Background Document for Meeting of Advisory Committee for Reproductive Health Drugs (June 18, 2010)

NDA 22-526

Flibanserin

(Proposed trade name: Girosa)

Boehringer Ingelheim

Proposed Indication:

Flibanserin is indicated for the treatment of hypoactive sexual desire disorder in premenopausal women

Dosing regimen

100 mg tablet orally once daily at bedtime

Prepared by the Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE(s)	Adverse event(s)
ANCOVA	Analysis of covariance
ASEX	Arizona Sexual Experiences scale
BID	Twice daily dosing (morning and evening)
CI	Confidence interval
DHEAS	Dehydroepiandrosterone sulfate
eDiary	Electronic diary
FAS	Full analysis set
FLI	Flibanserin
FSDS-R	Female Sexual Distress Scale- Revised
FSFI	Female Sexual Function Index
ITT	Intent-to-treat
LOCF	Last observation carried forward
MDD	Major depressive disorder
NA	North American or not-applicable
prn	As needed dosing
PT	Preferred term
qd	Daily dosing
qhs	at bedtime dosing
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SD	Standard deviation
tdd	Total daily dose
TID	Three times daily dosing

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 22-526 to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

1. BACKGROUND

1.1 Objective of Meeting and Overview of Development Program

The purpose of this Advisory Committee meeting is to review and discuss the safety, efficacy, and overall risk/benefit profile of flibanserin, dosed at 100 mg daily at bedtime (qhs) for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. HSDD is defined as the persistent or recurrent deficiency or absence of sexual thoughts, fantasies, and/or desire for sexual activity, which causes marked distress or interpersonal difficulty. Low sexual desire may be associated with low sexual activity, sexual arousal problems or orgasm difficulty.

Data in support of the efficacy of flibanserin treatment for the proposed indication is based primarily on two prospective, randomized, double-blind, North American clinical trials (Studies 511.71 and 511.75) that compared two doses of flibanserin (50 mg qhs and 100 mg daily [as 50 mg BID or 100 mg qhs]) to placebo in premenopausal women with documented HSDD. Supportive efficacy and safety data were obtained from three phase 3, randomized, double-blind placebo-controlled trials – Studies 511.70 and 511.74 (North American), and Study 511.77 (conducted in Europe). Women from the four North American trials were invited to participate in the open-label, uncontrolled, 52-week extension Study 511.84, which focused on long-term safety.

For efficacy determination, this Background Document will focus primarily on the two blinded 24-week trials (Studies 511.71 and 511.75) that used the 100 mg qhs flibanserin dose, as this is the only dose for which the Applicant is seeking approval. Safety assessment is based on data from all studies conducted in the HSDD population.

1.2 Background

Flibanserin was originally studied in men and women for the treatment of major depression. In phase 2a depression trials, in which flibanserin failed to demonstrate efficacy on the primary endpoint, little sexual dysfunction was noted. For that reason, in all four phase 2b depression studies, the Arizona Sexual Experiences Scale (ASEX) was included for comparison of flibanserin to an approved antidepressant and to placebo in its effect on sexual function. Although the phase 2b trials failed to demonstrate consistent efficacy for depression, flibanserin was found to be superior to both placebo and active comparator with respect to the "How strong

is your sex drive?" item on the ASEX scale. This finding was the basis for the Applicant's decision to pursue the indication of HSDD in premenopausal women.

1.3 Issues for Committee Consideration

The Issues for Committee Consideration include the following:

- Overall efficacy of flibanserin compared to placebo
- Interpretation of the effect of flibanserin on sexual desire
- Generalizability of study results to the likely target population of users
- Overall risk/benefit of flibanserin in premenopausal women with HSDD
- If approval is recommended, how to best manage the safety issues the Division has identified with this product

1.4 Hypoactive Sexual Desire Disorder

HSDD is characterized by a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that is associated with personal distress. Judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning (such as age, medications, and context of the person's life). The women studied in the flibanserin development program had acquired, as opposed to lifelong, and general, as opposed to situational, HSDD.

There are no drug products currently approved in the U.S. for the treatment of HSDD. A transdermal testosterone patch is approved for HSDD in several European countries.

1.5 5HT1A Agonist and 5HT2A Antagonist Drugs

Flibanserin is a post-synaptic 5-HT_{1A} agonist and 5-HT_{2A} antagonist that has been evaluated for indications of major depressive disorder (MDD) and for the treatment of HSDD in premenopausal women. In addition to its activity at serotonin receptors, flibanserin binds with moderate affinity to 5-HT_{2B}, 5-HT_{2C} and dopamine D_4 receptors. There are no currently marketed products with the same neurotransmitter activity as flibanserin.

Evidence from a variety of sources suggests that the neurotransmitter serotonin may have a role in HSDD by acting excessively as a sexual satiety signal. Serotonergic agents such as the selective serotonin reuptake inhibitors (SSRIs) inhibit all phases of sex including desire, arousal, and orgasm. Addition of the 5-HT_{1A} receptor partial agonist, buspirone, to SSRI treatment has been shown to counteract these negative sexual side effects. The 5-HT_{1A} receptor mediates inhibitory neurotransmission. Flibanserin, as a full 5-HT1A receptor agonist, is presumed to have similar or even more pronounced pro-sexual effects as buspirone.

Stimulation of the serotonin 5-HT_{2A} receptor in male rodents has been associated with decreased sexual behavior. Thus, 5-HT_{2A} antagonism is theorized to have pro-sexual effects. Supporting this notion is the fact that nefazodone, an SSRI with inherent 5-HT_{2A} receptor antagonist activity, has fewer negative sexual side effects than other SSRIs without such activity. Flibanserin has been shown to block central 5-HT_{2A} receptors, and thus might reverse sexual inhibition caused by an excess of serotonin activity in the brain.

Although flibanserin's effect is believed to be related to its activity at the 5-HT_{1A} and 5-HT_{2A} receptors, its mechanism of action in the treatment of HSDD is unknown.

1.6 Regulatory Guidance for the Development of Products for Treatment of HSDD

In May 2000, the Division of Reproductive/Urologic Drug Products (DRUP) issued a draft guidance for industry entitled, *Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment* (see Section 6.2). Important recommendations pertaining to products indicated for HSDD contained in this document are the following:

- The change from baseline for satisfactory sexual events (SSEs) should be the primary endpoint, and SSEs should be recorded daily by the subject
- Two randomized, blinded, controlled six-month studies are required to support a marketing application for HSDD

In practice, the Division has typically advised sponsors of products intended to treat HSDD that the co-primary efficacy endpoints should include change from baseline in SSEs and sexual desire, and that change from baseline in personal distress due to HSDD should be a key secondary endpoint (or a co-primary endpoint).

2. CLINICAL DEVELOPMENT OF FLIBANSERIN

2.1 Overview of Preclinical Studies

Important issues related to pharmacology/toxicology evaluations were as follows:

2.1.1 Primary Pharmacodynamics

Flibanserin binds to the serotonin receptor and functions as a 5-hydroxytryptamine ($5\text{-}HT_{1A}$) agonist and $5\text{-}HT_{2A}$ antagonist and decreases extracellular serotonin, increases norepinephrine and has mixed effects on dopamine in the rat prefrontal cortex, medial preoptic area and nucleus accumbens.

In a rat model of sexual activity, flibanserin increased solicitation behavior in females on two of the five days of assessment. No other measures of sexual motivation or behavior such as lordosis were observed.

2.1.2 Toxicology

Flibanserin had minimal toxicity in rats and produced corneal opacities and fatty accumulation in heart muscle in dogs at six times the human exposure.

2.1.3 Carcinogenicity

In mice, flibanserin administration for two years produced a significant dose-related increase in mammary gland carcinomas at three times the human exposure. This effect was not seen in rats.

Charles River CD-1 mice were given flibanserin orally at doses of 10, 80, 200 and 1000 (males), 1000/1200 mg/kg (raised to 1200 for females on drug week 23 due to lack of toxicity) for 104 weeks. Results of this two year carcinogenicity study are shown in Table 1.

Table 1 Mouse Mammary Tumor Incidence in Females

Dose level (mg/kg)	0	0	10	80	200	1200
# of animals examined	70	70	70	70	70	70
# with adenocarcinoma + adenoacanthoma*	0	1	3	3	6[@]	7[@,#]

*variation of adenocarcinoma
[@] $p < 0.01$ vs. combined controls
[#] $p < 0.005$ for trend compared to combined controls
Source: FDA Pharmacology/Toxicology review by Alex Jordan, Ph.D.

Flibanserin treatment resulted in a highly significant dose-related increase in the incidence of mammary tumors in female mice. The percent of malignant mammary tumors in flibanserin treated mice was 0.7% for the combined controls and 4.3, 4.3, 8.6, and 10% in low to high doses, respectively.

Data from female CD-1 mice from the same supplier show that control mice had an average incidence of malignant mammary gland tumors of 2.7% and a maximum incidence within any one group of 8.3%.

At the two highest doses in female mice (200 and 1200 mg/kg), the exposure to parent drug was approximately three and ten times the human exposure.

Division Comments:

- **Lifetime administration of flibanserin to female mice resulted in a significant increase in the incidence of malignant mammary tumors at drug exposure levels approximately three and ten times higher than those of women taking the recommended dose. Flibanserin is essentially non-genotoxic and does not increase serum prolactin levels in mice. However, flibanserin is a serotonin receptor agonist/antagonist with significant effects on brain neurotransmitter concentrations, which may have indirect effects on the growth of initiated cells of the mammary gland.**
- **Flibanserin administration had no effect on mammary tumor incidence in rats, which is reassuring and indicates that the effect in mice may be species-specific. Furthermore, although clearly drug- and dose-related, the mammary tumor incidence was not much greater than the highest incidence in the historical controls.**

2.1.4 Reproductive toxicology

Flibanserin had no effect on fertility in rats. Drug administration during fetal development produced a non dose-related increase in fetal malformations in rats. In rabbits, there were fetal resorptions at the high dose but no increase in fetal malformations. Flibanserin administration during peri- and postnatal development in rats had minimal adverse effects on the offspring.

2.2 Overview of Clinical Pharmacology

Flibanserin exhibits linear and dose proportional pharmacokinetics after single oral doses of 0.5 mg to 150 mg and after multiple doses of orally administrated flibanserin with total daily doses ranging from 60 mg to 300 mg. Steady state is achieved after approximately three days and the extent of exposure is increased 1.44-fold as compared to single dose during once-daily administration of 100 mg flibanserin.

Flibanserin is rapidly absorbed, with 90% of the dose reaching the systemic circulation as flibanserin or metabolites. After oral administration, maximum observed plasma concentrations (Cmax) are usually achieved in 45 to 60 minutes. Absolute bioavailability of flibanserin following oral dosing is 33%. Food moderately affects the rate and extent of flibanserin absorption. Peak plasma concentrations of flibanserin occur at 1.75 to 4 hours post-dosing with food, and the extent of exposure is increased up to 56% after a high-fat, high caloric meal.

Following oral administration, flibanserin is moderately distributed in body tissues, including the central nervous system. The volume of distribution after intravenous administration is high with 183 L. Approximately 98% of the drug is bound to human serum proteins, mainly to albumin. Flibanserin is extensively metabolized to at least 35 metabolites, most of them occurring in low concentrations in plasma or urine. Two metabolites could be characterized that show plasma concentrations similar to flibanserin: flibanserin-6-sulfate (M38) and flibanserin-6, 21 disulfate (M25). These two metabolites are not considered to be active. CYP3A4 and to a minor extent CYP2D6 are the main cytochrome P450 isoenzymes involved in the oxidative metabolism of flibanserin. Flibanserin is excreted predominately as conjugated metabolites via the bile (~51% of the dose) and the kidney (~44% of the dose). Flibanserin total plasma clearance after intravenous administration is 425 mL/min. The mean terminal half-life of flibanserin at steady state after oral administration is approximately 10 hours. The terminal half-life of total drug related-material (flibanserin and metabolites) is 66 hours. The terminal half-life of the two major metabolites was comparable to flibanserin.

The sponsor evaluated the effect of flibanserin on QT prolongation in a randomized, blinded, multiple dose, four-period crossover study. Up to 56 healthy subjects received flibanserin 50 mg bid, flibanserin 100 mg tid, placebo, and a single oral dose of moxifloxacin 400 mg (positive control). No significant QT prolongation effect of flibanserin was detected in this study. Baseline-corrected QTc based on the individual correction method (QTcI) was 0.7 and 2.0 ms for the 50 mg bid and 100 mg tid group, respectively; both are below 10 ms, the threshold for regulatory concern.

Of the intrinsic and extrinsic factors evaluated by the sponsor, interaction with a strong CYP3A4 inhibitor and liver impairment were the two key factors that significantly impact the exposure of flibanserin. In general, the exposure (area under the curve [AUC]) increased approximately 4.5 fold under both scenarios, compared to no CYP3A4 inhibitor and no liver impairment. For more detailed discussion of the pharmacokinetics and pharmacodynamics of flibanserin in specific populations and with concomitant use of CYP3A4 inhibitors, see Sections 5.2.4.1 and 5.2.6.

2.3 Specific Regulatory Guidance for the Development of Flibanserin for the HSDD Indication

Throughout the development program for flibanserin for the treatment of HSDD, the Division and the Applicant had regular interactions. The Division's guidance followed the recommendations contained in this document. Key points and agreements conveyed to the Applicant regarding the phase 3 safety and efficacy studies are:

- The co-primary efficacy endpoints should be change from baseline in SSEs and desire, both to be measured by subject responses in an electronic diary (eDiary).

- The Division recommended testing and cognitive debriefing by pilot users of the eDiary, particularly when a new daily question about level of sexual desire was added.
- Success on the co-primary efficacy endpoints would require demonstration of both statistical significant and clinically meaningful treatment effects.
- Decrease in distress related to HSDD should be a key secondary endpoint.
- The Female Sexual Function Index (FSFI) was discussed with the Applicant by both the Division and the FDA Study Endpoints and Label Development (SEALD) team. Significant limitations of the FSFI as an endpoint instrument were noted, including the following:
    - use of four-week recall, because of the concern about recall bias
    - lack of determination of what magnitude of change in the FSFI would constitute a meaningful treatment effect.

The protocol for Study 511.70 (protocols for Studies 511.71 and 511.75 were to be identical) was submitted for review under Special Protocol Assessment, a process which can provide a binding agreement between the Division and an Applicant on the details of a protocol. The Division generally agreed with the planned methods of data collection and analysis for the endpoints of desire and distress. However, formal agreement was not reached. Specific issues included:

- Concern about use of the Female Sexual Dysfunction Scale-Revised (FSDS-R) to collect information on distress due to HSDD, because it measures distress related to a variety of diverse FSD complaints
- Need to evaluate the clinical meaningfulness of the treatment benefit with respect to SSEs, desire and distress. The Division noted that the proposed responder analysis could serve this purpose, provided that the criteria for defining a responder on each endpoint "should be validated by the level of change that subjects themselves perceive as a meaningful improvement." The Applicant should specify the procedure to be used to determine clinical meaningfulness. Failure to demonstrate a statistically significant benefit of flibanserin over that of placebo in the responder analyses would be a review issue.

The Division held a pre-NDA meeting with the Applicant in 2007 and the following items were discussed:

- The plan to evaluate SSEs as a calculated count to standardize over a four-week evaluation was of concern; however, as the Division had previously agreed to this plan, it would continue to accept this calculation. The Division requested that a sensitivity analysis also be provided, using only those SSEs actually reported, even if the reporting interval fell short of 28 days.
- Missing data on desire would be imputed by using the average daily desire score from non-missing days; this was acceptable to the Division, although a similar sensitivity analysis using only reported data was requested.
- The Division did not recommend use of the total FSDS-R as the instrument to evaluate distress. The Division requested that the Applicant evaluate change in distress using Item 13 on the FSDS, which is specific to distress related to HSDD. Imputation of missing data by last observation carried forward (LOCF) for this item would be acceptable.

