 (0.9)
FLI 100 q.h.s.	608	8 (1.3)	11 (1.8)	0	6 (1.0)	532 (87.5)	28 (4.6)	0	19 (3.1)	4 (0.7)
Sodium										
Placebo	915	0	0	0	0	879 (96.1)	8 (0.9)	0	27 (3.0)	1 (0.1)
FLI 100 q.h.s.	626	0	1 (0.2)	0	0	607 (97.0)	4 (0.6)	0	14 (2.2)	0
Glucose										
Placebo	911	3 (0.3)	15 (1.6)	1 (0.1)	13 (1.4)	854 (93.7)	13 (1.4)	0	8 (0.9)	4 (0.4)
FLI 100 q.h.s.	624	0	8 (1.3)	0	11 (1.8)	579 (92.8)	17 (2.7)	0	5 (0.8)	4 (0.6)

Table 7.2.3: 2 (continued) Frequency of subjects [N (%)] with transitions from baseline to last value on treatment relative to the reference range - treated set - Phase III placebo-controlled HSDD trials (Page 3 of 5)

		Baseline Low			Baseline Normal			Baseline High		
Parameter/ Treatment	N	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Alkaline Phosphatase										
Placebo	916	4 (0.4)	0	0	4 (0.4)	885 (96.6)	6 (0.7)	0	8 (0.9)	9 (1.0)
FLI 100 q.h.s.	627	5 (0.8)	3 (0.5)	0	2 (0.3)	596 (95.1)	3 (0.5)	0	9 (1.4)	9 (1.4)
ALT/SGPT										
Placebo	910	2 (0.2)	2 (0.2)	0	1 (0.1)	856 (94.1)	18 (2.0)	0	20 (2.2)	11 (1.2)
FLI 100 q.h.s.	625	0	0	0	3 (0.5)	578 (92.5)	15 (2.4)	0	20 (3.2)	9 (1.4)
AST/SGOT										
Placebo	901	0	0	0	2 (0.2)	871 (96.7)	13 (1.4)	0	12 (1.3)	3 (0.3)
FLI 100 q.h.s.	620	0	2 (0.3)	0	1 (0.2)	593 (95.6)	10 (1.6)	0	12 (1.9)	2 (0.3)
Creatinine										
Placebo	916	0	0	0	0	911 (99.5)	2 (0.2)	0	1 (0.1)	2 (0.2)
FLI 100 q.h.s.	627	0	0	0	0	624 (99.5)	2 (0.3)	0	1 (0.2)	0
BUN										
Placebo	916	0	0	0	0	910 (99.3)	6 (0.7)	0	0	0
FLI 100 q.h.s.	627	0	0	0	0	625 (99.7)	2 (0.3)	0	0	0
Cholesterol (total)										
Placebo	916	24 (2.6)	25 (2.7)	0	23 (2.5)	753 (82.2)	22 (2.4)	0	39 (4.3)	30 (3.3)
FLI 100 q.h.s.	627	21 (3.3)	17 (2.7)	0	24 (3.8)	500 (79.7)	12 (1.9)	0	35 (5.6)	18 (2.9)

Table 7.2.3: 2 (continued) Frequency of subjects [N (%)] with transitions from baseline to last value on treatment relative to the reference range - treated set - Phase III placebo-controlled HSDD trials (Page 4 of 5)

		Baseline Low			Baseline Normal			Baseline High		
Parameter/ Treatment	N	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Free testosterone										
Placebo	911	213 (23.4)	108 (11.9)	2 (0.2)	102 (11.2)	476 (52.3)	5 (0.5)	0	4 (0.4)	1 (0.1)
FLI 100 q.h.s.	607	162 (26.7)	67 (11.0)	0	75 (12.4)	300 (49.4)	1 (0.2)	0	2 (0.3)	0
Percent free testosterone										
Placebo	915	452 (49.4)	93 (10.2)	5 (0.5)	85 (9.3)	212 (23.2)	21 (2.3)	2 (0.2)	24 (2.6)	21 (2.3)
FLI 100 q.h.s.	612	333 (54.4)	60 (9.8)	3 (0.5)	60 (9.8)	121 (19.8)	11 (1.8)	2 (0.3)	7 (1.1)	15 (2.5)
Total testosterone										
Placebo	956	4 (0.4)	14 (1.5)	0	10 (1.0)	888 (92.9)	18 (1.9)	0	15 (1.6)	7 (0.7)
FLI 100 q.h.s.	618	5 (0.8)	12 (1.9)	0	13 (2.1)	565 (91.4)	8 (1.3)	0	14 (2.3)	1 (0.2)
Sex hormone binding protein										
Placebo	930	19 (2.0)	13 (1.4)	0	16 (1.7)	406 (43.7)	55 (5.9)	2 (0.2)	65 (7.0)	354 (38.1)
FLI 100 q.h.s.	620	11 (1.8)	8 (1.3)	1 (0.2)	11 (1.8)	231 (37.3)	49 (7.9)	1 (0.2)	56 (9.0)	252 (40.6)
Estradiol										
Placebo	814	146 (17.9)	57 (7.0)	4 (0.5)	64 (7.9)	492 (60.4)	28 (3.4)	2 (0.2)	20 (2.5)	1 (0.1)
FLI 100 q.h.s.	558	128 (22.9)	56 (10.0)	2 (0.4)	37 (6.6)	302 (54.1)	12 (2.2)	2 (0.4)	18 (3.2)	1 (0.2)
Progesterone										
Placebo	915	380 (41.5)	118 (12.9)	1 (0.1)	146 (6.0)	268 (29.3)	1 (0.1)	0	1 (0.1)	0
FLI 100 q.h.s.	606	284 (46.9)	98 (16.2)	0	88 (14.5)	135 (22.3)	0	0	1 (0.2)	0

Table 7.2.3: 2 (continued) Frequency of subjects [N (%)] with transitions from baseline to last value on treatment relative to the reference range - treated set - Phase III placebo-controlled HSDD trials (Page 5 of 5)