- The Applicant planned to use desire and SSE data for a given four-week interval only where at least 14 days of data were recorded. The Division encouraged the Applicant to use a sliding window (using data from the most recent previous four-week interval) whenever there were < 21 days of data collection in a four-week interval.
- The proposal for determining responder criteria for SSEs, desire and distress (an anchor-based analysis using the Patient Global Impression – Improvement [PGI-I], with mean change from baseline in each of the three major endpoints calculated for each level of response on the PGI-I) was acceptable.
- The definition of the Full Analysis Set (women randomized who received at least one dose of study drug and had at least one on-treatment efficacy assessment), to be used as the primary analysis population, was acceptable.
- The plan to address data that is missing due to missed visits by using LOCF and mixed model approaches, depending on the pattern of missing data, was acceptable.

In 2008, the Applicant initially requested a meeting to discuss a proposed change to the desire co-primary endpoint prior to unbinding Studies 511.70 and 511.71. The meeting request was withdrawn, but resubmitted later and the Division and the Applicant met in January 2009 to discuss the Applicant's proposal to use the desire items from the FSFI as the instrument to assess the desire endpoint. The Applicant indicated that the desire endpoint based on the e-diary had failed to attain statistical significance in Studies 511.70, 511.71 and 511.75. The Division provided the following guidance:

- The Division will not accept the FSFI desire items as the primary measure of desire in Studies 511.70, 511.71 and 511.75, as failure to meet an efficacy endpoint does not constitute an acceptable reason to alter a prespecified and agreed-upon endpoint.
- If evidence of appropriate validation were provided, the Division might consider the FSFI desire items as appropriate measures of sexual desire. However, the re-analysis of the current studies using this endpoint is considered exploratory and hypothesis-generating, and an additional trial with the FSFI desire items as a prespecified co-primary efficacy endpoint instrument would be required to demonstrate efficacy based on these items.
- The Division would review a revision to the protocol for ongoing (not yet unblinded) European Study 511.77, to elevate the FSFI desire items to a prespecified endpoint that would be analyzed in a hierarchical manner if the SSE endpoint attained statistical significance. The Applicant would like to propose this as a confirmatory study if the Division agreed that the FSFI had been adequately validated.
- The Division noted that responder criteria were being determined using the difference between "minimally changed" and "no change" on the PGI-I. The Division noted that this might represent a minimally detectable change, rather than the desired minimum clinically important difference. For this reason, DRUP requested that responders be defined as those having a change <u>greater than</u> the criterion.

The Division reviewed the revised protocol for Study 511.77, which proposed to elevate the secondary endpoint of the desire items on the FSFI to a prespecified endpoint that would be analyzed in a hierarchical manner if the primary endpoint, change in SSEs, attained statistical significance. The revision also deleted the eDiary desire score as the protocol-specified key secondary endpoint of the trial. The Division found the proposed revisions acceptable but noted

that "we reserve comment on the weight that will be accorded this study (i.e., whether it will be considered a pivotal or supportive study) until the data regarding the development and validation of the ... [FSFI] desire items have been submitted by you and reviewed by the Division and the ... SEALD team."

2.4 Overview of Clinical Studies

Data from the following studies were submitted with the marketing application for the pre-menopausal HSDD indication:

- 7 bioavailability studies
- 15 pharmacokinetic (PK) studies
- 6 pharmacodynamic studies
- 7 validation studies
- 9 efficacy trials for major depression in men and women
- 9 efficacy/safety trials for HSDD in premenopausal women (phase 2 and 3)

The phase 2 and phase 3 safety and efficacy studies are summarized in Table 2.

Table 2 Overview of Clinical Safety and Efficacy Studies

Study	Objective	Design	Flibanserin Doses (mg)	# Subjects	Duration (wks)
Phase 2 Studies					
511.68 **US**	Proof of Concept Efficacy/Safety	R, DB, PC	50 BID; option to ↑ to 100 mg BID	Flibanserin - 77 Placebo - 75	12
511.69 **US**	Proof of Concept Efficacy/Safety	R, DB, PC	50 BID; option to ↑ to 100 mg BID	Flibanserin - 76 Placebo - 75	12
Phase 3 Studies – Primary Efficacy Trials					
511.71 **US/Can**	Pivotal Efficacy/Safety	R, DB, PC	50 qhs **100 qhs**	Flibanserin – 585 - 295 @ 50 qhs - 290 @ 100 qhs Placebo - 295	24
511.75 **US/Can**	Pivotal Efficacy/Safety	R, DB, PC	25 BID 50 BID (titrated) **100 qhs (titrated)**	Flibanserin - 1,185 - 396 @ 25 BID - 393 @ 50 qhs - 396 @ 100 qhs Placebo - 399	24
Phase 3 Studies – Supportive Efficacy Trials					
511.70 **US**	Efficacy/Safety	R, DB, PC	25 BID 50 qhs 50 BID	Flibanserin - 1,042 - 350 @ 25 BID - 340 @ 50 qhs - 365 @ 50 BID Placebo - 350	24
511.77 **EU**	Efficacy/Safety	R, DB, PC	50 qhs **100 qhs (titrated)**	Flibanserin – 631 - 314 @ 50 qhs - 317 @ 100 qhs Placebo - 318	24
Special Studies (Long-term)					
511.74 Part 1	Long-term safety;	Open-label, (24+ wk)	flexible regimen: 50 qhs 50 BID **100 qhs**	Open-label, all on flibanserin – 749	24
511.74 Part 2 **US/Can**	Withdrawal effects	R, DB, PC (24 wk)		Double blind: 163 on flibanserin, 170 on placebo	24
511.84 **US**	Long-term safety and efficacy; Flexible-dose	Open-label, uncontrolled	flexible regimen: 50 or **100 qhs** 25 or 50 BID	Flibanserin - 1,725 from Studies 511.70, 511.71 & 511.75	52 (ongoing)
511.118 **EU**	Long-term safety and efficacy	Open-label, uncontrolled	flexible regimen: 50 or **100 qhs** 25 or 50 BID	Flibanserin - 470 from Study 511.77	28 (ongoing)

R = randomized, DB = double blind; PC = placebo-controlled
Source: NDA 22-526, Module 5.2 - Listing of Clinical Trials, pp 14-16, and Table 1.1:2, p 13, Table 3.1.1: 1, p 47, and Table 3.1.1: 2, p 48 in the Summary of Clinical Efficacy

Division Comment:
The three long-term studies (one in Europe) were conducted primarily to evaluate safety, although some efficacy measures were collected.

2.5 Dose Selection for Phase 3 HSDD Studies

The range and exposure of daily doses of flibanserin that have been investigated in the clinical development program for HSDD are listed in Table 3.

Table 3 Long-term Exposure to Flibanserin (FLI) – 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.

Source: Table 4: 1, p 100, Summary of Clinical Efficacy

From the phase 2 trials, the Applicant concluded that flibanserin at 50-100 mg BID showed efficacy above the placebo effect. The Applicant then wanted to study lower doses and to determine whether up-titration to 50 mg BID or 100 mg qhs would result in improved tolerability. Therefore, in the phase 3 trials, doses ranging from 25 mg BID to 100 mg (given as 50 mg BID or as 100 mg qhs) were studied.

Division Comment:
The Division concurred with the Applicant's decision to evaluate doses of 50-100 mg in the phase 3 trials.

3. PHASE 3 TRIALS

3.1 Overview of Phase 3 Clinical Program

As shown in Table 2, the Applicant conducted a total of seven phase 3 studies. The Division considers only two of these (Studies 511.71 and 511.75) to be primary trials in support of efficacy for marketing approval. Reasons for considering the remaining five trials as supportive only include:

- Study 511.70 did not evaluate the 100 mg qhs dose that is proposed for marketing.
- Study 511.74 began with a 24-week open label phase, which then enrolled only "responders" into the randomized withdrawal phase.
- Study 511.77 was conducted in Europe, and evaluated a single primary efficacy endpoint, namely SSEs.
- Studies 511.84 and 511.118 were open label, uncontrolled extension studies that used flexible dosing regimens not proposed for marketing.

Division Comment:
In their Summary of Clinical Efficacy, the Applicant lists Studies 511.71, 74, and 75 as pivotal, and Studies 511.70, 77, and 84 as supportive. As noted above, the Division considers only Studies 71 and 75 to be pivotal, and this background document mainly

limits discussion of efficacy results to these two studies. All of these phase 3 studies, however, were considered in the overall evaluation of the safety, efficacy, and best dosing regimen of the product for treating HSDD in premenopausal women.

3.2 Study Objectives and Overall Study Design and Assessments (Studies 511.71 and 511.75)

3.2.1 Study Objectives

To document the safety profile and efficacy of flibanserin in producing a clinically meaningful therapeutic response after 24 weeks of treatment in premenopausal women with HSDD

3.2.2 Overall Study Design

The two trials were prospective, randomized, double-blind, North American (US and Canada) studies in premenopausal women with general acquired HSDD. The total study duration was 28 weeks and consisted of a four week baseline period followed by 24 weeks of blinded treatment. Following screening and consent, eligible subjects entered the trial and began treatment.

3.2.3 Treatment Groups

In Study 511.71, eligible subjects were randomized to one of three treatment groups:

- placebo
- flibanserin 50 mg qhs
- flibanserin 100 mg qhs

In Study 511.75, subjects were randomized into one of four treatment groups:

- placebo
- flibanserin 25 mg BID
- flibanserin 50 mg BID or
- flibanserin 100 mg qhs

An up-titration regimen was used in Study 511.75 for subjects on the two higher doses, whereby they initially received 50 mg qhs for 14 days and then were titrated up to their final doses.

3.2.4 Entry Criteria

Key eligibility criteria for both studies are described below.

<u>Inclusion Criteria</u>

1. Premenopausal women >18 years of age with a primary diagnosis of HSDD for at least 24 weeks' duration. Secondary Female Sexual Arousal Disorder and/or Female Orgasmic Disorder were allowed if co-morbid with HSDD, but must have been preceded by HSDD and be of lesser importance to the participant.
2. A score of 15 or higher on the Female Sexual Distress Scale (FSDS-R, see Appendix 1) at the Screen Visit. (The range of scores for this 13-item instrument is from 0 to 52; the higher the score, the greater the distress.)
3. A score of 0 or 1 on Item #2 of the Sexual Interest and Desire Inventory - Female (SIDI-F, see Appendix 1) at screening. Item #2 asks, "How satisfied are you with the sexual aspect of your

relationship with your partner?" Possible responses range from 0 (dissatisfied) to 5 (very satisfied).

4. In a stable, monogamous, heterosexual relationship that was secure and communicative, for at least one year prior to the Screen Visit. The relationship had to be with the same partner, who was sexually functional, both psychologically and physically, and the partner was expected to be physically present at least 50% of each month during the screen period and the 24-week efficacy period of the trial.
5. Using a medically acceptable method of contraception, hormonal therapy, intrauterine device, tubal sterilization, or partner's surgical sterilization for at least three months before the Baseline Visit and had to continue using that medically acceptable method of contraception during the trial.

Exclusion Criteria

1. There was a 5-page list of prohibited medications that included antiarrhythmics, anticoagulants, beta blockers, CNS stimulants, dopamine-receptor agonists, fertility agents, all hormonal agonists/antagonists, over-the-counter "sexual enhancers," muscle relaxants, psychotherapeutics (five broad subcategories), anti-epileptics, controlled sedatives, respiratory agents and systemic corticosteroids (if used in high enough doses to cause CNS effects), narcotics (for frequent or prn. use), triptan antimigraine agents, and non-benzodiazepine sleep aids.
2. Current (or within 14 days of study drug administration) use of a CYP3A4 inhibitor (including grapefruit juice) or CYP3A4 inducers.
3. Current or past six month history of pregnancy or breast-feeding.
4. Peri-menopausal and postmenopausal women.
5. Recent major depressive disorder or a score ≥ 14 on the Beck Depression Inventory II, or a history of suicide attempt. History of any psychiatric disorder that could influence sexual function, compliance, or safety.
6. Started non-drug therapy for HSDD within 12 weeks of the baseline visit.
7. Recent experience of a major life stress or relationship discord that could interfere with sexual activity.
8. Any ongoing medical condition in the following categories: neurologic, GI and hepatic, cardiovascular or abnormal ECG, renal, hematologic, respiratory, endocrinologic, glaucoma, HIV positive, significant immunologic or auto-immune disorders, breast or other cancer within the last 10 years (except skin cancer), or significant ocular disease.

Division Comments:

- **The women enrolled in the pivotal efficacy studies were generally healthy, without any significant medical conditions or concomitant medications.**
- **There was an extensive list of medications and drug classes that were exclusionary of participation and prohibited during the trials (See Section 6.3.) This may limit the generalizability of the trial results, particularly the safety findings. As discussed in Section 5.2.4, women who did take certain prohibited concomitant medications had higher rates of adverse events.**

3.2.5 Efficacy Endpoints

The two co-primary endpoints in Studies 511.71 and 511.75 were:

- Change in the number of satisfactory sexual events (SSEs) from the four-week baseline to the 28 days prior to the final clinic visit (without spanning into the previous clinic visit)
- Change in the eDiary sexual desire score from the four-week baseline sum to the 28 days prior to the final clinic visit (without spanning into the previous clinic visit).

Study subjects used a personal handheld electronic device (eDiary, see Section 6.1) to record on a daily basis information about sexual activity, including sexual encounters and orgasms, and desire.

Division Comments:

- **Although eDiary data were collected daily, the eDiary data were divided into four-week intervals that were anchored to a subject's study visits and the eDiary data were computed as a 28-day average of all data collected between visits. The statistical analyses reported by the Applicant used the 28-day windows that are anchored to the study visits. However, the Division indicated concern with this plan, and requested that the Applicant also provide data based only on recorded events and desire scores as sensitivity analyses.**
- **In actual practice, study visits did not necessarily occur every four weeks. For example, a visit scheduled for Week 24 could have occurred at Week 23. In that case, instead of using the eDiary data collected during the 28 days ending with Week 24, the data collected during the 28 days ending with Week 23 would have been designated as the eDiary data for Weeks 21-24. Moreover, if the first week of a 4-week interval overlapped with the 4-week interval of the previous clinic visit, then only three weeks of data were used for the 4-week interval, and the calculation described in the next section was used to impute the number of events expected in four weeks based on the three-week reports.**

As agreed with the Division, and as specified in the protocols, in order for a study to be considered successful, the change from baseline for active treatment compared to placebo treatment needed to be both statistically and clinically significant. Clinical significance was determined on the basis of a responder analysis.

3.2.5.1 SSEs

Women indicated daily if they had experienced a sexual event. If a sexual event occurred, the SSE primary endpoint was 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 woman (not the partner) judged whether or not the event was satisfying.

Subjects were prompted to complete missed entries the next time she used the diary, for up to three days. SSE data that were not entered within the 72 hour recall period were locked out of the diary and were considered missing.

The protocols called for analyses of the change from the four-week baseline data to the data collected at Weeks 21 to 24, and the statistical analysis plans called for analyses of change from

the baseline to the final visit period. However, the Applicant's analyses of the co-primary endpoints did not adhere strictly to the protocol's description of the analyses. Nor, because of the way a visit was defined, do the analyses necessarily represent the last four weeks in the study. Although eDiary data were collected daily, the eDiary data were divided into four-week intervals that were anchored to the planned study visits and the eDiary data were computed as a 28-day average of all data collected between the actual study visits.

However, the actual study visits did not necessarily occur every four weeks. For example, a visit scheduled for Week 24 could have occurred at Week 23. In that case, instead of using the eDiary data collected during the 28 days ending with Week 24, the data collected during the 28 days ending with Week 23 would have been designated as the eDiary data for Week 24. Moreover, if the first week of a four-week interval overlapped with the four-week interval of the previous clinic visit, then only three weeks of data were used for the four-week interval.

Subjects could enter data for differing number of days per four-week evaluation period because the protocol allowed for study visits at 28 ± 7 days and the four-week evaluation periods were anchored to the planned visits. Therefore, the daily average of the number of SSEs entered into the eDiary in the 28 days prior to the clinic visit (without spanning into the previous clinic visit) was multiplied by 28 to arrive at the monthly (28 day) total count as shown in the following algorithm:

> Total monthly count of SSEs = 28 x (sum of the number of SSEs entered) / (sum of number of days entered)

For example, if a subject had entered data on 24 of the days since the last clinic visit, and had counted 6 SSEs, her monthly SSE score would be 28 x 6/24 = 7.

Division Comments:

- **The Division has inquired as to why diary data were anchored to clinic visits, given that the protocols state that comparisons of the co-primary endpoints would be made between the 4-week baseline and Week 21 to 24, and do not appear to mention the anchoring of the eDiary to clinic visits. The Applicant responded that the intent in the protocols was to "capture the clinic visit period represented by those time windows." This anchoring was to allow for "all endpoints to be captured for the same snapshot in time synchronizing the time period with those measures taken during the clinic visit."**
- **The Division does not concur with this anchoring, as it may result in less than full use of data, and greater rates of missing data. Of the primary and key secondary endpoints, only the FSDS-R was completed at the study visit. Some lack of synchrony between this measure of distress and the co-primary efficacy endpoints would be of less concern than the artificial linking of daily diary data to a clinic visit schedule.**

3.2.5.2 eDiary Sexual Desire Score

The eDiary daily sexual desire question was: "Indicate your most intense level of sexual desire." Possible responses were 0 (No desire), 1 (Low desire), 2 (Moderate desire), or 3 (Strong desire), with the resultant range for the monthly score from 0 to 84 if data were entered on all 28 days. Sexual desire on the date of the final clinic visit was not included in the calculations.

For missed entries into the eDiary regarding sexual desire, subjects were only allowed to enter data from the previous 24 hours. If a subject had failed to enter desire data on more than one day, desire data prior to the past 24 hours was locked out. As with SSEs, desire data were anchored to the study visits. The monthly desire score was calculated as follows:

Monthly sexual desire = 28 x (sum of desire scores) / (sum of number of days entered)

Division Comment:
The Applicant allowed a 72 hour window to enter data on SSEs with the rationale that women would likely be able to remember accurately such events for up to three days. However, the Applicant believed that accurate recall of a state, such as desire, would be more difficult as the recall period extended; for this reason, only a 24 hour window of data entry was allowed for the desire endpoint.

3.2.5.3 Key Secondary Endpoint

The protocol-specified key secondary endpoint was the change in distress from baseline to endpoint as assessed by the total score for the 13-item Female Sexual Distress Scale-Revised (FSDS-R).

The FSDS-R (see Section 6.1.2.) is a 13-item questionnaire that asks women to evaluate how often a given problem has "bothered you or caused you distress" over the past four weeks, with response options (0-4) that range from "never," "rarely," "occasionally," "frequently," to "always," respectively. The Applicant modified the FSDS-R to use seven-day recall, rather than the four-week recall used in the original development of the instrument. The effect of this modification was evaluated in Study 511.106, and the Applicant concluded that the instrument, with seven-day recall, had good discriminant validity, high test-retest reliability and a high degree of internal consistency.

As noted in Section 2.3, the Division had informed the Applicant that the FSDS-R Question 13 ("How often did you feel bothered by low sexual desire?") would constitute the Division's primary evaluation of change in distress.

Division Comment:
For Studies 511.71 and 511.75, the Division reached agreement with the Applicant on the instruments to be used for the primary endpoints. However, subsequently, the Division stated a strong preference for using only Item 13 of the FSDS-R as the measure of distress due to HSDD, because this question focuses specifically on distress related to lack of desire, while the FSDS overall includes distress relating to various other aspects of sexual dysfunction. Consequently, in the NDA submission, the Applicant presented the results for the FSDS-R Item 13 as well as the FSDS-R total score.

3.2.5.4 Other Secondary Measures of Efficacy

The Female Sexual Function Index (FSFI) domain for sexual desire was upgraded by the Applicant to a key secondary endpoint in Study 511.71 only. This revision to the Statistical Analysis Plan may have occurred in 2008, and was not agreed to by the Division. In Study 511.75, the FSFI desire domain was a secondary endpoint.

The FSFI is a self-administered questionnaire for the assessment of female sexual function and dysfunction in a variety of research applications, including HSDD. The instrument contains six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain; and a total of 19 questions that are scored from 0 to 5. The desire domain contains two questions:

- Over the past 4 weeks, how often did you feel sexual desire or interest? [The five possible responses range from the least "almost never or never" (scored as 1) to the most "almost always or always" (scored as 5). The middle responses are "a few times" (2), "sometimes" (3), and "most times" (4).]
- Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest? [The five possible responses range from the least "very low or none at all" scored as 1 to the most "very high" scored as a 5. The middle responses are "low" (2), "moderate" (3), and "high" (4).]

Responder Analysis

If the co-primary efficacy endpoints were successful, the protocol stated that the Applicant would then perform a formal responder analysis. This was to form the basis of the determination of the clinical meaningfulness of the treatment effect of flibanserin as measured by the change in SSEs and desire.

A responder analysis of patient-reported outcomes is a descriptive technique that is used to help determine whether changes observed during a clinical study are clinically meaningful. In a responder analysis, subjects from both treatment arms are queried as to whether or not they have experienced a change in their condition as a result of treatment, and asked to rate any change on a Likert-type scale that allows for levels of worsening, no change and levels of improvement. The scores on the endpoint items that are associated with a specified level of change are determined, and subjects exceeding those scores are classified as responders. The proportion of responders is then compared between treatment arms, and a statistically significantly higher response rate in the active treatment arm is considered to be evidence of a clinically meaningful treatment benefit.

The methodology for the responder analyses for this NDA entailed anchoring a subject's individual assessment of her improvement on the PGI-I to her scores for SSEs and desire. The PGI-I (see Section 6.1.3.2) is a simple evaluation completed by the subject to assess the subject's overall impression of the change in her HSDD condition following treatment. The question asked is: "How is your condition – meaning decreased sexual desire and feeling bothered by it - today compared to when you started study medication?"

The PGI-I is rated ordinally from 1 ("very much improved") to 7 ("very much worse"); therefore, a negative corrected value indicates improvement as compared to placebo. A value of 4 meant "no change" and 3 meant "minimal improvement." Since this instrument evaluates change with treatment, the instrument was not used at baseline, and the actual value, as opposed to change from baseline, was used in the Applicant's analysis. The instrument was administered at Weeks 4, 8, 16, and 24.

The proportion of responders was analyzed using the following definitions of response:

- increase of 2/month in SSEs
- increase of 4/month in "desire-days" (a day scored as moderate or strong desire)

- PGI-I score of 1 or 2 (very much improved or much improved, respectively)
- Patient Benefit Evaluation (a single question asking whether or not the subject experienced a meaningful benefit from the study medication, answered yes/no)
- Responder endpoint based on desire
- Responder endpoint based on distress

Division Comment:
The Division had advised the Applicant that the criteria for defining a responder on each endpoint should be validated by the subjects' own determination of treatment benefit. In other words, an arbitrary definition of response, such as an increase of 2 SSEs/month, would be acceptable only if this also was associated with what subjects indicated constituted a meaningful treatment response.

3.3 Schedule of Events

Table 4 Study Flow Chart – Studies 511.71 and 511.75

	Screen	Baseline	Treatment							Post-Treatment	
Trial Periods:											
Clinic Visit (±7 days)	1	2		4	5		7		9		11
Telephone Visit (±3 days)			*3*			*6*		*8*		*10*	
Week	-4	0	*1*	4	8	*12*	16	*20*	24	*25*	28
Trial Evaluations:											
Informed Consent	X										
Medical and Sexual History	X										
Beck Depression Inventory® II	X										
Beck Scale for Suicide Ideation®*	X	X		X	X		X		X	*X*	X
DSM-IV-TR® Diagnosis[1]	X										
Blood Pressure and Pulse[2], *	X	X		X	X		X		X		X
Weight*	X	X		X	X		X		X		X
Menses Evaluation*	X	X		X	X		X		X		X
Physical Examination[3], *	X								X		
Pelvic Examination[4]	X										
Laboratory Tests[5], *	X								X		
Electrocardiogram*	X	X							X		
Ophthalmological Exam[6], *	X								X		
Inclusion/Exclusion Criteria[7]	X	X									
Adverse Events[8], *	X	X	*X*	X	X	*X*	X	*X*	X	*X*	X
Concomitant Therapy*	X	X	*X*	X	X	*X*	X	*X*	X	*X*	X
eDiary	**Completed Daily by the Patient**										
FSDS-R©*	X	X		X	X		X		X		
FSFI©*		X		X	X		X		X		
PGI of Improvement*				X	X		X		X		
Patient Benefit Evaluation*									X		
Randomization		X									
Medication Dispensing		X		X	X		X				
Medication Compliance*			*X*	X	X	*X*	X	*X*	X		
Termination of Trial Medication*									X		
Trial Completion											X

1. Established after the Clinical Interview for Female Sexual Dysfunction, Sexual Symptom Checklist, and the Contributing Factors case report forms have been completed.
2. Performed after sitting for 5 minutes.
3. Includes height, which will be assessed only at the Screen Visit.
4. Includes a Pap smear.
5. Taken after fasting for 4 hours and between 6 a.m. and 10 a.m. Laboratory tests include urinalysis, routine blood tests, hormone assays, serum pregnancy test, and a urine drug screen (Screen Visit only).
6. Screen (Visit 1) exam may be performed anytime prior to Baseline Visit, results must be available prior to Baseline Visit. End of Treatment (Visit 9) exam must be completed within 4 weeks of treatment discontinuation.
7. Includes the assessment of the inclusion criterion SIDI-F© Question Two at Screen.
8. Adverse events that are continuing at the End of Trial Visit must be followed until resolution or follow-up is agreed adequate by the Investigator and Clinical Monitor.

* Whether a patient prematurely discontinues or completes from the trial, all Visit 9 (end of treatment) evaluations must be completed. All Visit 10 and 11 (post-treatment) evaluations must also be completed.

DSM-IV-TR®: Diagnostic and Statistical Manual, Fourth Edition, Text Revision, FSDS-R©: Female Sexual Distress Scale-Revised, FSFI©: Female Sexual Functioning Index, PGI: Patient Global Impression

Source: Protocol for Study 511.71, p 7

3.4 Statistical Analysis Plan for Efficacy Endpoints

3.4.1 Primary Analysis Set

The primary efficacy analysis was based on the full analysis set (FAS). The FAS consists of women who were randomized to a treatment group, received at least one dose of study medication, and had at least one on-treatment efficacy assessment.

SSEs were analyzed using Wilcoxon rank sum test stratified by pooled center (centers that entered fewer subjects than a complete block were pooled by country). The eDiary sexual desire score was analyzed using analysis of covariance (ANCOVA) with treatment and center as fixed effects and baseline score as covariates (two-sided test, $\alpha = 0.05$). The Hochberg procedure was used to adjust for multiple comparisons with placebo. First, SSEs were analyzed for each dose compared to placebo; then, for the dose(s) that were significant on the SSE endpoint, the eDiary sexual desire endpoint was analyzed. The daily desire analysis was performed on the FAS using the last observation carried forward (LOCF) method of data imputation.

The statistical analysis plans (SAPs) stipulated the following. In Study 511.71, for all doses that were found to be statistically significant on both co-primary endpoints, further testing was planned for change from baseline to the final visit on the following important secondary endpoints:

- the FSDS-R total score with a seven day recall period
- the FSFI desire domain (specified as a key secondary endpoint only in Study 511.71)

In Study 511.75, the FSDS-R was the only key secondary endpoint and was identified for further hypothesis testing.

A Hochberg procedure was planned for each of these secondary endpoints. The p-value to be used in the Hochberg procedure for these secondary endpoints was the p-value used to declare statistical significance for both co-primary endpoints.

Division Comment:
The SAPs did not discuss any multiplicity adjustments involving analyses of the other secondary endpoints. In addition, analyses did not control for multiplicity introduced by using two secondary endpoints in Study 511.71. In contrast to the SAPs, note that the study reports state that only the FSDS-R total score would be analyzed in this fashion, and that all other secondary analyses were supportive. The reports also identify FSDS-R and FSFI-desire as key secondary endpoints for Study 511.71, and FSDS-R alone as the key secondary endpoint for Study 511.75.

3.4.2 Handling of Missing Data

The protocols stipulated that subjects were to be discontinued from the study for:

- Any concomitant illness that prevents compliance
- Failure to take any study medication for more than seven consecutive days

Division Comments:

- **Although the data analyses appear to have followed an intent-to-treat (ITT) principle, the analysis can not be considered an ITT analysis in the true sense of the term. In a true ITT analysis, all subjects would have recorded eDiary data throughout the**

24-week study regardless of their treatment status or whether they were complying with the study protocol.

- **These stipulations for discontinuing study subjects due to non-compliance are not desirable. As a result of protocol-mandated discontinuations for non-compliance, missing data had to be imputed at a much greater rate than would have been needed if subjects had remained in the study.**

Last observation carried forward (LOCF) was used to impute missing data; however, baseline data were not carried forward for subjects who did not have sufficient on-treatment data. 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).

4. FINDINGS FROM PRIMARY PHASE 3 EFFICACY TRIALS (511.71 and 511.75)

4.1 Subject Enrollment and Disposition

A total of 2,462 premenopausal women were randomized to treatment with placebo or with flibanserin at different doses over the two primary phase 3 trials (see Table 5).

Table 5 Screening, Randomization and Completion Rates – Studies 511.71 and 511.75

Treatment	Completion Rates at 24 weeks	
	Trial 511.71	**Trial 511.75**
Screened	1, 429	2,486
Randomized	**880 (61.6%)**	**1,582 (63.6%)**
Placebo	295	399
25 mg BID	NA	396
50 mg qhs	295	NA
50 mg BID	NA	393
100 mg qhs	290	396
Completed	**663**	**1,071**
Placebo	234 (79%)	287 (72%)
25 mg BID	NA	274 (69%)
50 mg qhs	230 (78%)	NA
50 mg BID	NA	259 (66%)
100 mg qhs	199 (69%)	251 (63%)

NA = not applicable because the dose was not used in the trial.
Source: Study Report for Study 511.71, Figure 10.1: 1, p 68;
Study Report for Study 511.75, Figure 10.1: 1, p 67

Subject disposition by trial and by treatment are shown in Table 6 and Table 7. The major reasons for discontinuation in each trial are listed as "administrative" and adverse events.

Table 6 Subject Disposition in Study 511.71

		Flibanserin			
	Placebo N (%)	50 mg q.h.s. N (%)	100 mg q.h.s. N (%)	Flibanserin Total N (%)	Total N (%)
Treated	295 (100.0)	295 (100.0)	290 (100.0)	585 (100.0)	880 (100.0)
Completed	234 (79.3)	230 (78.0)	199 (68.6)	429 (73.3)	663 (75.3)
Discontinued	61 (20.7)	65 (22.0)	91 (31.4)	156 (26.7)	217 (24.7)
Adverse events[1]	10 (3.4)	23 (7.8)	33 (11.4)	56 (9.6)	66 (7.5)
Administrative[2]	39 (13.2)	27 (9.2)	42 (14.5)	69 (11.8)	108 (12.3)
Lack of efficacy	8 (2.7)	6 (2.0)	5 (1.7)	11 (1.9)	19 (2.2)
Other[3]	4 (1.4)	9 (3.1)	11 (3.8)	20 (3.4)	24 (2.7)

[1] Includes all patients who discontinued due to an adverse event that started in either the screening and/or treatment period (includes patient 26334 who discontinued for adverse event starting in screening).
[2] Includes consent withdrawn, lost to follow-up, and non-compliance with protocol.
[3] Includes pregnancy, personal reasons, moving away, etc.