		Baseline Low			Baseline Normal			Baseline High		
Parameter/ Treatment	N	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Lutenizing hormone										
Placebo	923	25 (2.7)	15 (1.6)	0	22 (2.4)	860 (93.2)	1 (0.1)	0	0	0
FLI 100 q.h.s.	625	19 (3.0)	17 (2.7)	0	20 (3.2)	569 (91.0)	0	0	0	0
Prolactin										
Placebo	925	0	1 (0.1)	0	1 (0.1)	855 (92.4)	32 (3.5)	0	26 (2.8)	10 (1.1)
FLI 100 q.h.s.	626	0	3 (0.5)	0	0	569 (90.9)	21 (3.4)	0	20 (3.2)	13 (2.1)
FSH										
Placebo	922	22 (2.4)	21 (2.3.)	0	25 (2.7)	854 (92.6)	0	0	0	0
FLI 100 q.h.s.	625	16 (2.6)	23 (3.7)	0	22 (3.5)	563 (90.1)	0	0	1 (0.2)	0
DHEA										
Placebo	950	17 (1.8)	26 (2.7)	0	24 (2.5)	748 (78.7)	51 (5.4)	0	57 (6.0)	27 (2.8)
FLI 100 q.h.s.	607	20 (3.3)	28 (4.6)	0	12 (2.0)	457 (75.3)	36 (5.9)	1 (0.2)	32 (5.3)	21 (3.5)
DHEAS										
Placebo	958	23 (2.4)	12 (1.3)	0	25 (2.6)	875 (91.3)	1 (0.1)	0	17 (1.8)	5 (0.5)
FLI 100 q.h.s.	620	14 (2.3)	10 (1.6)	0	19 (3.1)	560 (90.3)	2 (0.3)	0	14 (2.3)	1 (0.2)

Includes Trials 511.70, .71, .75, .77

a Subjects in 511.75 start on flibanserin 50 mg q.h.s. for the first 2 weeks, then up-titrate to 50 mg b.i.d.

b Subjects in 511.75 start on flibanserin 50 mg q.h.s. for the first 2 weeks, then up-titrate to 100 mg q.h.s.

Table 7.2.3: 3 Frequency of subjects treated with flibanserin 100 mg q.h.s. [N (%)] with possible clinically significant abnormalities by randomized treatment - treated set – Phase III placebo-controlled HSDD trials

Parameter/ Treatment	**N**	**Decrease**	**Increase**
Hematocrit			
Placebo	883	4 (0.5)	0
FLI 100 q.h.s.	615	3 (0.5)	0
Hemoglobin			
Placebo	890	6 (0.7)	0
FLI 100 q.h.s.	619	4 (0.6)	0
Platelets			
Placebo	881	1 (0.1)	0
FLI 100 q.h.s.	618	0	0
WBC			
Placebo	890	2 (0.2)	0
FLI 100 q.h.s.	619	3 (0.5)	0
Neutrophil (absolute)			
Placebo	890	23 (2.6)	0
FLI 100 q.h.s.	619	9 (1.5)	0
AST			
Placebo	908	0	2 (0.2)
FLI 100 q.h.s.	625	0	4 (0.6)
ALT			
Placebo	912	0	2 (0.2)
FLI 100 q.h.s.	627	0	2 (0.3)

Table 7.2.3: 3 (continued) Frequency of subjects treated with flibanserin 100 mg q.h.s. [N (%)] with possible clinically significant abnormalities by randomized treatment - treated set – Phase III placebo-controlled HSDD trials (Page 2 of 3)

Parameter/ Treatment	**N**	**Decrease**	**Increase**
Alkaline phosphatase			
Placebo	917	0	1 (0.1)
FLI 100 q.h.s.	629	0	0
Glucose			
Placebo	913	2 (0.2)	3 (0.3)
FLI 100 q.h.s.	627	1 (0.2)	6 (1.0)
Cholesterol			
Placebo	917	0	82 (8.9)
FLI 100 q.h.s.	629	0	37 (5.9)
BUN			
Placebo	917	0	1 (0.1)
FLI 100 q.h.s.	629	0	0
Creatinine			
Placebo	917	0	1 (0.1)
FLI 100 q.h.s.	629	0	2 (0.3)
Sex hormone binding protein			
Placebo	937	20 (2.1)	59 (6.3)
FLI 100 q.h.s.	621	12 (1.9)	51 (8.2)
Progesterone			
Placebo	930	153 (16.5)	2 (0.2)
FLI 100 q.h.s.	614	89 (14.5)	0

Table 7.2.3: 3 (continued) Frequency of subjects treated with flibanserin 100 mg q.h.s. [N (%)] with possible clinically significant abnormalities by randomized treatment - treated set – Phase III placebo-controlled HSDD trials (Page 3 of 3)

Parameter/ Treatment	N	Decrease	Increase
Prolactin			
Placebo	936	0	34 (3.6)
FLI 100 q.h.s.	626	0	21 (3.4)

Trials include 511.70, .71, .75, .77

a Subjects in 511.75 start on flibanserin 50 mg q.h.s. for the first 2 weeks, then up-titrate to 50 mg b.i.d.

b Subjects in 511.75 start on flibanserin 50 mg q.h.s. for the first 2 weeks, then up-titrate to 100 mg q.h.s.

Based on ranges in Appendix 7, Table 7.1.2

7.2.4 Other safety tables: Pelvic examinations, Cytological Smears, BSS and Pregnancies

Table 7.2.4: 1 Subjects with clinically relevant changes for pelvic examinations, including cytological smears - Phase III HSDD trials

			Had Normal Baseline			Had Abnormal Baseline		
Exam	Total treated	Total with baseline and final	N (%)	Normal at final (%)	Abnormal at final N (%)	N (%)	Normal at final (%)	Abnormal at final (%)
Bimanual exam	3594	1771	1753 (100.00)	1737 (99.09)	16 (0.91)	18 (100.00)	13 (72.22)	5 (27.78)
Cervix exam	3594	1774	1750 (100.00)	1728 (98.74)	22 (1.26)	24 (100.00)	20 (83.33)	4 (16.67)
Clitoris exam	3594	1778	1774 (100.00)	1772 (99.89)	2 (0.11)	4 (100.00)	4 (100.00)	0 (0.00)
Vagina exam	3594	1776	1768 (100.00)	1753 (99.15)	15 (0.85)	8 (100.00)	6 (75.00)	2 (25.00)
Vulva exam	3594	1777	1770 (100.00)	1760 (99.44)	10 (0.56)	7 (100.00)	7 (100.00)	0 (0.00)
Pap smear exam	3594	1746	1708 (100.00)	1629 (95.37)	79 (4.63)	38 (100.00)	34 (89.47)	4 (10.53)

Includes Trials 511.70, .71, .74, .75, .77, .84 and .118.
For 511.74, only women who received flibanserin in the randomized withdrawal period were included (i.e. those who received placebo are not included).
Patients from 511.105 did not have a pre-treatment baseline exam and are therefore not included in this table.
Patient 511.77/037842 is not included in this table due to a typographical error on the pelvic eCRF for the date of last pap smear.
Includes all data from these trials that are in the project database as of 17 Nov 2009.
Subjects from 511.84 sites 1021, 1078 and 1128 are not included in this table. Refer to Notes to Reviewer.