Source: Study Report for Study 511.71, Table 10.1: 1, p 69

Table 7 Subject Disposition in Study 511.75

		Flibanserin				
	Placebo N (%)	25 mg b.i.d. N (%)	50 mg b.i.d. N (%)	100 mg q.h.s N (%)	Flibanserin Total N (%)	Total N (%)
Treated	398 (100)	396 (100)	392 (100)	395 (100)	1183 (100)	1581 (100)
Completed	287 (72.1)	274 (69.2)	259 (66.1)	251 (63.5)	784 (66.3)	1071 (67.7)
Discontinued	111 (27.9)	122 (30.8)	133 (33.9)	144 (36.5)	399 (33.7)	510 (32.3)
Adverse events	43 (10.8)	30 (7.6)	67 (17.1)	62 (15.7)	159 (13.4)	202 (12.8)
Administrative[1]	53 (13.3)	75 (18.9)	49 (12.5)	62 (15.7)	186 (15.7)	239 (15.1)
Lack of efficacy	11 (2.8)	6 (1.5)	13 (3.3)	13 (3.3)	32 (2.7)	43 (2.7)
Other[2]	4 (1.0)	11 (2.8)	4 (1.0)	7 (1.8)	22 (1.9)	26 (1.6)

[1] Includes consent withdrawn, lost to follow-up, and non-compliance with protocol
[2] Includes pregnancy, personal reasons, moving away, etc.

Source: Study Report for Study 511.75, Table 10.1: 1, p 68

Division Comments:

- **In Study 511.71, there is a dose-response observed in the rate of discontinuations due to adverse events in the flibanserin arms. There is a similar trend in Study 511.75, although the 100 mg qhs dose appears to be slightly better tolerated than is the 50 mg BID dose.**
- **Although lack of efficacy was identified as the factor leading to discontinuation in only 2-3% of the subjects, it is likely that the reasons included under "administrative" may include concerns about efficacy and tolerability.**
- **It is noteworthy that more placebo subjects (~75%) completed the two 6-month trials than did the flibanserin 100 mg qhs-treated subjects (64-69%).**

4.2 Demographic Data

The mean age in the phase 3 efficacy trials was approximately 35-36 years in each treatment group. Caucasian women comprised the largest percentage of the study population

(approximately 90%). Demographic characteristics of subjects in Studies 511.71 and 511.75 are shown in Table 8 and Table 9, respectively.

Table 8 Demographics in Study 511.71 (All Treated Subjects)

	Placebo	Flibanserin 50 mg q.h.s.	Flibanserin 100 mg q.h.s.	Total
Treated	295 (100.0)	295 (100.0)	290 (100.0)	880 (100.0)
Age [years]				
Mean	35.5	36.3	35.6	35.8
Age group: N (%)				
18 - 34 years	126 (42.7)	127 (43.1)	134 (46.2)	387 (44.0)
35 - 44 years	136 (46.1)	125 (42.4)	118 (40.7)	379 (43.1)
≥45 years	33 (11.2)	43 (14.6)	38 (13.1)	114 (13.0)
Race/Ethnicity: N (%)				
White Non-Hispanic	235 (79.7)	237 (80.3)	229 (79.0)	701 (79.7)
White Hispanic	21 (7.1)	26 (8.8)	19 (6.6)	66 (7.5)
Black Non-Hispanic	31 (10.5)	29 (9.8)	35 (12.1)	95 (10.8)
Black Hispanic	2 (0.7)	1 (0.3)	1 (0.3)	4 (0.5)
Asian Non-Hispanic	6 (2.0)	2 (0.7)	4 (1.4)	12 (1.4)
Asian Hispanic	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Missing	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Weight [kg]				
Mean	71.1	72.8	74.2	72.7
Body mass index [kg/m²]				
Mean	26.4	26.9	27.0	26.8
Marital status: N (%)				
Married	237 (80.3)	214 (72.5)	229 (79.0)	680 (77.3)
Unmarried	58 (19.7)	81 (27.5)	61 (21.0)	200 (22.7)
Education level: N (%)				
Partial high school	1 (0.3)	6 (2.0)	3 (1.0)	10 (1.1)
High school graduate	35 (11.9)	33 (11.2)	26 (9.0)	94 (10.7)
Partial college	78 (26.4)	80 (27.1)	85 (29.3)	243 (27.6)
College graduate	139 (47.1)	131 (44.4)	130 (44.8)	400 (45.5)
Post graduate	42 (14.2)	45 (15.3)	46 (15.9)	133 (15.1)
How long in present relationship?				
Mean	10.4	11.1	10.5	10.6

Time in present relationship is in years.
Source: Study Report for Study 511.71, Table 11.2: 1, p 72

Table 9 Demographics in Study 511.75 (All Treated Subjects)

	Placebo	Flibanserin 25 mg b.i.d.	Flibanserin 50 mg b.i.d.	Flibanserin 100 mg q.h.s	Total
Treated	398 (100.0)	396 (100.0)	392 (100.0)	395(100.0)	1581 (100.0)
Age [years]					
Mean	36.2	34.9	35.7	35.4	35.5
Age group: N (%)					
18-34 years	157 (39.4)	187 (47.2)	165 (42.1)	179 (45.3)	688 (43.5)
35-44 years	195 (49.0)	169 (42.7)	183 (46.7)	177 (44.8)	724 (45.8)
≥45 years	46 (11.6)	40 (10.1)	44 (11.2)	39 (9.9)	169 (10.7)
Race and Ethnicity: N (%)					
White Non-Hispanic	343 (86.2)	341 (86.1)	345 (88.0)	334 (84.6)	1363 (86.2)
White Hispanic	27 (6.8)	16 (4.0)	16 (4.1)	24 (6.1)	83 (5.2)
Black Non-Hispanic	21 (5.3)	33 (8.3)	27 (6.9)	29 (7.3)	110 (7.0)
Black Hispanic	1 (0.3)	1 (0.3)	0 (0)	0 (0.0)	2 (0.1)
Asian Non-Hispanic	6 (1.5)	5 (1.3)	4 (1.0)	8 (2.0)	23 (1.5)
Asian Hispanic	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)
Marital status: N (%)					
Married	338 (84.9)	302 (76.3)	317 (80.9)	294 (74.4)	1251 (79.1)
Unmarried	60 (15.1)	94 (23.7)	75 (19.1)	101 (25.6)	330 (20.9)
Education level: N (%)					
Partial high school	3 (0.8)	6 (1.5)	4 (1.0)	8 (2.0)	21 (1.3)
High school graduate	41 (10.3)	65 (16.4)	39 (9.9)	51 (12.9)	196 (12.4)
Partial college	137 (34.4)	104 (26.3)	127 (32.4)	136 (34.4)	504 (31.9)
College graduate	152 (38.2)	172 (43.4)	162 (41.3)	152 (38.5)	638 (40.4)
Post graduate	65 (16.3)	49 (12.4)	60 (15.3)	48 (12.2)	222 (14.0)
How long in present relationship?					
Mean	11.4	10.2	10.8	10.5	10.7
Weight [kg]					
Mean	71.5	72.7	72.1	72.1	72.1
Body mass index [kg/m^2]					
Mean	26.3	26.6	26.6	26.5	26.5

Time in present relationship is in years.
Source: Study Report for Study 511.75, Table 11.2: 1, p 71

Division Comments:

When the demographics are examined by treatment assignment, the percentages are very similar, as would be expected in double-blind, controlled trials. It is notable that subjects in the two pivotal efficacy trials were predominantly white non-Hispanics with a high level of education and a long present relationship.

4.3 Efficacy Findings

4.3.1 Primary and Key Secondary Efficacy Endpoint Analysis

Table 10 displays the major efficacy results for the 100 mg qhs dose vs. placebo in both Studies 511.71 and 511.75. Flibanserin 100 mg qhs led to a statistically significant increase from baseline in number of **SSEs** compared to placebo in each study. However, the co-primary endpoint of change from baseline in **desire**, as assessed by the eDiary desire score, did not demonstrate statistically significant improvement for flibanserin 100 mg qhs as compared to placebo.

Division Comment:
Because flibanserin 100 mg qhs failed to demonstrate statistically significant improvements in both co-primary efficacy endpoints, according to the protocols and statistical analysis plans, analysis of the secondary endpoints should not have been conducted. Thus, the results of the analysis of secondary endpoints (distress) are included for illustration only.

Table 10 Primary and Most Important Secondary Endpoints – Studies 511.71 and 511.75 (FAS-LOCF)

Treatment Arm	N	Baseline (4 weeks)	N	End of Treatment (approximately Weeks 21-24)	Change from baseline (over 4 weeks)*	Placebo-Subtracted Change	p-value**
SSEs							
Study 511.71							
Flibanserin 100 mg qhs	280	3.0 (2.8)	275	4.6 (4.2)	1.6 (3.8)	0.8	**0.005**
Placebo	288	2.7 (2.8)	286	3.5 (3.6)	0.8 (3.4)		
Study 511.75							
Flibanserin 100 mg qhs	377	2.6 (2.9)	373	4.4 (5.3)	1.9 (5.3)	0.8	**0.024**
Placebo	388	2.7 (2.8)	382	3.7 (3.8)	1.1 (3.4)		
eDiary Desire							
Study 511.71							
Flibanserin 100 mg qhs	280	12.9 (10.5)	275	21.2 (17.1)	9.1 (1.0)	2.2	0.132
Placebo	288	11.8 (9.6)	286	18.1 (16.2)	6.9 (0.9)		
Study 511.75							
Flibanserin 100 mg qhs	377	12.0 (9.8)	373	20.1 (17.9)	8.5 (0.8)	1.7	0.346
Placebo	388	10.2 (8.8)	382	16.9 (16.9)	6.8 (0.8)		
Distress – FSDS-R Item 13							
Study 511.71							
Flibanserin 100 mg qhs	280	3.2 (0.9)	280	2.4 (1.2)	-0.8 (0.1)	-0.4	**0.0001**
Placebo	290	3.2 (0.8)	289	2.7 (1.1)	-0.5 (0.1)		
Study 511.75							
Flibanserin 100 mg qhs	380	3.3 (0.7)	380	2.5 (1.2)	-0.7 (0.1)	-0.3	**0.0006**
Placebo	389	3.2 (0.8)	389	2.7 (1.1)	-0.5 (0.1)		
Distress – FSDS-R Total							
Study 511.71							
Flibanserin 100 mg qhs	280	30.7 (10.0)	280	21.6 (12.3)	-8.9 (0.7)	-3.9	**<0.0001**
Placebo	290	30.1 (9.9)	289	25.2 (11.4)	-4.9 (0.7)		
Study 511.75							
Flibanserin 100 mg qhs	380	30.6 (9.3)	380	22.9 (12.5)	-7.8 (0.5)	-2.5	**0.0004**
Placebo	389	30.2 (9.9)	389	25.3 (11.9)	-5.2 (0.5)		

Scores reported as mean (standard deviation)
*Least squares mean change from baseline for eDiary Desire, FSDS-R Item 13, FSDS-R Total & FSFI Desire Items
**p-values for the co-primary efficacy endpoints have been adjusted for consistency with the Hochberg procedure. The p-values for secondary endpoints have not been adjusted.
Source: Study report for Study 511.71: Table 15.2.1: 1, p 183; Table 15.2.1: 2, p 185; Table 15.2.1: 4, p 188; Table 15.2.1: 5, p 190; Table 15.2.1: 8, p 194; Table 15.2.1: 9, p 196; Table 15.2.2: 3, p 232; Table 15.2.2: 4, p 234; Table 15.2.1: 10, p 198; Table 15.2.2: 4, p 234
Study report for Study 511.75: Table 15.2.1: 1, pp 181-2; Table 15.2.1: 2, p 184; Table 15.2.1: 4, pp 187-8; Table 15.2.1: 5, p 190; Table 15.2.1: 8, p 194; Table 15.2.1: 9, p 196; Table 15.2.2: 3, p 231; Table 15.2.2: 4, p 233; Table 15.2.2.3: 4, p 246; Table 15.2.2.3: 5, p 247

Division Comments:

- **The ranges of possible scores per four-week period for the various endpoints are as follows:**
    - **eDiary desire: 0 – 84 (0 – 3 per day)**
    - **FSDS-R Item 13: 0 – 16 (0 – 4 per week)**
    - **FSDS-R total: 0 – 208 (0 – 52 per week)**

- **To put the observed placebo-corrected changes in context, for eDiary desire, flibanserin subjects increased by 1.7 – 2.2 points on an 84-point scale, relative to placebo-treated subjects. For distress (using the FSDS-R Item 13), the relative improvement was 0.3 to 0.4 points on a 16-point scale.**

The Applicant also provided a sensitivity analysis, as requested by the Division, based on actual counts of SSEs prior to a clinic visit, without standardization to a 28-day period. Results are presented in Table 11. A similar analysis was requested for desire, but has not been provided.

Table 11 Sensitivity Analysis Limited to Observed SSEs – Studies 511.71 and 511.75 (FAS, LOCF)

Treatment Arm	N	Baseline (4 weeks)	N	End of Treatment (approximately Weeks 21-24)	Change from baseline (over 4 weeks)*	Placebo-Subtracted Change	p-value*
SSEs							
Study 511.71							
Flibanserin 100 mg qhs	280	3.0 (2.8)	275	4.3 (4.0)	1.3 (3.8)	0.6	**0.007 (0.014)**
Placebo	288	2.7 (2.7)	286	3.3 (3.5)	0.7 (3.3)		
Study 511.75							
Flibanserin 100 mg qhs	377	2.5 (2.8)	373	4.1 (4.8)	1.6 (4.9)	0.7	**0.002 (0.006)**
Placebo	388	2.6 (2.7)	382	3.4 (3.6)	0.9 (3.2)		

* p-values are provided as reported by the Applicant (and as adjusted in accordance with the Hochberg procedure)
Source: Study Report for Study 511.71, Table 15.2.2.1.1: 4, p 209 and Table 15.2.2.1.1: 5, p 211;
Study Report for Study 511.75, Table 15.2.2.1.1: 4, pp 206-7 and Table 15.2.2.1.1: 5, p 209

Division Comment:
When SSEs are no longer standardized to a 28-day reporting window, but are reported as recorded, the endpoint remains statistically significant in both studies. However, the change from baseline and placebo-subtracted change attributable to flibanserin treatment are both decreased slightly.

Results with the 25 mg bid or 50 mg qhs doses were less favorable than those for the 100 mg qhs dose (data not shown). The 100 mg qhs dose was superior to 50 mg bid in terms of tolerability. Therefore, the Applicant considered 100 mg qhs to be optimal for the HSDD indication and this is the only dose being considered for approval.

Division Comment:
The Division agrees with the Applicant's conclusion that doses other than 100 mg qhs did not demonstrate adequate efficacy/tolerability for further consideration.

4.3.2 Supportive Efficacy Analyses

4.3.2.1 FSFI Desire Score in Studies 511.71 and 511.75

The FSFI desire domain (two questions) was considered a key secondary endpoint by the Applicant in the statistical analysis plan (SAP) for Study 511.71 (but not 511.75). This was a change made to the original SAP and was not agreed to by the Division.

As noted in Section 2.3, when the Applicant learned that the eDiary desire scores did not attain statistical significance in either Study 511.71 or 511.75, they sought to modify the desire endpoint to that measured by the FSFI desire items. Rationale provided included the lack of compliance with diary entry for desire as the trial went on, and concerns about the adequacy of the eDiary question as a measure of sexual desire.

Results for this secondary endpoint are provided in Table 12.