Table 7.2.4: 2 Beck Scale for Suicide Ideation - Phase III placebo-controlled HSDD trials

Visit	Endpoint	Treatment	Total N	N with score > 0	% with score > 0	List of subject numbers
Screen	BSS Part I	Placebo	1360	0	0.0%	
		Flibanserin	3431	4	0.1%	26763, 28515, 28517, 37273
	BSS Group 20	Placebo	1360	0	0.0%	
		Flibanserin	3431	5	0.1%	28440d, 36169d, 36189d, 37060d, 38202d
Baseline	BSS Part I	Placebo	1042	0	0.0%	
		Flibanserin	2804	1	0.0%	28515
	BSS Group 20	Placebo	1042	0	0.0%	
		Flibanserin	2804	2	0.1%	28440d, 29199d
On-treatmenta	BSS Part I	Placebo	1312	6	0.5%	19167, 27934, 37243, 37285, 37293, 37588
		Flibanserin	3283	12	0.4%	17260, 21988, 36189d, 36471, 36701, 37274, 37406, 37409d, 37416, 37884, 38068, 38169
	BSS Group 20	Placebo	1312	0	0.0%	
		Flibanserin	3283	7	0.2%	28440d, 29199d, 36169d, 36189d, 37060d, 37409d, 38202d
Post-treatmentb	BSS Part I	Placebo	972	2	0.2%	37243, 37588
		Flibanserin	2579	2	0.1%	36471, 38169d
	BSS Group 20	Placebo	972	0	0.0%	
		Flibanserin	2579	1	0.0%	28440d

Includes Trials 511.70, .71, .75, .74, and .77

a Value > 0 anytime on treatment

b Value > 0 anytime post−treatment

c Group 20 = suicide attempt (history)

d Six subjects (28440, 36169, 36189, 37060, 29199, 38202) recorded historical responses at on−treatment visits and Subject 37409 was incorrectly assessed at final visit

Table 7.2.4: 3 Number of pregnancies that occurred on treatment - Phase II/III HSDD trials

	-- Placebo	Flibanserin
Total number of Subjects	1530	4815
No. of pregnancies	17 (100.0)	44 (100.0)
Live Births	12 (70.6)	29 (65.9)
Congenital Malformation/Anomaly	1 (5.9)	1 (2.3)
Spontaneous abortion	0 (0.0)	5 (11.4)
Therapeutic abortion	4 (23.5)	4 (9.1)
Unknown outcome	0 (0.0)	3 (6.8)
Ectopic pregnancy	0 (0.0)	2 (4.5)

Trials include 511.70, 511,71, 511.74, 511.75, 511.77, 511.84 and 511.118
For 511.68 and 69 this information was not captured , so these patients are not counted in the number of subjects
For 511.118 there were no pregnancies.
For the 5 Spontaneous Abortions which occurred in the Flibanserin group, 4 patients were randomized to 50 mg qhs and 1 was randomized to 100 mg qhs.

For the total number of subjects, patients in the open label phase of the 511.74 trial are counted in both flibanserin group and the placebo group if they were randomized to placebo in the double blind phase.

Table 7.2.4: 4 Number (%) of subjects with selected AEs by anti-histamine use - Phase III placebo-controlled HSDD trials

System Organ Classa/Preferred Term	Placebo N (%)	FLI 100 qhs N (%)
Total treated	1360	1001
Non-user	1138(100.0)	836 (100.0)
User	222(100.0)	165 (100.0)
Total treated with events		
Non-user	622 (54.7)	556 (66.5)
User	163 (73.4)	140 (84.8)
Cardiac disorders		
Non-user	9 (0.8)	16(1.9)
User	1 (0.5)	5 (3.0)
Palpitations		
Non-user	6 (0.5)	7 (0.8)
User	0 (0.0)	3 (1.8)
Ear and labyrinth disorders		
Non-user	4 (0.4)	11 (1.3)
User	3 (1.4)	5 (3.0)
Vertigo		
Non-user	2 (0.2)	7 (0.8)
User	2 (0.9)	3 (1.8)
Gastrointestinal disorders		
Non-user	122 (10.7)	175 (20.0)
User	38 (17.1)	50 (30.3)
Nausea		
Non-user	43 (3.8)	92 (11.0)
User	15 (6.8)	27 (16.4)
Vomiting		
Non-user	21 (1.8)	20 (2.4)
User	3 (1.4)	4 (2.4)
General disorders and administrations site conditions		
Non-user	109 (9.6)	136 (16.3)
User	20 (9.0)	31 (18.8)
Fatigue		
Non-user	65 (5.7)	90 (10.8)
User	12 (5.4)	20 (12.1)
Nervous system disorders		
Non-user	177 (15.6)	258 (30.9)
User	49 (22.1)	64 (38.8)
Dizziness		
Non-user	28 (2.5)	97 (11.6)
User	6 (2.7)	23 (13.9)
Headache		
Non-user	100 (8.8)	100 (12.0)
User	27 (12.2)	20 (12.1)

Table 7.2.4: 4 (continued) Number (%) of subjects with selected AEs by anti-histamine use - Phase III placebo-controlled HSDD trials (Page 2 of 2)

Sedation		
Non-user	2 (0.2)	12 (1.4)
User	0 (0.0)	5 (3.0)
Somnolence		
Non-user	31 (2.7)	71 (8.5)
User	9 (4.1)	24(14.5)
Syncope		
Non-user	1 (0.1)	3 (0.4)
User	0 (0.0)	0 (0.0)
Syncope vasovagal		
Non-user	1 (0.1)	0 (0.0)
User	0 (0.0)	0 (0.0)
Psychiatric disorders		
Non-user	90 (7.9)	121(14.5)
User	24 (10.8)	38(23.0)
Depression		
Non-user	12 (1.1))	10 (1.2)
User	0.(0.0)	1 (0.6)
Insomnia		
Non-user	20 (1.8)	32 (3.8)
User	12 (5.4)	19(11.5)
Renal and urinary disorders		
Non-user	20 (1.8)	13 (1.6)
User	3 (1.4)	9 (5.5)
Nocturia		
Non-user	3 (0.3)	7 (0.8)
User	0 (0.0)	5 (3.0)
Vascular disorders		
Non-user	9 (0.8)	11 (1.3)
User	3 (1.4)	1 (0.6)
Hypotension		
Non-user	0 (0.0)	3 (0.4)
User	0 (0.0)	0 (0.0)
Circulatory collapse		
Non-user	1 (0.1)	1 (0.1)
User	0 (0.0)	0 (0.0)

Source: Table 5.2.3.1 ISS

Trials include 511.70, 511.71, 511.75, and 511.77

Tallies by usage group may differ from those in the corresponding rate difference table because subjects are classified by use anytime during the trial and trial 511.70 (which did not include flibanserin 100 mg qhs) is included in this table.