Table 12 FSFI Desire Items – Studies 511.71 and 511.75

Treatment Arm	N	Baseline (4 weeks)	N	End of Treatment (approximately Weeks 21-24)	Change from baseline (over 4 weeks)*	Placebo-Subtracted Change	p-value
FSFI Desire Items							
Study 511.71							
Flibanserin 100 mg qhs	280	1.9 (0.7)	280	2.8 (1.2)	0.9	0.4	**<0.0001**
Placebo	290	1.9 (0.7)	290	2.4 (1.2)	0.5		
Study 511.75							
Flibanserin 100 mg qhs	380	1.8 (0.7)	379	2.7 (1.2)	0.9 (0.1)	0.3	**<0.0001**
Placebo	388	1.8 (0.7)	389	2.4 (1.1)	0.6 (0.1)		

Source: Study report for Study 511.71: Table 15.2.1: 10, p 198; Table 15.2.2: 4, p 234
Study report for Study 511.75: Table 15.2.2.3: 4, p 246; Table 15.2.2.3: 5, p 247

Division Comments:

- **The range of possible scores per four-week period for the FSFI desire items is 1.2 – 6 (1-5 for each of two questions, with a weighting factor of 0.6). Thus, compared with placebo-treated subjects, flibanserin subjects increased by 0.3 – 0.4 points on a 6-point scale.**
- **The Division does not agree that the FSFI desire items should provide the primary support for efficacy on the co-primary endpoint of sexual desire. It is inappropriate to modify prespecified endpoints after results of the studies are known. In addition, the Division had expressed concern prior to NDA submission about the utility of the FSFI as an endpoint instrument.**
- **The Division never agreed that the FSFI sexual desire domain was an acceptable primary or key secondary endpoint. On the contrary, the Division provided early guidance in a 2005 meeting that the evaluation of change in sexual desire (a critical component for both the diagnosis of HSDD and treatment evaluation of flibanserin) should not be based on a 28-day recall (as is the case with the FSFI sexual desire domain), but rather on a more frequent recording (i.e., daily) of the endpoint. For this reason, the Division recommended that the eDiary Question 2 ("how would you rate your level of sexual desire?") be used as a key efficacy endpoint.**
- **In consultation with the FDA Study Endpoints and Label Development (SEALD) team, the Division clearly stated at the end of phase 2 meeting in 2005 the reasons it believed daily use of the eDiary would be a better method for the collection of data for sexual desire. The Division wanted to see that an effect of treatment is an overall increase in sexual desire regardless of whether a sexual event occurred or not. Decreased sexual desire, along with personal distress, is a critical component for the**

diagnosis of HSDD, so it seems imperative that sexual desire should be carefully and regularly recorded.

- **The Applicant's own validation studies of the eDiary desire question showed the following:**
    - **Responses from patients on an eDiary feedback questionnaire indicated overall very high evaluations regarding the wording of questions and the usability of the eDiary.**
    - **In Study 511.106, 100% of the 60 subjects who participated in cognitive debriefing understood the eDiary question about intensity of sexual desire, thought the response options were sufficient, and thought the answers captured how they felt about their sexual desire.**
    - **The results supported the effectiveness of the eDiary as a method for collecting daily information regarding sexual activities and attitudes.**
    - **Further support for using the eDiary is found in Study 511.106, which conducted cognitive debriefing on selected eDiary questions relevant to the HSDD population. The debriefing showed "a high level of understanding and acceptance of the question and answer sets." In addition, the results also provide "strong support for the discriminant and convergent validity of the desire endpoints from the eDiary in measuring the sexual desire level and desire frequency."**
- **Although the Applicant conducted two studies (511.144 and 511.151) to demonstrate the content validity of the FSFI and the use of the two sexual desire items, there were only 15 and 30 premenopausal women in these studies. Furthermore, as stated by the Applicant in the study synopsis, "there was no clear preference for a 1-, 2-, or 4-week recall period."**
- **The Applicant provided data (pooled over both flibanserin and placebo arms) on the mean SSE score associated with each level of eDiary desire, including missing desire data. There was a strong trend of increasing numbers of SSEs with increasing levels of desire. Where desire data were missing, the mean number of SSEs fell between the numbers associated with "no desire" and "low desire." Thus, missing desire data is informative and does not merely represent poor compliance, but likely also reflects poor treatment benefit.**

4.3.2.2 Results of Study 511.77

Also as discussed in Section 2.3, the Applicant proposed modifying the analysis of ongoing Study 511.77 (the European phase 3 trial, see Table 2) prior to unblinding of results, to evaluate desire using to the FSFI desire domain as the endpoint instrument. The Division was willing to consider these data, provided review of the development and validation of the FSFI indicated that it was an appropriate instrument to be used in support of labeling claims. That review is ongoing.

The revised protocol for Study 511.77 specified SSEs as the single primary efficacy endpoint, with FSFI desire items elevated to a key secondary endpoint. The analysis plan specified a hierarchical analysis, in which the FSFI desire would be analyzed only if the SSE endpoint for the 100 mg qhs dose had attained statistical significance. Desire as measured by the eDiary was a secondary endpoint. Results are displayed in Table 13.

Table 13 Efficacy Results for Study 511.77

Treatment Arm	N	Baseline	N	End of Treatment (Weeks 21-24)	Change from baseline*	Placebo-Subtracted Change	p-value
SSEs							
Flibanserin 100 mg qhs	305	2.4 (2.6)	302	3.3 (3.7)	0.9 (2.9)	0.6	0.140
Placebo	308	2.3 (2.5)	312	3.1 (3.5)	0.6 (2.6)		
FSFI Desire Items							
Flibanserin 100 mg qhs	308	1.9 (0.8)	308	2.5 (1.1)	0.7 (1.1)	0.1	0.082
Placebo	313	1.9 (0.8)	313	2.3 (1.1)	0.5 (1.1)		
eDiary Desire							
Flibanserin 100 mg qhs	305	9.5 (8.8)	302	16.1 (15.9)	7.7 (0.8)	2.3	**0.024**
Placebo	308	9.1 (8.2)	312	13.2 (13.1)	5.4 (0.8)		

Source: Study report for Study 511.77: Table 15.2.1: 1, p 177; Table 15.2.1: 2, p 179; Table 15.2.1: 3, p 181; Table 15.2.1: 4, p 183; Table 15.2.1: 8, p 190; Table 15.2.1: 9, p 191

Division Comments:

- **Per protocol, the analysis of the desire items (either the key secondary endpoint based on the FSFI desire items or the secondary endpoint based on the eDiary) should not have been analyzed after the primary efficacy endpoint of SSEs failed to demonstrate statistical significance.**
- **Nevertheless, it is of interest that the change in desire as measured by the FSFI also failed to attain statistical significance, while desire as measured by the eDiary question did show a statistically significant increase with treatment. This undercuts the Applicant's argument that the failure to show a treatment benefit on desire in Studies 511.71 and 511.75 is due to an inadequate endpoint instrument.**

4.3.2.3 Responder Endpoints

To determine whether the changes observed for the endpoints SSEs and sexual desire were meaningful to the subjects, the Applicant conducted responder analyses.

The Applicant calculated responder definitions by using the differences between the SSE and desire scores associated with "minimally improved" and "no change" on the PGI-I as the responder criteria. However, calculations were also done, as an exploratory analysis, using scores associated with "minimally improved" and "much improved."

Results are displayed in Table 14. PGI-I anchor-based responder endpoints were defined for SSEs, desire (both eDiary and FSFI domain-measured), and distress (FSDS-R total and Item 13-measured). Analyses were then conducted by the Applicant comparing the percentages of women in the flibanserin and placebo arms who exceeded the specified criteria for each endpoint.

Table 14 Responder Criteria Definitions based on PGI-I Anchoring – Studies 511.71 and 511.75

Study	SSE	Desire – eDiary	Distress – FSDS-R – Item 13	Distress – FSDS-R Total	Desire - FSFI
No Change vs. Minimally Improved					
511.71	1.22	7.80	-0.44	-5.63	0.83
511.75	1.25	7.91	-0.41	-5.07	0.80
Minimally Improved vs. Much Improved					
511.71	2.00	8.88	-1.1	-8.82	0.86
511.75	2.39	9.23	-0.92	-7.37	0.93

Source: Modified from Applicant Table 1.1: 1, p 2, and Table 1.2: 1, p 3, in the Responder Criteria Method Report

Division Comment:

- **No pre-specified responder endpoints were agreed to during the meetings with the Applicant. Use of data-driven endpoints were discussed and the Division's preference was to use responder criteria definitions determined by anchoring the endpoints (change from baseline) to levels of the PGI-I or a similar instrument with a range of responses. The Division did agree that the simple Patient Benefit Evaluation should not be used as the anchor.**
- **For determining what is clinically meaningful, the Division believes that a better contrast is between "minimally improved" and "much improved." The contrast between "no change" and "minimally improved" is likely to reflect the minimum clinically detectable change, rather than what is meaningful to women.**

For each trial, all women with values greater than the responder criteria were considered responders. Response rates based on the two definitions of responder are displayed in Table 15.

Table 15 Responder Rates – Studies 511.71 and 511.75

	511.75							
	Percent difference between minimally improved and no change[1]				Percent difference between much improved and minimally improved[2]			
	Placebo	FLI 100qhs	**Delta**	P-value	Placebo	FLI 100qhs	**Delta**	P-value
Responder Endpoint (%)								
SSE (standardized)	34.1	44.2	**10.1**	0.0054	22.0	31.8	**9.8**	0.0059
eDiary SDS	32.0	38.0	**6.0**	0.0638	31.0	35.6	**4.6**	0.1563
FSFI desire	32.7	45.6	**12.9**	0.0002	32.7	45.6	**12.9**	0.0002
FSDS-R Q13	40.1	49.5	**9.4**	0.0133	40.1	49.5	**9.4**	0.0133
FSDS-R total	40.9	52.1	**9.2**	0.0010	33.4	43.2	**9.8**	0.0053

	511.71							
	Difference between minimally improved and no change[1]				Difference between much improved and minimally improved[2]			
	Placebo	FLI 100qhs	**Delta**	P-value	Placebo	FLI 100qhs	**Delta**	P-value
Responder Endpoint (%)								
SSE (standardized)	33.0	47.6	**14.6**	0.0004	29.1	41.1	**12.0**	0.0031
eDiary SDS	38.2	41.1	**2.9**	0.4920	33.3	38.5	**5.2**	0.1563
FSFI desire	30.7	42.9	**11.8**	0.0033	30.7	42.9	**11.8**	0.0033
FSDS-R Q13	42.9	54.6	**11.7**	0.0049	14.2	27.5	**13.3**	0.0001
FSDS-R total	43.9	55.7	**11.8**	0.0064	32.5	45.4	**12.9**	0.0053

Source: Table 1.2: 2, p 4, in the Responder Criteria Method Report

Division Comments:

- **The difference in proportion of responders is quite consistent, whichever definition of responder is used. Response rates for SSEs and distress are statistically significantly greater for flibanserin-treated subjects; the response rate for the eDiary desire score is not statistically significant in either Study, under either responder definition. These results are consistent with the prespecified analyses of the co-primary endpoints, in that the treatment effect on SSEs were shown to be statistically significant and clinically meaningful, while the treatment effect on desire was neither statistically significant nor clinically meaningful.**
- **Although many of the differences in response rates are statistically significant, the overall response rate (about 30-40% in the flibanserin arm is not compelling, particularly when contrasted with the placebo response rates of about 15-30%. Specifically, the treatment effect for SSEs is about 10-15%, for eDiary desire about 3-6%, and for distress about 9-13%.**
- **In addition, the numerous analyses are not adjusted for multiple comparisons.**

4.4 Efficacy Conclusion

Although the two North American trials that used the flibanserin 100 mg qhs dose showed a statistically significant difference between flibanserin and placebo for the endpoint of SSEs, they both failed to demonstrate a statistically significant improvement on the co-primary endpoint of sexual desire. Therefore, neither study met the agreed-upon criteria for success in establishing the efficacy of flibanserin for the treatment of HSDD.

At issue and a major concern of the Division are the following findings:

1. The trials did not show a statistically significant difference for the co-primary endpoint, the eDiary sexual desire score.
2. The Applicant's request to use the FSFI desire items as the alternative instrument to evaluate the co-primary endpoint of sexual desire is not statistically justified and, in fact, was not supported by exploratory data from Study 511.77, which also failed to demonstrate a statistically significant treatment benefit on desire using the FSFI desire items.
3. The responder rates on the important efficacy endpoints for the flibanserin-treated subjects, intended to demonstrate the clinical meaningfulness, are only 3-15% greater than those in the placebo arm.
4. There were many significant medical and medication exclusion criteria for the efficacy trials, so it is not clear whether the safety and efficacy data from these trials are generalizable to the target population for the drug.

5. Overview of the Safety Database for Flibanserin

The assessment of the clinical safety of flibanserin is based on 27 phase 1 studies, 11 phase 2 studies in men and women with major depressive disorder (MDD), and 9 studies (two phase 2 and seven phase 3) in premenopausal women with HSDD. As of the cut-off date for the four-month Safety Update (November 17, 2009), the overall HSDD clinical program included data from 5,018 subjects (see Table 16).

Table 16 Exposure to Flibanserin by Cumulative Interval – All HSDD Trials*

Exposure (days)	FLI 25 bid N (%) 814	FLI 50 qhs N (%) 3,839	FLI 50 bid N (%) 1,257	FLI 100 qhs N (%) 2,938	FLI 100 bid N (%) 72	FLI total N (%) 5,018
≥1	814	3,839	1,257	2,938	72	5,018
≥84	605 (74.3)	1,255 (32.7)	666 (53.0)	2,144 (73.0)	0	3,850
≥365	2 (0.2)	89 (2.3)	13 (1.0)	213 (7.2)	0	1,130 (22.5)
≥547	0	6 (0.2)	1 (0.1)	38 (1.3)	0	185 (3.7)
Subject years	297.5	925.8	364.0	1,525.6	4.6	3,117.5

* Includes all HSDD studies, completed and ongoing: 511.68, .69, .70, .71, .74, .75, .77, .84, .105, .118
Source: Table 1.2.2.1: 1, p 35, Table 1.2.2.21: 1, p 36, Table 1.2.2.2.2: 1, p 37, Table 1.2.2.2.2: 2, p 39, Table 1.2.2.2.3: 1, p 41, and Table 1.2.2.3: 1, p 42, Summary of Clinical Safety

This review focuses primarily on data from the four phase 3 placebo-controlled trials conducted in premenopausal women with HSDD that were combined in the Applicant's integrated summary of safety (ISS). Results of the two open-label, long-term extension studies (511.84 and 511.118) in premenopausal women with HSDD were evaluated for the safety of chronic flibanserin therapy. Safety

data from the following additional sources were reviewed for deaths and significant safety signals identified during analysis of the primary database:

- A 48-week, phase 3 randomized withdrawal study in premenopausal females with HSDD (Study 511.74)
- Two randomized, double-blind, placebo-controlled phase 2 trials in premenopausal women with HSDD
- Select phase 1 trials in healthy volunteers
- Select phase 2 trials conducted in subjects with MDD

Summary information for all phase 2 and phase 3 trials in the premenopausal HSDD population is found in Table 2.

All adverse events (AEs) were recorded at each clinic and telephone visit through spontaneous subject reports and direct inquiry (i.e., "How have you felt since your last clinic visit?"). Any clinically relevant change from baseline in the laboratory findings requiring medical intervention was also recorded as an AE.

Adverse events captured by the study investigators (verbatim adverse event terms) were then coded by the Applicant to preferred terms (PTs) using a medical coding dictionary [the Medical Dictionary for Regulatory Activities (MedDRA); the version used at time of analysis was 11.1]. MedDRA is organized in the following hierarchical manner:

System Organ Class (SOC)
High Level Group Term (HLGT)
High Level Term (HLT)
Preferred Term (PT)

The Applicant performed adverse event analyses in two ways: by randomized treatment and by treatment at onset. Treatment at onset refers to the dose of medication the subject was taking at the time of the adverse event. It differs from randomized treatment analysis only when the administration regimen involved a changing of dosage during the trial, as was done in Studies 511.75 and 511.77. Both of those trials included a two-week up-titration phase in which subjects randomized to 100 mg qhs or 50 mg bid were administered 50 mg qhs for the first two weeks of treatment. The randomized treatment analysis groups adverse events according to the dose group to which the subject was assigned (e.g. 50 mg qhs or 100 mg qhs), regardless of the treatment receiving at the time of the adverse event.

5.1 Safety Findings from the Flibanserin Clinical Development Program

5.1.1 Deaths

Deaths that occurred on study or within 30 days of terminating flibanserin treatment were recorded. In all HSDD trials (phase 1-3, including open-label safety extensions), one death occurred, in a subject in Study 511.74 who received placebo. She died as a passenger in an airplane crash on Day 19 of the double-blind period.

Division Comment:
The death was clearly unrelated to study drug or procedures.

There were no deaths among subjects in the MDD trials.