Table 7.2.4: 5 Number (%) of subjects with selected AEs by hormonal contraceptive use - Phase III placebo-controlled HSDD trials

System Organ Class/Preferred Term	Placebo N (%)	FLI 100 qhs N (%)
Total treated	1360	1001
Non-user	775 (100.0)	556 (100.0)
User	585 (100.0)	445 (100.0)
Total treated with events		
Non-user	452 (58.3)	371 (66.7)
User	333 (56.9)	325 (73.0)
Cardiac disorders		
Non-user	5 (0.6)	7 (1.3)
User	5 (0.9)	14 (3.1)
Palpitations		
Non-user	4 (0.5)	2 (0.4)
User	2 (0.3)	8 (1.8)
Ear and labyrinth disorders		
Non-user	7 (0.9)	5 (0.9)
User	0 (0.0)	11 (2.5)
Vertigo		
Non-user	4 (0.5)	3 (0.5)
User	0 (0.0)	7 (1.6)
Gastrointestinal disorders		
Non-user	91 (11.7)	112 (20.1)
User	69 (11.8)	113 (25.4)
Nausea		
Non-user	31 (4.0)	59 (10.6)
User	27 (4.6)	60 (13.5)
Vomiting		
Non-user	15 (1.9)	14 (2.5)
User	9 (1.5)	10 (2.2)
General disorders and administrations site conditions		
Non-user	72 (9.3)	80 (14.4)
User	57 (9.7)	87 (19.6)
Fatigue		
Non-user	44 (5.7)	49 (8.8)
User	33 (5.6)	61 (13.7)
Nervous system disorders		
Non-user	131(16.9)	153 (27.5)
User	95(16.2)	169 (38.0)
Dizziness		
Non-user	19 (2.5)	55 (9.9)
User	15 (2.6)	65 (14.6)
Headache		
Non-user	75 (9.7)	60 (10.8)
User	52 (8.9)	60 (13.5)

Table 7.2.4: 5 (continued) Number (%) of subjects with selected AEs by hormonal contraceptive use - Phase III placebo-controlled HSDD trials (Page 2 of 2)

Sedation		
Non-user	2 (0.3)	9 (1.6)
User	0 (0.0)	8 (1.8)
Somnolence		
Non-user	22 (2.8)	46 (8.3)
User	18 (3.1)	49(11.0)
Syncope		
Non-user	1 (0.1)	1 (0.2)
User	0 (0.0)	2 (0.4)
Syncope vasovagal		
Non-user	0 (0.0)	0 (0.0)
User	1 (0.2)	0 (0.0)
Psychiatric disorders		
Non-user	71 (9.2)	82 (14.7)
User	43 (7.4)	77 (17.3)
Depression		
Non-user	7 (0.9)	4 (0.7)
User	5 (0.9)	7 (1.6)
Insomnia		
Non-user	23 (3.0)	28 (5.0)
User	9 (1.5)	23 (5.2)
Renal and urinary disorders		
Non-user	14 (1.8)	7 (1.3)
User	9 (1.5)	15 (3.4)
Nocturia		
Non-user	2 (0.3)	2 (0.4)
User	1 (0.2)	10 (2.2)
Vascular disorders		
Non-user	6 (0.8)	6 (1.1)
User	6 (1.0)	6 (1.3)
Hypotension		
Non-user	0 (0.0)	0 (0.0)
User	0 (0.0)	3 (0.7)
Circulatory collapse		
Non-user	0 (0.0)	0 (0.0)
User	1 (0.2)	1 (0.2)

Source: Table 5.2.1.1 ISS

Trials include 511.70, 511.71, 511.75, and 511.77

Tallies by usage group may differ from those in the corresponding rate difference table because subjects are classified by use anytime during the trial and trial 511.70 (which did not include flibanserin 100 mg qhs) is included in this table.

Table 7.2.4: 6 Number (%) of subjects with AEs by CYP-3A4 inhibitor use - Phase III Placebo-controlled trials

System organ class Preferred term	Placebo N (%)	25 mg bid N (%)	50 mg qhs N (%)	50 mg bid N (%)	FLI 100 qhs N (%)
Total treated	1360	733	969	728	1001
None	1323 (100.0)	718(100.0)	932 (100.0)	719 (100.0)	975 (100.0)
Weak/moderate	34 (100.0)	9 (100.0)	31 (100.0)	7 (100.0)	20 (100.0)
Strong	3 (100.0)	6 (100.0)	6 (100.0)	2 (100.0)	6 (100.0)
Total treated with events					
None	755 (57.1)	416 (57.9)	598 (64.2)	508 (70.7)	674 (69.1)
Weak/moderate	27 (79.4)	9 (100.0)	25 (80.6)	7 (100.0)	16 (80.0)
Strong	3(100.0)	5 (83.3)	5 (83.3)	2 (100.0)	6 (100.0)
Gastrointestinal disorders					
None	153 (11.6)	0 (0.0)	140 (15.0)	145 (20.2)	218 (22.4)
Weak/moderate	5 (14.7)	0 (0.0)	9 (29.0)	2 (28.6)	5 (25.0)
Strong	2 (66.7)	0 (0.0)	1 (16.7)	1 (50.0)	2 (33.3)
Dry mouth					
None	8 (0.6)	6 (0.8)	10 (1.1)	10 (1.4)	22 (2.3)
Weak/moderate	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)	1 (5.0)
Strong	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea					
None	55 (4.2)	37 (5.2)	66 (7.1)	90 (12.5)	118 (12.1)
Weak/moderate	3 (8.8)	3 (33.3)	2 (6.5)	0 (0.0)	1 (5.0)
Strong	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions					
None	123 (9.3)	56(7.8)	98 (10.5)	123 (17.1)	163 (16.7)
Weak/moderate	6 (17.6)	0 (0.0)	2 (6.5)	1 (14.3)	3 (15.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Fatigue					
None	77 (5.8)	35 (4.9)	57 (6.1)	100 (13.9)	107 (11.0)
Weak/moderate	0 (0.0)	0 (0.0)	2 (6.5)	1 (14.3)	2 (10.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Nervous system disorders					
None	220(16.6)	137 (19.1)	200 (21.5)	270 (37.6)	312 (32.2)
Weak/moderate	5(14.7)	3 (33.3)	11 (35.5)	3 (42.9)	8 (40.0)
Strong	1 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	2 (33.3)
Dizziness					
None	32 (2.4)	30 (4.2)	59 (6.3)	110 (15.3)	115 (11.8)
Weak/moderate	2 (5.9)	1 (11.1)	2 (6.5)	1 (14.3)	4 (20.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Sedation					
None	2 (0.2)	1 (0.1)	6 (0.6)	10 (1.4)	17 (1.7)
Weak/moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence					
None	38 (2.9)	49 (6.8)	51 (5.5)	120 (16.7)	91 (9.3)
Weak/moderate	2 (5.9)	1 (11.1)	4 (12.9)	2 (28.6)	3 (15.0)
Strong	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Syncope					
None	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)	3 (0.3)
Weak/moderate	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders					
None	111 (8.4)	47 (6.5)	103 (11.1)	71 (9.9)	154 (15.8)
Weak/moderate	3 (8.8)	2 (22.2)	4 (12.9)	0 (0.0)	4 (20.0)
Strong	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Insomnia					
None	32 (2.4)	13 (1.8)	19 (2.0)	20 (2.8)	50 (5.1)
Weak/moderate	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (5.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 7.2.4: 6 (continued) Number (%) of subjects with AEs by CYP-3A4 inhibitor use - Phase III Placebo-controlled trials (Page 2 of 2)

Vascular disorders					
None	11 (0.8)	8 (1.1)	9 (1.0)	8 (1.1)	11 (1.2)
Weak/moderate	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Circulatory collapse					
None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Weak/moderate	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension					
None	0 (0.0)			1 (0.1)	2 (0.2)
Weak/moderate	0 (0.0)			0 (0.0)	1 (5.0)
Strong	0 (0.0)			0 (0.0)	0 (0.0)

Trials include: 511.70, 511.71, 511.75, and 511.77

7.2.5 Serious adverse events

Table 7.2.5: 1 List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects

Subject	Trial No.	SAE Preferred term	Start Day b	Duration	Intensity	Action taken	Related to study druga
Placebo							
14104	511.74	Accidental death	19	19	Severe	Resulted in death	No
19837	511.70	Erythema infectiosum	101	128	Moderate	Hospitalized/Discontinued	No
31652	511.70	Breast cancer	91	40	Severe	Hospitalized/Discontinued	No
32070	511.75	Biliary colic; cholethiasis	42	2	Moderate	Hospitalized/Discontinued	No
32123	511.75	Phlebitis unspecified	148	161	Moderate	Discontinued	No
36770	511.77	Hematuria	40	2	Moderate	Prolonged hospitalization	No
37308	511.77	Cholethiasis	119	9	Severe	Hospitalized	No
37629	511.77	Parovarian cyst	169	35	Moderate	Hospitalized	No
38179	511.77	Ovarian cyst ruptured	94	1	Moderate	Hospitalized/discontinued	No
Flibanserin 25 mg b.i.d.							
16974	511.70	Invertebral disc protrusion	68	108	Severe	Hospitalized	No
27535	511.75	Avulsion fracture/femur fracture/road traffic accident	70	3/3/1	Severe	Hospitalization/discontinued	No
29300	511.75	Appendicitis	24	4	Severe	Hospitalized	No
30770	511.75	Ovarian cyst	82	33	Moderate	Hospitalized/discontinued	No
36459	511.118	Breast cancer in situ	11	91	Severe	Other/discontinued	No
39112	511.105	Depression	4	8	Severe	Hospitalized/discontinued	No

Table 7.2.5: 1 (continued) List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects (Page 2 of 7)

Subject	Trial No.	SAE Preferred term	Start Day	Duration	Intensity	Action taken	Related to study druga
Flibanserin 50 mg q.h.s.							
22444	511.70	Appendicitis	160	3	Severe	Hospitalization	No
25647	511.71	Appendicitis	36	1	Severe	Hospitalization/discontinued	No
27890	511.75	Appendicitis	3	1	Severe	Hospitalization	No
31381	511.75	Appendicitis	3	2	Mild	Hospitalization	No
23349	511.71	Gastroenteritis/ urinary tract infection	110/110	10/10	Severe/moderate	Hospitalization/ Hospitalization	No/no
20265	511.70	Basal cell carcinoma	73	29	Moderate	Other	No
38162	511.77	Gliosis	16	-	Severe	Hospitalization/Discontinued	No
21902	511.70	Cholethiasis	79	2	Moderate	Other/discontinuation	No
37170	511.77	Invertebral disc protrusion	22	55	Severe	Hospitalization	No
38383	511.77	Metorrhagia	91	2	Moderate	Hospitalization	No
28435	511.75	Appendicitis	112	2	Severe	Hospitalization/discontinued	No
17636	511.70	Breast cancer in situ	81	148	Severe	Other	No
30501	511.75	Cholethiasis acute, cholethiasis	84	8	Severe	Hospitalization/discontinued	No
38300	511.77	Thoracic vertebral fracture	142	244	Severe	Hospitalization	No
37524	511.77	Abdominal pain	166	189	Severe	Hospitalization	No
12612	511.74	Cholelithiasis	47	64	Severe	Hospitalization/discontinued	No

Table 7.2.5: 1 (continued) List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects (Page 3 of 7)

Subject	Trial No.	SAE Preferred term	Start Day	Duration	Intensity	Action taken	Related to study druga
Flibanserin 50 mg q.h.s.							
28817	511.84	Thyroid cancer	86	198	Severe	Hospitalization/discontinued	No
		Thyroid neoplasm	32	73	Moderate	Hospitalization/discontinued	No
30933	511.84	Intervertebral disc degeneration	7	391	Severe	Hospitalization	No
24143	511.84	Pneumonia	43	6	Severe	Hospitalization	No
25494	511.84	Asthma	10	3	Moderate	Hospitalization/discontinued	No
31009	511.84	Gastroesophageal reflux disease	221	2	Moderate	Hospitalization	No
36715	511.118	Abdominal pain	69	2	Severe	Hospitalization	No
37279	511.118	Gastroenteritis	26	7	Severe	Hospitalization	No
37784	511.118	Femur fracture	28	42	Severe	Hospitalization/discontinued	No
38159	511.118	Migraine with aura	31	3	Severe	Hospitalization/discontinued	No
37138	511.118	Ovarian cyst; uterine polyp	103	69	Moderate	Discontinued	Yes
37890	511.118	Ectopic pregnancy	169	1	-	Hospitalization	No

Table 7.2.5: 1 (continued) List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects (Page 4 of 7)

Subject	Trial No.	SAE Preferred term	Start Day	Duration	Intensity	Action taken	Related to study druga
Flibanserin 50 mg b.i.d.							
30241	511.84	Abdominal abscess	20	21	Moderate	Hospitalization/discontinued	No
28435	511.75	Appendicitis	112	2	Severe	Hospitalization/discontinued	No
30241	511.84	Urinary tract infection	48	21	Moderate	Hospitalization/discontinued	No
17636	511.70	Breast cancer in situ	81	148	Severe	Other/discontinuation	No
11101	511.74	Malignant melanoma	38	305	Mild	Other	No
30501	511.75	Cholecystitis acute/ Cholelithiasis	84	8	Severe	Hospitalization/discontinued	No
17703	511.84	Ovarian cyst	72	42	Moderate	Hospitalization/discontinued	No
11800	511.74	Tibia fracture	48	7	Severe	Hospitalization	No
28811	511.84	Uterine leiomyoma	189	46	Severe	Hospitalization	No