5.1.2 Serious Adverse Events

5.1.2.1 Phase 2/3 placebo-controlled HSDD trials

In the phase 2/3 placebo-controlled HSDD trials, serious adverse events (SAEs) occurred in <1% of subjects receiving any dose of flibanserin. The incidence of SAEs was slightly more common among subjects receiving flibanserin 100 mg qhs than other doses. The most frequently reported SAE among flibanserin subjects was appendicitis. None of the SAEs were considered related to flibanserin by any investigator, nor by the Applicant.

SAEs which occurred in more than one flibanserin-treated subject (any dose) are displayed in Table 17. The table also includes other notable SAEs.

Table 17 Frequency of Subjects with Serious Adverse Events – HSDD Phase 2/3 Database

Preferred Term	Placebo	FLI 25 mg bid	FLI 50 mg qhs	FLI 50 mg bid	FLI 100 mg qhs
Phase 2/3 placebo-controlled HSDD Trials*					
Total N	1,508	733	2,072	862	978
Total with SAEs n (%)	8 (0.5)	4 (0.5)	13 (0.6)	3 (0.3)	9 (0.9)
Appendicitis	0 (0.0)	1 (0.1)	4 (0.2)	1 (0.1)	0
Suicide attempt	0	0	0	0	1 (0.1)
Circulatory collapse	0	0	1 (<0.1)	0	0
Cholelithiasis	2 (0.1)	0	1 (<0.1)	1 (0.1)	0 (0.1)
Concussion	0	0	1 (<0.1)	0	1 (0.1)
Intervertebral disc protrusion	0	1 (0.1)	1 (<0.1)	0	1 (0.1)
Double-blind Period of Study 511.74 (randomized withdrawal study in HSDD population)					
Total N	170	NA	35	13	115
Total with SAEs n (%)	3 (1.8)	NA	1 (2.6)	0	0
Phase 3 open-label HSDD Trials (Studies 511.118 and 511.84)					
Total N	NA	57	2,197	305	1791
Total with SAEs n (%)	NA	1 (1.8)	9 (0.4)	4 (1.3)	16 (0.9)
Appendicitis	NA	0	0	0	2 (0.1)
Ovarian cyst	NA	0	1 (0.0)	1 (0.3)	0
Uterine polyp	NA	0	1 (0.0)	1 (0.3)	0
Open-label Phase of HSDD randomized withdrawal study (511.74)					
Total N	NA	NA	738		
Total with SAEs n (%)	NA	NA	6 (0.8)		
Suicidal ideation	NA	NA	1 (0.1)		
Tibia fracture	NA	NA	1 (0.1)		

* includes studies 511.68, -.69, -.70, -.71, -.75, -.77

Source: Table 2.3: 1, pp 84-86, Summary of Clinical Safety

Division Comments:

- **Narratives for all serious adverse events were reviewed.**
- **The reason for the excess prevalence of appendicitis among flibanserin-treated subjects is not clear. Affected subjects ranged in age from 23 – 42 years. The estimated annual incidence of appendicitis among women aged 20-44 years ranges from 152 per 100,000 (ages 20-24) to 74 per 100,000 (ages 40-44), respectively (annual**

risk of 0.074 –0.15%).[1] A total of 0.13% of flibanserin-treated subjects (all doses) experienced appendicitis over a potential six month exposure period. The incidence is only slightly greater than would be expected based on background risk.

- **It is possible that flibanserin, by virtue of causing constipation (constipation is a commonly reported treatment-emergent AE, see Table 19), can slightly increase the risk of appendicitis. None of the subjects experiencing appendicitis, however, reported an adverse event of constipation.**
- **There were no serious adverse events of intestinal obstruction.**
- **The SAEs of circulatory collapse and suicide attempt are addressed in Sections 5.2.2.1 and 5.2.1.2, respectively. One event of concussion occurred in the subject experiencing circulatory collapse. The second event, which was a result of a road traffic accident, is discussed in Section 5.2.3.1.**
- **Two of the events of intervertebral disc protrusion do not appear to be related to study drug. The third event, in a subject on flibanserin 25 mg bid, occurred 68 days after initiating flibanserin and followed a motor vehicle accident. Narrative for this subject is also found in Section 5.2.3.1.**
- **Cholelithiasis occurred with the same frequency in the placebo group. None of the events could be clearly attributed to flibanserin.**

5.1.2.2 Double-blind period of study 511.74 (randomized withdrawal study in HSDD population)

No notable SAEs were reported during this phase of study 511.74. The frequency of all SAEs is shown in Table 17.

5.1.2.3 Phase 3 open-label HSDD trials (Studies 511.118 and 511.84)

In the phase 3 open-label safety extension studies, the frequency of SAEs was not dose-proportional. Single SAEs that occurred in more than one flibanserin treated subject (at any dose) are shown in Table 17.

Division Comment:
Narratives were reviewed. Adverse events of uterine polyp and ovarian cyst do not appear to be related to flibanserin therapy.

5.1.2.4 Open-label phase of HSDD randomized withdrawal study (511.74)

In the open-label phase of study 511.74, SAEs occurred in 6/738 subjects (0.1%). SAEs of note were suicidal ideation (N=1) and tibial fracture (N=1); see Table 17.

Division Comments:

- **Because subjects were allowed to switch flibanserin dose during the open-label phase (i.e., increase from 50 mg to 100 mg qhs, etc.), an analysis of adverse events**

[1] Addiss, D.G., Shaffer, N., Fowler, B.S., Tauxe, R.V. The epidemiology of appendicitis and appendectomy in the United States. *Amer J Epi 1990; 132 (5): 910-25*

according to dose group was not possible (i.e., a given subject may be represented in more than one dose group).

- **The tibia fracture occurred after a motorcycle accident and is discussed in Section 5.2.3.1.**
- **The event of suicidal ideation is addressed in Section 5.2.1.2.**

5.1.2.5 Phase 1 database

A single serious adverse event of depression occurred in a phase 1 open-label study of flibanserin in premenopausal women with HSDD (Study 511.105). This event is discussed in Section 5.1.2.5

5.1.3 Discontinuations Due to Adverse Events

More flibanserin-treated subjects discontinued prematurely due to an adverse event than those on placebo; discontinuation due to AEs was also dose-related. The most common AEs leading to treatment discontinuation are shown in Table 18.

Table 18 Adverse Events Leading to Treatment Discontinuation in >1% of Subjects, Phase 3 Placebo-Controlled HSDD Trials* (By Randomized Treatment)

	Placebo N (%)	50 mg qhs N (%)	100 mg qhs N (%)
	1,360 (100)	**969 (100)**	**1,001 (100)**
Total with AEs leading to 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)

* Includes trials 511.70, 511.71, 511.75, and 511.77
Source: Table 2.4.1.1: 1, p 94, Summary of Clinical Safety

Division Comment:
It is notable that nearly 15% of subjects receiving flibanserin 100 mg qhs discontinued prematurely due to an adverse event compared to 6.8% for placebo subjects.

5.1.4 Common Treatment-Emergent Adverse Events (AEs)

In the four phase 3 placebo-controlled HSDD trials, more subjects in the flibanserin groups (any dose) reported an adverse event compared to those on placebo (66.2% vs. 57.7%, respectively). This reviewer considered adverse events occurring in >1% of flibanserin subjects and at twice the rate observed in placebo to be possibly related to study drug. Adverse events meeting these criteria are shown in Table 19.

Table 19 Adverse Events Occurring in >1% and at Least Twice that of Placebo in the Flibanserin 100 mg Group (Randomized Treatment) – Phase 3 Placebo-Controlled HSDD Trials*

	Placebo	25 mg bid	50 mg qhs	50 mg bid	100 mg qhs
	N = 1360	N = 733	N = 969	N = 728	N = 1001
Any event	785 (57.7)	430 (58.7)	628 (64.8)	517 (71.0)	696 (69.5)
Subjects with severe AE's	71 (5.2)	32 (4.4)	69 (7.1)	44 (6.0)	83 (8.3)
Dizziness	34 (2.5)	31 (4.23)	61 (6.30)	111 (15.25)	120 (11.99)
Nausea	58 (4.26)	41 (5.59)	68 (7.02)	90 (12.36)	119 (11.89)
Fatigue	77 (5.66)	35 (4.77)	59 (6.09)	101 (13.87)	110 (10.99)
Somnolence	40 (2.94)	51 (6.96)	55 (5.68)	122 (16.76)	95 (9.49)
Insomnia	32 (2.35)	14 (1.91)	19 (1.96)	20 (2.75)	51 (5.09)
Dry mouth	9 (0.66)	6 (0.82)	12 (1.24)	10 (1.37)	23 (2.30)
Anxiety	9 (0.66)	5 (0.68)	19 (1.96)	10 (1.37)	20 (2.00)
Abdominal pain	11 (0.81)	5 (0.68)	17 (1.75)	8 (1.10)	18 (1.80)
Constipation	4 (0.29)	4 (0.55)	4 (0.41)	9 (1.24)	17 (1.70)
Sedation	2 (0.15)	1 (0.14)	6 (0.62)	10 (1.37)	17 (1.70)
Nocturia	3 (0.22)	3 (0.41)	5 (0.52)	4 (0.55)	12 (1.20)
Sleep disorder	1 (0.07)	1 (0.14)	5 (0.52)	4 (0.55)	12 (1.20)
Palpitations	6 (0.44)	3 (0.41)	5 (0.52)	5 (0.69)	10 (1.00)
Stress	2 (0.15)	3 (0.41)	4 (0.41)	0	10 (1.00)
Vertigo	4 (0.29)	1 (0.14)	3 (0.31)	5 (0.69)	10 (1.00)

* Includes trials 511.70, 511.71, 511.75 and 511.77;
Source: Table 2.1.2.1.1, p 93, Integrated Summary of Safety

Division Comments:

- **The most common treatment-emergent adverse events for subjects treated with flibanserin 100 mg qhs are dizziness, nausea, fatigue, and somnolence. The majority of AEs were mild to moderate. For the four most common AEs, the 100 mg qhs dose appeared to be better tolerated than the 50 mg bid dose.**
- **The Applicant studied two dosing schemes – a fixed dose regimen wherein subjects were immediately started on the 100 mg qhs dose, and an up-titration regimen in which 50 mg qhs was administered for two weeks and then increased to 100 mg qhs. The incidence of common adverse events in the first four weeks of treatment for the two dosing regimens was similar (e.g., incidence of somnolence, fatigue or sedation was 19.4% in the fixed-dose group vs. 17.7% in the up-titration group). Therefore, the Division agrees with the Applicant's assessment that up-titration is not necessary, and a 100 mg qhs starting dose is appropriate.**

5.2 Safety Issues of Particular Concern or Interest

5.2.1 Depression and Suicidality

Because of flibanserin's central mechanism of action, the Applicant examined their database for adverse events of depression. For this reason, as well as the drug's shared pharmacologic properties to some approved anti-depressants (e.g., nefazodone), the Division requested that the potential for flibanserin to cause suicide/self-injury be assessed during clinical development.

5.2.1.1 Depression

5.2.1.1.1 Phase 2/3 Placebo-controlled HSDD Trials

The Applicant searched the phase 2/3 HSDD database for depression-related adverse events using the standard MedDRA query (SMQ). Preferred terms included in the depression SMQ were *disturbance in attention, depression, middle insomnia, depressed mood, mood altered, mood swings, poor quality sleep, affect lability, dysphoria, tearfulness, apathy, crying, early morning awakening, major depression, memory impairment, blunted affect, decreased interest, depressive symptom, dyssomnia, emotional distress, hypersomnia, initial insomnia, psychomotor hyperactivity, and listless.*

Subjects on flibanserin 100 mg daily (either as 50 mg bid or 100 mg qhs) had a slightly higher incidence of depression identified using the SMQ than those on placebo (Table 20). Depression appears to be dose-related.

Table 20 Frequency of Subjects with Depression (SMQ) by Flibanserin Dose – All HSDD Trials

Adverse Event category	Placebo	FLI 25 bid	FLI 50 qhs	FLI 50 bid	FLI 100 qhs
Phase 2/3 placebo-controlled HSDD trials					
Total N	1508	733	2072	862	978
Depression n (%)	47 (3.1)	20 (2.7)	62 (3.0)	37 (4.3)	**41 (4.2)**
Double-blind portion of Study 511.74 (randomized withdrawal)					
Total N	170	NA	35	13	115
Depression n (%)	10 (5.9)	NA	2 (5.8)	0	**8 (7.0)**
Phase 3 Open-label HSDD trials (studies 511.118 and 511.84)					
Total N	NA	57	2197	305	1791
Depression n (%)	NA	0	43 (2.0)	6 (2.0)	**64 (3.6)**
Open-label portion of Study 511.74 (randomized withdrawal)					
Total N	NA	NA	738*		
Depression n (%)	NA	NA	45 (6.1)		

In the open-label phase of study 511.74, subjects were allowed to switch flibanserin dose (e.g. increase from 50 mg qhs to 100 mg qhs); therefore, an analysis of adverse events by dose group was not possible. These data include all three doses studied – 50 mg qhs, 50 mg bid and 100 mg qhs.

Source: Table 2.6:1, pp 102-3, Summary of Clinical Safety; and Table 2.1.1 from Applicant submission dated April 30, 2010

Division Comment:
None of the adverse events of depression in the phase 2/3 HSDD trials were serious.

5.2.1.1.2 Double-blind period of Study 511.74 (randomized withdrawal study in HSDD population)

Depression (SMQ) was more common among subjects receiving flibanserin 100 mg qhs than those on placebo or flibanserin 50 mg qhs (Table 20).

5.2.1.1.3 Phase 3 open-label HSDD trials (Studies 511.118 and 511.84)

In the two phase 3 open-label extension studies, the frequency of depression-related adverse events was greatest among subjects receiving flibanserin 100 mg qhs (see Table 20).

5.2.1.1.4 Open-label phase of HSDD randomized withdrawal study (511.74)

In the open-label phase of HSDD Study 511.74, a total of 6.1% (45/738) subjects experienced an adverse event within the depression (SMQ) category (Table 20).

5.2.1.1.5 Phase 1 database

An SAE of depression occurred in Study 511.105, a phase 1 open-label, parallel, and within-groups sequential trial of flibanserin in premenopausal women with HSDD.

> *Subject 511.105-39112* was a 47 year-old female patient with no significant past medical history who was randomized on October 8, 2007, to flibanserin 25 mg bid. The last dose of flibanserin was on the night of October 10, 2007. On October 11, 2007, the subject experienced a depressive episode following a break-up with her boyfriend and was hospitalized. Treatment administered for the event included citalopram 40 mg daily and trazodone. The patient recovered and was discharged from the hospital on October 15, 2007. The investigator judged that there was no reasonable possibility that the event was related to study drug.

Division Summary Comment:
The data from all HSDD trials suggest that flibanserin may be associated with a dose-proportional increase in depression-related adverse events.

5.2.1.2 Suicidality

5.2.1.2.1 Screening for Suicidality

The Applicant administered the Beck Scale for Suicide Ideation (BSS) in the phase 3 placebo-controlled HSDD trials at screening, baseline, on-treatment and post-treatment visits.

The BSS is a 21-item instrument used to detect and measure the severity of suicidal ideation in adults. 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 last two questions [**Groups 20 and 21** (if applicable)] relate to the number of previous suicide attempts and the seriousness of intention to die associated with the last attempt.

5.2.1.2.2 Results

In the phase 3 placebo-controlled HSDD trials, the incidence of a non-zero score on the BSS Part I while on-treatment was similar between flibanserin and placebo groups (Table 21). One subject in the flibanserin group who had a negative history of suicide attempts at screening reported a positive response to BSS Group 20 while on treatment. However, there is no report of this subject experiencing the adverse event of suicide *attempt* during the trial.

Division Comment:
None of the 12 flibanserin subjects who responded positively to the BSS Part 1 during treatment reported an adverse event of suicidal ideation or attempt.