Table 7.2.5: 1 (continued) List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects (Page 5 of 7)

Subject	Trial No.	SAE Preferred term	Start Day	Duration	Intensity	Action taken	Related to study druga
Flibanserin 100 mg q.h.s.							
10506	511.74	Suicidal ideation	93	20	Moderate	Hospitalization	No
26316	511.71	Crohn's disease	102	268	Severe	Hospitalization	No
37759	511.77	Subileus	53	20	moderate	Hospitalization	No
37779	511.77	Concussion	11	2	Severe	Hospitalization	No
		Circulatory collapse	11	2	Severe	Hospitalization	No
18697	511.84	Appendicitis	244	3	Severe	Hospitalization	No
25268	511.84	Appendicitis	27	2	Severe	Hospitalization/discontinued	No
11706	511.74	Pyelonephritis /Bacterial sepsis	45/53	21/13	Severe/Severe	Hospitalization/discontinued Prolonged Hospitalization	No/no
29443	511.75	Invertebral disc degeneration	86	9	Moderate	Hospitalization/discontinued	No
30933	511.75	Invertebral disc protrusion	75	2	Severe	Hospitalization	No
28344	511.75	Concussion/ nerve root injury lumbar/road traffic accident/skin laceration	10/10/10/ 10	196/30/1/ 35	Severe/moderate/ severe/severe	Hospitalization/ Hospitalization/ Hospitalization/ Hospitalization	No/no/no/no
24654	511.71	Respiratory fume inhalation disorder	29	2	Severe	Immediately life threatening/discontinued	No
27303	511.75	Abortion induced	157	1	Moderate	Other	No
25186	511.71	Colon cancer/metastases to lymph nodes/large intestine perforation	94	215/215/ 2	Severe	Hospitalization/ discontinued	No/no/no

Table 7.2.5: 1 (continued) List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects (Page 6 of 7)

Subject	Trial No.	SAE Preferred term	Start Day	Duration	Intensity	Action taken	Related to study druga
Flibanserin 100 mg q.h.s.							
25204	511.84	Malignant melanoma	290	51	Mild	Other	No
36657	511.77	Suicide attempt	21	2	Severe	Hospitalization - life threatening	No
25494	511.84	Asthma	10	3	Modereate	Hospitalization/discontinued	No
27908	511.84	Thyroid mass	114	18	Severe	Hospitalization/discontinued	No
31009	511.84	Gastrooesophageal reflux disease	221	2	Moderate	Hospitalization	No
14417	511.84	Cervicobrachial syndrome	216	8	Severe	Hospitalization/discontinued	No
36164	511.118 Accident at work	Neuralgia	69 69	257 225	Severe Severe	Persistent or significant disability Persistent or significant disability	No No
10915	511.84	Mitral valve prolapse/Atrioventricular block complete/ Bradycardia/ aortic aneurysm/aortic stenosis/device dislocation	92/92/92/ 147/99/99	108/563/ 8/60/ 108/3	Severe/severe/ severe/severe/ severe	Hospitalization/discontinued/ prolonged hospitalization/prolonged hospitalization/ Hospitalization/discontinued/ Hospitalization/discontinued hospitalization	No/no/no/no /no/no
25262	511.84	Asthma/chronic obstructive pulmonary disease	145/145	12/	Moderate/ moderate	Hospitalization/hospitalization	No/no
25268	511.84	Abdominal adhesions	33	6	Severe	Hospitalization	No

Table 7.2.5: 1 (continued) List of serious adverse events by subject and actual treatment at onset - All Trials in HSDD subjects (Page 7 of 7)

Subject	Trial No.	SAE Preferred term	Start Day	Duration	Intensity	Action taken	Related to study druga
Flibanserin 100 mg q.h.s.							
10905	511.74	Abdominal pain/cholelithiasis/ovarian cyst ruptured	17/130/ 17	3/2/ 4	Severe/severe/ severe	Hospitalization/discontinued	No/no/no
30402	511.84	Gastritis	168	6	Severe	Hospitalization	No
14914	511.74	Hiatus hernia	196	58	Moderate	Hospitalization	No
14417	511.84	Neck pain	209	331	Severe	Hospitalization/discontinued	No
14322	511.84	Osteoarthritis	79	4	Severe	Hospitalization/discontinued	No
19755	511.84	Spinal osteoarthritis	75	2	Severe	Hospitalization/discontinued	No
25943	511.84	Nephrolithiasis	12	3	Severe	Hospitalization/discontinued	No
32186	511.84	Pelvic pain	40	-	Severe	Hospitalization	No
25156	511.84	Worsening menorrhagia/dysmenorhagia	356	3	-	Hospitalization	No
38067	511.118	Surgery of old ankle injury	159	9	Severe	Hospitalization/discontinued	No
38363	511.118	Examphalos/umbilical hernia	51		20	Hospitalization	No

Trials include 511.68, .69, 511.105, .70, .71, .74, .75, .77, .84, and .118

a Relationship as determined by investigator

b Start day is related to start of study treatment

7.2.6 Adverse events with daily doses higher than 100mg

Table 7.2.6: 1 Number of subjects with adverse events - Phase I single increasing oral administration in healthy male subjects.

		Fli 150 mg
511.1	Total number of subjects with events	6
	Fatigue	3
	Somnolence	1
	Nausea	1
		Fli 150 mg
511.9	Total number of subjects with events	6
	Fatigue	6
	Somnolence	5
	Asthenia	4
	Nausea	3
	Pallor	3
	Speech disorder	3
	Mouth dry	2
	Headache	1
	Impaired concentration	1
	Vertigo	1
	Hot flushes	1
	Taste perversion	1
	Dysphagia	1
	Agitation	1

Source: eCTR 511.01.02 [U96-2372] Table 10.2.1:1 and eCTR 511.9 [U96-2373] Table 10.2.1:1

Table 7.2.6: 2 Frequency [N (%)] of subjects with adverse events –Phase I multiple increasing doses in healthy male and female subjects.

		Placebo	100 mg t.i.d.
511.2	Total number of subjects	20	13
	Total number of subjects with events	7 (35.0)	13 (100.0)
	Fatigue	2(10.0)	8 (61.5)
	Dizziness	1 (5.0)	7 (53.9)
	Polyuria	0 (0.00)	7 (53.9)
	Headache	4 (20.0)	7 (53.9)
	Nausea	0 (0.0)	3 (23.1)
	Insomnia	0 (0.0)	3 (23.1)
	Myasthenia Gravis-like syndrome	0 (0.0)	2(15.4)
	Chest Pain	0 (0.0)	2(15.4)
	Hiccup	0 (0.0)	2(15.4)
	Constipation	0 (0.0)	2(15.4)
	Aphasia	0 (0.0)	1 (7.7)
	Tremor	0 (0.0)	1 (7.7)
	Back Pain	1 (5.0)	1 (7.7)
	Dysuria	0 (0.0)	1 (7.7)
	Paroniria	1 (5.0)	1 (7.7)
	Somnolence	0 (0.0)	1 (7.7)
	Impotence	0 (0.0)	1 (7.7)
	Concentration Impaired	0 (0.0)	1 (7.7)
	Flatulence	0 (0.0)	1 (7.7)
	Anorexia	0 (0.0)	1 (7.7)
	Acne	0 (0.0)	1 (7.7)
	Pruritus	0 (0.0)	1 (7.7)
	Skin Dry	0 (0.0)	1 (7.7)
	Menstrual Disorder	0 (0.0)	1 (7.7)
511.90	Total number of subjects	54	56
	Total number with adverse events	22 (40.7)	36 (64.3)
	Fatigue	6 (11.1)	19 (33.9)
	Dizziness	3 (5.6)	15 (26.8)
	Nausea	2 (3.7)	14 (25.0)
	Headache	7 (13.0)	13 (23.2)
	Palpitations	0 (0.00)	3 (5.4)
	Somnolence	0 (0.00)	3 (5.4)
	Stomache discomfort	0 (0.00)	3 (5.4)
	Hiccups	0 (0.00)	2 (3.6)
	Abdominal distension	0 (0.00)	2 (3.6)
	Diarrhoea	3 (5.6)	2 (3.6)
	Dry mouth	0 (0.00)	2 (3.6)
	Acne	1 (1.9)	2 (3.6)
	Asthenia	0 (0.00)	2 (3.6)

Table 7.2.6: 2 (continued) Frequency [N (%)] of subjects with adverse events - Phase I multiple increasing doses in healthy male and female subjects (Page 2 of 2)

	Insomnia	0 (0.00)	1 (1.8)
	Dizziness postural	0 (0.00)	1 (1.8)
	Retching	0 (0.00)	1 (1.8)
	Panic Attack	0 (0.00)	1 (1.8)
	Hypoaesthesia	0 (0.00)	1 (1.8)
	Poor quality sleep	0 (0.00)	1 (1.8)
	Tachycardia	0 (0.00)	1 (1.8)
	Syncope	0 (0.00)	1 (1.8)
	Haematoma	0 (0.00)	1 (1.8)
	Hot flush	0 (0.00)	1 (1.8)
	Constipation	0 (0.00)	1 (1.8)
	Vomiting	0 (0.00)	1 (1.8)
	Sensation of heaviness	0 (0.00)	1 (1.8)
	Mictuition urgency	0 (0.00)	1 (1.8)
	Gait disturbance	0 (0.00)	1 (1.8)

Source: Clinical Trial Report 511.2 [U97-2256] Table 10.2.1:1 and Clinical Trial Report 511.90 [U07-1866] Table 15.3.2:2

Table 7.2.6: 3 Number (%) of subjects with adverse events occurring in >=1% by treatment at onset - Phase II placebo-controlled MDD trials

Preferred term	Placebo N (%)	FLI > 100 N (%)
Total number of subjects	718	211
Total with adverse events	520 (72.4)	179 (84.8)
Somnolence	63 (8.8)	84 (39.8)
Dizziness	34 (4.7)	59 (28.0)
Nausea	68 (9.5)	46 (21.8)
Headache	131 (18.2)	23 (10.9)
Dry mouth	52 (7.2)	22 (10.4)
Fatique	34 (4.7)	20 (9.5)
Insomia	43 (6.0)	15 (7.1)
Upper respiratory tract infection	55 (7.7)	13 (6.2)
Vomiting	9 (1.3)	10 (4.7)
Constipation	20 (2.8)	10 (4.7)
Anxiety	11 (1.5)	9 (4.3)
Diarrhoea	50 (7.0)	8 (3.8)
Dyspepsia	27 (3.8)	8 (3.8)
Pollakiuria	29 (4.0)	8 (3.8)
Asthenia	19 (2.6)	8 (3.8)
Accident at Home	11 (1.5)	7 (3.3)
Anorexia	11 (1.5)	6 (2.8)
Confusional state	3 (0.4)	6 (2.8)
Nervousness	19 (2.6)	6 (2.8)
Visual Impairment	10 (1.4)	6 (2.8)
Myalgia	13 (1.8)	6 (2.8)
Abdominal pain	40 (5.6)	6 (2.8)
Influenza like illness	30 (4.2)	6 (2.8)
Sinusitis	11 (1.5)	5 (2.4)
Rhinitis	6 (0.8)	5 (2.4)
Palpitations	20 (2.8)	5 (2.4)
Back Pain	23 (3.2)	5 (2.4)
Pain	14 (1.9)	5 (2.4)
Pharyngitis	12 (1.7)	4 (1.9)
Flatulence	22 (3.1)	4 (1.9)
Erectile dysfunction	2 (0.3)	3 (1.4)
Depression	6 (0.8)	3 (1.4)
Hypersensitivity	2 (0.3)	3 (1.4)
Paraesthesia	4 (0.6)	3 (1.4)
Libido decreased	4 (0.6)	3 (1.4)
Durturbance in attention	7(1.0)	3 (1.4)
Arthralgia	5 (0.7)	3 (1.4)
Amnesia	7 (1.0)	2 (0.9)
Tremor	10 (1.4)	2 (0.2)
Increased appetite	3 (0.4)	2 (0.9)
Abnormal dreams	17 (2.4)	2 (0.9)
Agitation	12 (1.7)	2 (0.9)
Tachycardia	11 (1.5)	2 (0.9)
Dyspnoea	5 (0.7)	2 (0.9)
Hyperhidrosis	22 (3.1)	2 (0.9)
Nightmare	8 (1.1)	1 (0.9)
Hypertonia	5 (0.9)	1 (0.5)
Hypoaesthesia	1 (0.1)	1 (0.5)

Table 7.2.6: 3 (continued) Number (%) of subjects with adverse events occurring in >=1% by treatment at onset – Phase II placebo-controlled MDD trials (Page 2 of 2)

Muscle contractions involuntary	5 (0.7)	1 (0.5)
Xerophthalmia	8 (1.1)	1 (0.5)
Tinnitus	5 (0.7)	1 (0.5)
Epistaxis	1 (0.1)	1 (0.5)
Rash	9 (1.3)	1 (0.5)
Photosensitivity reaction	2 (0.3)	1 (0.5)
Acne	2 (0.3)	1 (0.5)
Dysmenorrhoea	5 (0.7)	1 (0.5)
Chest Pain	14 (1.9)	1 (0.5)
Oedema Peripheral	0 (0.0)	1 (0.5)

Source: ISS, Table 2.1.3.1 Trials 511.10, 511.11, 511.12, 511.18, 511.28, 511.41, 511.42, 511.43