Table 21 Beck Scale for Suicide Ideation (Subjects with 0 Score at Baseline Who Scored >0 at Any Point on Treatment) – Phase 3 Placebo-Controlled HSDD Trials*

Visit	Instrument	Treatment	Total N	N (%) with score >0
On-treatment	BSS Part I	Placebo	1,312	6 (0.5)
		Flibanserin	3,283	12 (0.4)
	BSS Group 20 [suicide attempt (history)]	Placebo	1,312	0
		Flibanserin	3,283	1 (<0.1)

* includes Studies 511.70, 511.71, 511.75, 711.77 and 511.74
Source: Table 4.2.1:1, p 148, Summary of Clinical Safety

5.2.1.2.3 Adverse events of Suicidality

5.2.1.2.3.1 Phase 2/3 Placebo-controlled HSDD Trials

In the phase 2/3 HSDD trials, suicide/self injury (identified through a MedDRA SMQ that includes the preferred terms *suicidal ideation, suicide,* and *suicide attempt*) was reported by <1% of subjects in any treatment group (Table 22).

Table 22 Frequency of Subjects with Adverse Events in the Suicide/Self-Injury SMQ -- All HSDD Trials*

Adverse Event category/Preferred Term	Placebo	FLI 25 bid	FLI 50 qhs	FLI 50 bid	FLI 100 qhs
Phase 2/3 placebo-controlled HSDD trials					
Total N	1508	733	2072	862	978
Suicide/self-injury n (%)	1 (0.1)	0	3 (0.1)	0	1 (0.1)
Suicidal ideation	1 (0.1)	0	3 (0.1)	0	0
Suicide attempt	0	0	0	0	1 (0.1)
Double-blind portion of Study 511.74 (randomized withdrawal)					
Total N	170	NA	35	13	115
Suicide/self-injury n (%)	0	NA	0	0	0
Phase 3 Open-label HSDD trials (studies 511.118 and 511.84)					
Total N	NA	57	2197	305	1791
Suicide/self-injury n (%)	NA	0	1 (0)	0	0
Suicidal ideation	NA	0	1 (0)	0	0
Open-label portion of Study 511.74 (randomized withdrawal)					
Total N	NA	NA	**738**		
Suicide/self-injury n (%)	NA	NA	2 (0.3)		
Suicidal ideation	NA	NA	2 (0.3)		

*** Phase 2/3 placebo-controlled trials**
Source: Table 2.6:3, p 106, Summary of Clinical Safety

Of the three flibanserin subjects experiencing suicidal ideation, none recorded non-zero responses on the BSS at any time during treatment.

Narrative for the subject experiencing suicide attempt follows:

> *Subject 36657*, a 37-year old female 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 past 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 to 15 tablets of Ritalin (methylphenidate) and 10 to 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 investigator did not consider the adverse event to be related to study medication.

Division Comment:
It is impossible to determine if flibanserin contributed to this subject's suicide attempt.

5.2.1.2.3.2 Double-blind period of Study 511.74 (randomized withdrawal study in HSDD population)

No subject during the double-blind portion of the randomized withdrawal study experienced an event of suicidality.

5.2.1.2.3.3 Phase 3 open-label HSDD trials (Studies 511.118 and 511.84)

Through November 17, 2009 (date of data-lock for 120 day safety update), there have been no AEs of suicidal ideation, suicide attempt, or suicide in Study 511.118. There was one adverse event report of suicidal ideation in Study 511.84. Subject 16817, on flibanserin 50 mg qhs, reported suicidal ideation on Day 28. The AE was moderate and not considered related to study drug. The subject recovered from the event on Day 29 without therapy and continued in the trial.

5.2.1.2.3.4 Open-label phase of HSDD randomized withdrawal study (511.74)

In the open-label phase of HSDD Study 511.74, two subjects experienced adverse events of suicidal ideation. One event involved a 48-year-old subject who reported suicide ideation of moderate intensity on Day 85 while taking flibanserin 50 mg qhs. Flibanserin was continued and no therapy was initiated. The subject recovered from the event after 8 days.

The second incident was an SAE of suicidal ideation in a 40 year old female. Narrative follows.

Subject 10506: This patient, with a past medical history of panic attacks, depression, and alcohol, methamphetamine and marijuana abuse, started on open-label flibanserin 100 mg qhs on May 8, 2006. At screening, however, she had denied a history of psychiatric problems or suicide attempts.

On September 11, 2006, at a scheduled clinic visit, the patient reported a 3-week history of an increase in her anxiety. Per the patient's request, the study drug was held for a few days.

On September 12, 2006, the patient developed suicidal ideation which was not disclosed to the investigator. On 14 Sep 2006, the patient reported that she did not believe the drug was making her anxious and she felt better, so she agreed to resume the study drug.

On 25 Sep 2006, the patient called the clinic and stated that she was feeling very anxious and depressed and wanted to terminate her participation in the study. She had discontinued the drug two days earlier.

On 26 Sep 2006, the patient was seen at the clinic for an end of trial visit. She reported that she had been having thoughts of suicide and of hurting her 20 month-old daughter. The patient was sent to the emergency room for a psychiatric evaluation and treatment.

Psychiatric evaluation revealed that the patient had suffered multiple recent psychosocial stressors, including serious illness in her child, and a death in the family. She also reported a family history of mental illness, and a past suicide attempt as a 15 years earlier. The patient was diagnosed with Depressive Disorder, Panic Disorder with some agoraphobia and was admitted to the psychiatric unit for treatment.

The patient was discharged home on October 1, 2006. She had recovered from the event of suicidal ideation on 01 Oct 2006 and recovered from the event of anxiety on 02 Oct 2006. The investigator and the clinical monitor judged that there was no reasonable possibility that the events were related to the trial drug.

Division Comment:
This subject's history of depression as well as concurrent psychosocial stressors may have increased her vulnerability to suicidal ideation.

Division Summary Comments:

- **There have been a total of seven adverse events of suicidality (six suicidal ideation, one suicide attempt) in the entire HSDD database involving 5,018 subjects exposed to flibanserin (dose range of 25 mg bid to 100 mg bid). Two events resolved spontaneously without discontinuation of study drug. Two events occurred in subjects with a history of depression and a previous suicide attempt, respectively.**
- **The placebo-controlled data do not suggest a significant risk of suicidality associated with flibanserin in otherwise healthy subjects. Given the observation of an increase in depression-related adverse events in subjects taking flibanserin, it is possible that in a larger population, suicidality may emerge as a potential risk of flibanserin. This effect may be even more pronounced in women with an underlying predisposition to suicidality, such as those with a history of mental illness (subjects with a history of depression or suicide attempt were excluded from participation in the HSDD trials).**
- **The FDA Division of Psychiatric Products (DPP) was asked to comment on the sponsor's suicidality analysis. DPP noted that "***on face, no suicidality or other psychiatric safety signals arise from the flibanserin safety analysis reported by the sponsor. It is of note that, given the low frequency of treatment-emergent suicidal ideation and behavior, the detection of a suicidality signal is unlikely when analyzing the development program of a single drug. Given its mechanism of action, flibanserin would be considered to have antidepressant properties. For safety labeling purposes, DPP recommends that labeling for flibanserin include the boxed warning for suicidality and other relevant antidepressant class warnings and precautions, in the case DRUP decides to approve flibanserin for the treatment of HSDD. "*

5.2.2 Syncope

The Applicant searched the HSDD safety database for adverse events related to syncope. It is not clear what prompted the concern for syncope, though presumably it is due to the drug's central mechanism of action. It should be noted that in phase 3 placebo-controlled HSDD trials, flibanserin had no significant effect on blood pressure or pulse compared to placebo. However,

vital signs were measured after the subject had been seated for five minutes. Orthostatic measurements were not performed.

5.2.2.1 Phase 2/3 Placebo-controlled HSDD Trials

In placebo-controlled phase 2/3 HSDD trials, the incidence of the user-defined adverse event category of syncope was greater among subjects receiving flibanserin 100 mg qhs than among those on placebo or on lower doses of flibanserin (Table 23). The user-defined "syncope" AE category includes preferred terms of *hypotension, syncope, blood pressure decreased, circulatory collapse, dizziness postural, loss of consciousness* and *syncope vasovagal.*

Division Comment:
User-defined refers to preferred terms identified by the Applicant as belonging to a particular category.

Table 23 Frequency of Subjects with Syncope-Related Adverse Events – HSDD and MDD Database

— User-defined AE category* or Preferred Term (PT)++	Placebo	FLI 25 bid	FLI 50 qhs	FLI 50 bid	FLI 100 qhs	FLI 150 tdd	FLI 100 bid
Phase 2/3 placebo-controlled HSDD trials							
Total N	1508	733	2072	862	978	NA	NA
Syncope n (%)	4 (0.3)	0	6 (0.3)	3 (0.3)	7 (0.7)	NA	NA
Double-blind portion of Study 511.74 (randomized withdrawal)							
Total N	170	NA	35	13	115	NA	NA
Syncope n (%)	2 (1.1)	NA	0	0	2 (1.7)	NA	NA
Phase 3 Open-label HSDD trials (studies 511.118 and 511.84)							
Total N	NA	57	2197	305	1791	NA	NA
Syncope n (%)	NA	(0)	6 (0.3)	1 (0.3)	10 (0.6)	NA	NA
Open-label portion of Study 511.74 (randomized withdrawal)							
Total N	NA	NA	738				
Syncope n (%)			3 (0.4)				
Phase 2 placebo-controlled MDD trials (female subjects)							
Total N	417	240**	33	**313**	65	4	113
Orthostatic hypotension n (%)	0	0	0	1 (0.3)	2 (3.1)	0	0
Hypotension n (%)	1 (0.2)	0	0	4 (1.3)	0	0	1 (0.9)
Phase II, placebo-controlled MDD trials 511.11 and 511.12 (male and female subjects)							
Total N	260	247**	NA	121	NA	NA	120
Syncope n (%)	2 (0.8)	0	NA	0	NA	NA	2 (1.6)
Pre-syncope n (%)	6 (2.3)	5 (2.0)	NA	8 (6.6)	NA	NA	22 (18.3)

* User-defined refers to preferred terms identified by the Applicant as belonging to a particular category
++MDD database provides information by PT rather than user-defined AE category
**includes all subjects on < 50 mg total daily dose (tdd)
Source: Table 2.6: 6, p 109, Summary of Clinical Safety and Table 2.1.3.2, pp 292-6, Integrated Summary of Safety

Of the episodes categorized as syncope, one was a serious adverse event of circulatory collapse in a subject assigned to flibanserin 100 mg qhs. Narrative for this subject follows.

Subject 43002-37779 (trial 511.77) was a 34 year-old female patient with a past medical history of hypotension and orthostatic dysregulation who suffered circulatory collapse on Day 11 of treatment with flibanserin 100 mg qhs. She fell, suffered a concussion and was hospitalized. Concurrent AE's were nausea, headache, and pain. The patient was treated with intravenous fluids and discharged home after 24 hours. She recovered fully from the SAE. The SAE was not considered related to flibanserin treatment by the investigator.

Division Comment:
This subject's history of orthostatic dysregulation may have increased her risk of syncope in the setting of flibanserin therapy.

5.2.2.2 Double-blind period of Study 511.74 (randomized withdrawal study in HSDD population)

In the double-blind period of the randomized withdrawal study (511.74), the incidence of syncope was also greatest among subjects receiving flibanserin 100 mg qhs (Table 23).

5.2.2.3 Phase 3 open-label HSDD trials (Studies 511.118 and 511.84)

In the two phase 3 open-label safety extension trials, 511.118 and 511.84, syncope (user-defined category) occurred in a dose-proportional manner (Table 23).

5.2.2.4 Open-label phase of HSDD randomized withdrawal study (511.74)

In the open-label portion of the randomized withdrawal study (511.74), syncope (SMQ) occurred in (0.4%) of subjects (this includes all flibanserin doses – 50 mg qhs, 50 mg bid, 100 mg qhs). See Table 23.

5.2.2.5 MDD Database

Finally, in phase 2, placebo-controlled MDD trials, adverse events of orthostatic hypotension and hypotension were more common among flibanserin-treated subjects than among those receiving placebo. In this case, dose-proportionality was not observed. Data are shown in Table 23.

Division Comment:
The Applicant presented only the adverse events occurring in >1% of subjects in the integrated phase 2 MDD trial dataset. Therefore, a search for all preferred terms within the syncope SMQ was not performed.

This reviewer searched the adverse event data from two of the larger phase 2, double-blind, placebo-controlled MDD trials (Studies 511.11 and 511.12, both involving eight weeks of treatment) for adverse events that could be considered syncope or pre-syncope. Investigator terms *decreased blood pressure*, *hypotension, fainted, lightheadedness*, *unsteady feeling*, *feeling faint* and *lightheaded* were coded to pre-syncope. Investigator terms of *hypotension, decreased blood pressure, symptomatic orthostatic hypotension and fainted* were mapped to syncope.

Division Comment:
These two MDD trials utilized the WHO medical dictionary to code adverse events. MedDRA was used in the HSDD trials.

As shown in Table 23, a clearly dose-proportional increase in syncope and pre-syncope was observed in these two MDD trials.

Division Summary Comment:
Data from both HSDD and MDD clinical trial populations suggest that flibanserin causes an increased risk of syncope over placebo and that the risk is dose-proportional.

5.2.3 Accidental Injury

There was some indication in phase 1 studies that flibanserin had mild, dose-dependent sedative properties in healthy volunteers from one to 2.5 hours post-dose, as evidenced by declines in alertness and attention. Similarly, cognitive tests in phase 2 studies revealed mild, transient sedative-type effects that were maximal at two hours after the 100-mg dose, but mostly reversed six hours post-dose. For this reason, the Applicant examined safety data for adverse events (specifically, accidental injury) that could be related to an impairment in coordination or mental ability.

5.2.3.1 Phase 2/3 placebo-controlled HSDD trials

In phase 2/3 placebo-controlled HSDD trials, accidental injury (user-defined category) was more common among flibanserin-treated subjects (all doses) than those receiving placebo, as shown in Table 24. The incidence was not dose-proportional.

Table 24 Frequency of Adverse Events Related to Accidental Injury – HSDD and MDD Database

User-defined AE category* or (SOC)/Preferred Term**	Placebo	FLI 25 bid	FLI 50 qhs	FLI 50 bid	FLI 100 qhs	FLI 150 total daily dose (tdd)	FLI 100 bid
Phase 2/3 placebo-controlled HSDD trials							
Total N	1508	733	2072	862	978	NA	NA
Accidental injury n (%)	21 (1.4)	19 (2.6)	30 (1.4)	18 (2.1)	19 (1.9)	NA	NA
Double-blind portion of Study 511.74 (randomized withdrawal)							
Total N	170	NA	35	13	115	NA	NA
Accidental Injury n (%)	4 (2.3)	NA	2 (5.7)	0	5 (4.3)	NA	NA
HSDD Open-Label Database							
Total N	NA	57	2197	305	1791	NA	NA
Accidental Injury n (%)	NA	1 (1.8)	26 (1.2)	6 (2.0)	48 (2.7)	NA	NA
MDD Database							
Total N	417	240+	33	313	65	4	113
Injury, poisoning and procedural complication	**11 (2.6)**	**4 (1.7)**	**1 (3.0)**	**6 (1.9)**	**1 (1.5)**	**0**	**4 (3.5)**
Accident at home	7 (1.7)	2 (0.8)	1 (3.0)	5 (1.6)	0	0	3 (2.7)
Road traffic accident	2 (0.5)	0	0	0	1 (1.5)	0	1 (0.9)

* User-defined refers to preferred terms identified by the Applicant as belonging to a particular category.
**MDD database provides information by SOC/PT rather than user-defined AE category
+includes all subjects on < 50 mg total daily dose (tdd)
Source: Table 5.8.2 and Table 2.1.3.2, Integrated Summary of Safety and Table 2.1.1, Applicant submission dated April 30, 2010

Division Comment:
The user-defined AE category for accidental injury included the following preferred terms: *injury* [skeletal, soft tissue, joint, mouth, ligament, muscle, limb, neck, sciatic nerve, lumbar nerve root, bursa, tendon, face, cartilage, eye, chest, genital], *fracture* [thoracic vertebral, tibia, wrist, ankle, foot, hand, ligament, upper limb, femur, facial bones, patella, rib, coccyx, avulsion], *wound, tendon rupture, joint sprain, muscle strain, road traffic accident, skin laceration, concussion, excoriation, contusion, fall, periorbital hematoma, accident at work, brain contusion, eye penetration, scratch, joint dislocation*.