Table 7.2.6: 4 Number (%) of subjects with adverse events occuring in >=1% and twice that of placebo - Phase II placebo-controlled HSDD trials

Preferred term	Placebo N (%)	FLI 100 b.i.d. N (%)
Number of subjects	1508	72
Somnolence	43 (2.85)	14 (19.44)
Dizziness	40 (2.65)	9 (12.50)
Sedation	7 (0.46)	9 (12.50)
Nausea	71 (4.71)	8 (11.11)
Irritability	20 (1.33)	2 (2.78)
Nasal congestion	12(0.80)	2 (2.78)
Vulvovaginal dryness	4 (0.27)	2 (2.78)
Vertigo	4 (0.27)	2 (2.78)
Anxiety	9 (0.60)	1 (1.39)
Pain in estremity	8 (0.53)	1 (1.39)
Paraesthesia	7 (0.46)	1 (1.39)
Lethargy	7 (0.46)	1 (1.39)
Breast pain	7 (0.46)	1 (1.39)
Disturbance in attention	4 (0.27)	1 (1.39)
Hot flush	4 (0.27)	1 (1.39)
Flatulence	4 (0.27)	1 (1.39)
Pneumonia	3 (0.20)	1 (1.39)
Feeling abnormal	2 (0.13)	1 (1.39)
Thirst	2 (0.13)	1 (1.39)
Balance dirorder	1 (0.07)	1 (1.39)
Fall	1 (0.07)	1 (1.39)
Breast Engorgement	1 (0.07)	1 (1.39)
Cognitive disorder	1 (0.07)	1 (1.39)
Dyspareunia	1 (0.07)	1 (1.39)
Confusional state	0 (0.00)	1 (1.39)
Groin pain	0 (0.00)	1 (1.39)
Injury	0 (0.00)	1 (1.39)
Mental impairment	0 (0.00)	1 (1.39)
Scotoma	0 (0.00)	1 (1.39)

Source: ISS table Balance disorder 2.1.2.1.2; Trials: 511. 68 and 511.69

7.3 THE DECREASED SEXUAL DESIRE SCALE (DSDS): VALIDATION OF A BRIEF DIAGNOSTIC TOOL FOR WOMEN WITH GENERALIZED, ACQUIRED HYPOACTIVE SEXUAL DESIRE DISORDER

The estimated proportion of women with Female Sexual Dysfunction (FSD) varies widely; the majority of them, up to 10% of the population, appear to qualify for Hypoactive Sexual Desire Disorder (HSDD) in epidemiology surveys. In practice, however, the diagnosis of HSDD often occurs only after a time-consuming, extensive interview conducted by an expert. Given the time and knowledge requirements, many patients are left undiagnosed and therefore unable to be helped. Thus the sponsor developed in consultation with experts in the diagnosis of FSD and HSDD a brief diagnostic instrument for use by primary care practitioners.

Other short-form instruments to diagnose HSDD are likert scales covering symptoms of sexual function only. The DSDS was developed using simpler yes/no questions on sexual symptoms but adding the common extraneous causes of sexual dysfunction due to other illnesses, substance use, or relationship issues for greater diagnostic specificity.

This summarizes the sponsor's two trials using the DSDS, a brief 5-question screening instrument to diagnose HSDD (see Appendix), comparing results to an extensive diagnostic interview by a clinician experienced and trained in diagnosing HSDD.

7.3.1 Methods

1. Non-Treatment Study to estimate specificity and sensitivity

A total of 263 patients over 27 centers in a non-drug validation trial were given the DSDS by a clinician who decided whether or not the patient then merited a diagnosis of generalized, acquired HSDD. A second clinician, who was considered an expert in HSDD and had passed certification by an independent training body, and who was blinded to the results of the first clinician, then conducted an extensive clinical interview and gave the patient a diagnosis of HSDD, FSD but not HSDD, or no FSD. Results of the two groups of diagnosticians were compared. In addition, cognitive debriefing was performed in a subset of 89 women and with all non-expert clinicians.

2. Phase III Treatment Study of Flibanserin to estimate sensitivity in women recruited for distressing loss of sexual desire

A Phase III trial involving active drug (and thus a more extensive screening process) was then conducted involving 921 patients in 67 centers. Again, the initial, non-expert clinician used the DSDS to decide whether or not the patient had generalized, acquired HSDD, and a second, independently trained and certified, clinician, blinded to the results of the first clinician, conducted an extensive clinical interview and decided whether or not the patient had HSDD. Results of the two groups were compared.

7.3.2 Results

1. Non-Treatment Study

In the non-drug trial, the DSDS had a sensitivity of 83.6%, specificity of 87.8%, and accuracy of 85.2%. Cognitive debriefing showed that each question and answer set was understood by, and acceptable to, the vast majority of women and non-expert clinicians.

2. Phase III Treatment Study

In the treatment trial, the DSDS had a sensitivity of 94.6%. Anecdotally, the expert, standardized interview was reported to take approximately an hour to complete, while the DSDS took less than 15 minutes and in some cases less than 5 minutes. With no data collected on "normal" patients, estimation of specificity was not possible.

7.3.3 Conclusions

Expert diagnosis of HSDD remains an onerous and meticulous process. The sponsor's new validated diagnostic tool, the Decreased Sexual Desire Scale (DSDS), significantly assists the non-expert clinician in achieving an accurate diagnosis of generalized, acquired HSDD in women. The DSDS saves time without sacrificing accuracy, thus allowing this cohort of patients to be properly diagnosed and therefore take the necessary first step in seeking treatment.

7.3.4 The Decreased Sexual Desire Screener (DSDS©)

Dear Patient,

Please answer each of the following questions:

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 check 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

When complete, please give this form back to your clinician.

Thank you!

Clinician:

Verify with the patient each of the answers she has given.

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision® characterizes Hypoactive Sexual Desire Disorder (HSDD) as a deficiency 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. HSDD can be either generalized (not limited to certain types of stimulation, situations, or partners) or situational, and can be either acquired (develops only after a period of normal functioning) or lifelong. To determine if symptoms are acquired, ask if there was a period of normal functioning at any time in the past.

If the patient answers "NO" to any of the questions 1 through 4, then she does not qualify for the diagnosis of generalized, acquired HSDD.

If the patient answers "YES" to all of the questions 1 through 4, and your review confirms "NO" answers to all of the factors in question 5, then she does qualify for the diagnosis of generalized, acquired HSDD.

If the patient answers "YES" to all of the questions 1 through 4 and "YES" to any of the factors in question 5, then decide if the answers to question 5 indicate a primary diagnosis other than generalized, acquired HSDD. Co-morbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

Based on the above, does the patient have generalized, acquired Hypoactive Sexual Desire Disorder?

____YES ____NO

Thank you.