To determine whether events of accidental injury were related to the sedative effects of flibanserin, the Applicant performed an analysis of subjects experiencing accidental injury concomitant to an adverse event of somnolence, sedation, fatigue or dizziness. No relationship was found.

In the phase 2/3 placebo-controlled HSDD trials, three incidents of accidental injury were reported as serious adverse events. All were road traffic accidents. Narratives follow (preferred terms for serious adverse events are in bold).

> ***Case 1: Subject 28344 (trial 511.75)*** – This patient was a 29 year old female with a history of seasonal allergies (concomitant medication loratadine) who had been taking flibanserin 100 mg qhs for ten days when she was involved in a rollover road traffic accident. The patient had been off-road driving an all-terrain vehicle and was not wearing a helmet at the time of the accident. She suffered a **concussion, nerve root injury,** and **skin laceration** due to the accident. The

subject had reported no AEs related to sedative effects (somnolence, fatigue, dizziness) around the time of the accident.

***Case 2: Subject 38300* (*trial 511.77*) –** This 40-year old female with a history of hypothyroidism (on thyroid replacement therapy), assigned to flibanserin 50 mg qhs, suffered a SAE of **thoracic vertebral fracture** as a result of a **road traffic accident.** The patient reported that she was hit from behind and was not responsible for the accident. The accident occurred after being on flibanserin for 142 days. She did not report any AEs related to sedative effects during the course of the study.

Case 3: Subject 27535 (trial 511.75) was a 31 year-old female who was involved in a **motor vehicle accident** 8 days after starting flibanserin 25 mg b.i.d. As a result of the accident, she suffered an **avulsion fracture** of the right lesser trochanter. She was driving, but was reportedly not considered at fault. The subject had no AEs related to sedative effects at the time of the accident. Her only concomitant medication was ibuprofen prn for headaches and menstrual cramps. The investigator considered the SAE of road traffic accident to be unrelated to flibanserin treatment.

5.2.3.2 Double-blind period of Study 511.74 (randomized withdrawal study in HSDD population)

This reviewer searched the adverse event database of the double-blind period of the randomized withdrawal study for adverse event terms related to accidental injury (same terms as used by Applicant in their search of the phase 2/3 HSDD database). A greater percentage of subjects on flibanserin experienced accidental injury than those on placebo (Table 24).

Division Comment:
No subjects in the flibanserin 50 mg bid group experienced accidental injury; however, this may be due to the very small sample size of that group.

5.2.3.3 HSDD Open-Label Database

In the ongoing, open-label, uncontrolled HSDD extension trials (Studies 511.84 and 511.118), the incidence of accidental injury (user-defined AE category) was greatest in the highest flibanserin dose group (see Table 24).

One subject suffered a serious adverse event as a result of accidental injury, which is discussed in the narrative below.

***Subject 37784 (open-label extension trial 511.118*) –** This patient**,** 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 and collided with 2 other motorbikes. The reason is unknown. The subject did not report any sedative effects of flibanserin and had no concomitant medications or significant past medical history.

5.2.3.4 Open-label Phase of HSDD Randomized Withdrawal Study (511.74)

A total of 2.7% (20/738) of flibanserin-treated subjects (all doses) experienced an adverse event of accidental injury (user-defined AE category); see Table 24.

One event of accidental injury was reported as serious:

Subject 11800 (open-label period of study 511.74) was a 46 year-old female with no significant medical history and on no concomitant medications who experienced **motorcycle accident** 2 months after starting flibanserin 50 mg qhs. She suffered a **fractured tibia** as a result of the accident. Treatment included open reduction/internal fixation of the fracture. She recovered two weeks later. The patient reported no other adverse events during the trial.

5.2.3.5 MDD Database

In phase 2 placebo-controlled MDD trials (female subjects only), injuries were most common in the highest flibanserin dose group (Table 24).

Division Comment:
The Applicant presented only the adverse events occurring in >1% of subjects in the integrated phase 2 MDD trial dataset. Therefore, a search for all preferred terms within the accidental injury category was not performed, which may have minimized the frequency of such adverse events.

Division Summary Comment:
In the HSDD population, flibanserin, at all doses, was consistently associated with a higher rate of accidental injury than placebo. The risk is not clearly dose-proportional. However, the risk of accidental injury may increase further at doses of flibanserin >100 mg daily (or in situations in which systemic exposure is greater than that obtained with 100 mg daily), based on data from the MDD trials (Table 24).

5.2.4 Drug Interactions

5.2.4.1 CYP3A4 inhibitors

Because flibanserin is metabolized primarily by CYP3A4, the Applicant performed a phase 1 study of the effect of a potent CYP3A4 inhibitor (ketoconazole) on the pharmacokinetics of flibanserin and its major metabolites (Study 511.111). In this open-label, randomized, two-way crossover study, 24 healthy female subjects received a single dose of flibanserin 50 mg alone or following pre-treatment with ketoconazole 400 mg daily for three days. There was a 14 day wash-out period between treatments.

5.2.4.1.1 Pharmacokinetic Results

Exposure to flibanserin and its major metabolites increased significantly following ketoconazole administration (AUC increased 4.5 times over that observed for flibanserin administered alone, and Cmax increased 1.9 times). The formation of its minor metabolite, TFMPP, decreased to near negligible levels. This indicates that the metabolism of flibanserin is inhibited markedly when given in the presence of a strong CYP3A4 inhibitor.

Division Comment:
According FDA's draft *Guidance to Industry on Drug Interactions Studies*, the Agency recommends that an Applicant evaluate the effect of other CYP3A4 inhibitors if there is a significant interaction in the presence of a strong CYP3A4 inhibitor, in order to determine if a dose adjustment is needed. However, the Applicant did not evaluate the effect of mild or moderate CYP3A4 inhibitors on flibanserin.

5.2.4.1.2 Pharmacodynamics

Flibanserin combined with ketoconazole was poorly tolerated. The proportion of adverse events was significantly greater when the drugs were combined than when either was administered alone (Table 25). Dizziness, nausea and vomiting, and syncope were notably more common with concomitant administration of ketoconazole and flibanserin.

Table 25 Frequency of Subjects with Adverse Events by Treatment - Study 511.111

Preferred Term	Ket+FLI	FLI alone	Ket alone
Total N	24	21	24
Any AE	**23 (95.8)**	17 (81)	13 (54.2)
Dizziness	**15 (62.5)**	5 (23.8)	0
Fatigue	11 (45.8)	12 (57.1)	7 (29.2)
Nausea	**8 (33.3)**	2 (0.5)	0
Somnolence	7 (29.2)	6 (28.6)	0
Vomiting	**4 (16.7)**	1 (4.8)	0
Headache	3 (12.5)	4 (19.0)	7 (29.2)
Syncope	**1 (4.2)**	0	0

Bold = AE more common with ketoconazole + flibanserin
Source: Study Report for Study 511.111, Table 15.3.2: 3, p 120

Vital signs (blood pressure and pulse), recorded after five minutes in the supine position, were monitored at several time points on dosing days. No subject had a systolic BP <90 or pulse >100 at any time point.

Division Comments:

- **This drug interaction study used a dose lower than the proposed therapeutic dose of flibanserin (i.e., 100 mg qhs). It is likely that systemic flibanserin exposure following co-administration of ketoconazole with flibanserin 100 mg qhs would have been greater and tolerability worse.**
- **Orthostatic vital signs were not measured during the trial. Routine vital signs for the subject who experienced syncope were normal during treatment. Vital signs during the episode of syncope were not provided.**
- **The Applicant recommends that flibanserin not be used by women taking strong CYP3A4 inhibitors. The effect of mild-moderate CYP3A4 inhibitors on flibanserin metabolism is not known.**
- **The Division is concerned that labeling alone may not be enough to prevent subjects from inadvertently taking flibanserin with a CYP3A4 inhibitor, and the consequences of concomitant administration could be serious.**

5.2.4.2 Common prescription drugs

5.2.4.2.1 Selective Serotonin Reuptake Inhibitors and Selective Norepinephrine Reuptake Inhibitors (SRI/SNRI)

Although concomitant use of SSRI/SNRIs was prohibited per protocol in the phase 3 placebo-controlled trials, 2.8% (28/1001) of subjects in the flibanserin 100 mg qhs group and 1.7% (23/1360) of placebo subjects used an SSRI/SNRI during the trials. More subjects taking a

concomitant SSRI/SNRI experienced an adverse event than those on flibanserin or placebo alone. The combination of flibanserin with an SSRI/SNRI significantly increased the frequency of *anxiety, dizziness, insomnia, increased blood pressure* and *paresthesias* compared to an SSRI/SNRI with placebo or to flibanserin alone (Table 26).

Table 26 Frequency of Subjects with Adverse Events by Treatment (Flibanserin with or without an SSRI/SNRI) – Phase 3 Placebo-Controlled HSDD Trials

	FLI N = 973	FLI + SSRI/SNRI N = 28	PLACEBO N =1,337	PLACEBO + SSRI/SNRI N = 23
	n (%)	n (%)	n (%)	n (%)
Any Adverse Event	670 (68.9)	26 (92.9)	765 (57.2)	20 (87)
Anxiety	14 (1.4)	**6 (21.4)**	9 (0.7)	0
Depression	5 (0.5)	6 (21.4)	8 (0.6)	4 (17.4)
Dizziness	115 (11.8)	**5 (17.9)**	33 (2.5)	1 (4.3)
Insomnia	46 (4.7)	**5 (17.9)**	29 (2.2)	3 (13.0)
Nausea	115 (11.8)	4 (14.3)	57 (4.3)	1 (4.3)
Somnolence	91 (9.4)	4 (14.3)	37 (2.8)	3 (13.0)
Blood Pressure increased	4 (0.4)	**2 (7.1)**	4 (0.3)	0
Paresthesia	6 (0.6)	**1 (3.6)**	1 (0.1)	0

Bold = AE more common with SSRI/SNRI + flibanserin
Source: Table 5.2.4.1, pp 2706-64, Integrated Summary of Safety

5.2.4.2.2 Hormonal Contraceptives

Women receiving flibanserin and using hormonal contraceptives tended to have slightly higher overall rates of AEs compared to those taking placebo with a hormonal contraceptive. Specific adverse events that occurred more frequently in subjects using both flibanserin and a hormonal contraceptive compared to either drug alone represent a range of system organ classes, as shown in Table 27.

Table 27 Frequency of Subjects with Adverse Events by Treatment (Flibanserin with or without a Hormonal Contraceptive) – Phase 3 Placebo-Controlled HSDD Trials

	FLI 100 qhs N = 556	FLI 100 qhs + HC N = 445	PLACEBO N = 775	PLACEBO + HC N = 585
	n (%)	n (%)	n (%)	n (%)
Any Adverse Event	371 (66.7)	325 (73.0)	452 (58.3)	333 (56.9)
Dizziness	55 (9.9)	**65 (14.6)**	19 (2.5)	15 (2.6)
Fatigue	49 (8.8)	**61 (13.7)**	44 (5.7)	33 (5.6)
Nausea	59 (10.6)	60 (13.5)	31 (4.0)	27 (4.6)
Headache	60 (10.8)	60 (13.5)	75 (9.7)	52 (8.9)
Somnolence	46 (8.3)	49 (11.0)	22 (2.8)	18 (3.1)
Back pain	8 (1.4)	14 (3.1)	16 (2.1)	13 (2.2)
Migraine	4 (0.7)	12 (2.7)	7 (0.9)	10 (1.7)
Abdominal pain	7 (1.3)	11 (2.5)	7 (0.9)	4 (0.7)
Nocturia	2 (0.4)	10 (2.2)	2 (0.3)	1 (0.2)
Palpitations	2 (0.4)	8 (1.8)	4 (0.5)	2 (0.3)
Vertigo	3 (0.5)	7 (1.6)	4 (0.5)	0

Bold = AE more common with hormonal contraceptive + flibanserin
Source: Table 5.2.1.1, pp 2327- 85, Integrated Summary of Safety

Division Comment:
The mechanism by which a hormonal contraceptive would increase these adverse events is unclear. However, these data suggest that tolerability of flibanserin may be negatively impacted by concomitant HC use.

5.2.4.2.3 Triptans

Triptans were prohibited per protocol in the phase 3 placebo-controlled trials. Nonetheless, 3.6% of subjects in the flibanserin 100 mg qhs group and 3.2% of placebo treated subjects used triptans during the studies.

Division Comment:
Triptans are selective agonists for the vascular 5-HT_1 receptor and cause vasoconstriction. They are used in the treatment of migraine and cluster headaches. Common treatment-emergent adverse reactions in clinical trials of sumatriptan for migraine headaches among sumatriptan-treated subjects were atypical sensations (e.g., tingling), dizziness/vertigo and flushing.

Concomitant use of flibanserin with a triptan was associated with an increased frequency of several adverse events compared to taking either drug alone (Table 28).

Table 28 Frequency of Adverse Events in Flibanserin 100 Mg qhs vs. Placebo, by Triptan Use – Phase 3 Placebo-Controlled HSDD Trials

	FLI 100 qhs N = 965	FLI 100 qhs + triptan N = 36	PLACEBO N = 1,317	PLACEBO + triptan N = 43
	n (%)	n (%)	n (%)	n (%)
Any Adverse Event	663 (68.7)	**33 (91.7)**	758 (57.6)	27 (62.8)
Somnolence	88 (9.1)	**7 (19.4)**	38 (2.9)	2 (4.7)
URI	37 (3.8)	**4 (11.1)**	45 (3.4)	1 (2.3)
Depression	8 (0.8)	**3 (8.3)**	10 (0.8)	2 (4.7)
Anxiety	18 (1.9)	**2 (5.6)**	9 (0.7)	0
Irritability	20 (2.1)	**2 (5.6)**	18 (1.4)	1 (2.3)
Stress	8 (0.8)	**2 (5.6)**	2 (0.2)	0
Menorrhagia	34 (3.5)	2 (5.6)	42 (3.2)	0

Bold = AE more common with triptan + flibanserin
Source: Table 5.2.5.1, pp 2833- 91, Integrated Summary of Safety

Division Comment:
Most concerning from a safety perspective is the increased incidence of somnolence and depression among subjects using flibanserin with a triptan.

5.2.4.2.4 Alcohol

In the phase 3 flibanserin trials, alcohol status was only captured at baseline and subjects were classified as "drinker" or "non-drinker." Alcohol use was not monitored during the treatment phase of the studies.

The difference in the percentage of drinking and non-drinking flibanserin subjects who experienced an AE was larger than the difference between drinking and non-drinking placebo subjects. CNS-related adverse events were most frequent among subjects who were drinkers

assigned to flibanserin 100 mg qhs (see Table 29). This suggests there may be a synergy between flibanserin and alcohol use relative to the occurrence of these AEs.

Table 29 Frequency of Adverse Events in Flibanserin 100 Mg qhs vs. Placebo, by Alcohol Use – Phase 3 Placebo-Controlled HSDD Trials

	FLI 100 qhs		Placebo	
	Drinker	Non-drinker	Drinker	Non-drinker
Total N (%)	759 (75.8)	242	784 (77.5)	227
Any Adverse Event	551 (72.6)	145 (59.9)	491 (62.6)	125 (55.1)
Fatigue	**90 (11.9)**	20 (8.3)	54 (6.9)	14 (6.2)
Dizziness	**100 (13.2)**	20 (8.3)	20 (2.6)	7 (3.1)
Somnolence	**77 (10.1)**	18 (7.4)	18 (2.3)	8 (3.5)
Anxiety	**19 (2.5)**	1 (0.4)	7 (0.9)	0
Insomnia	**44 (5.8)**	7 (2.9)	24 (3.1)	5 (2.2)

Source: Table 5.2.7.1, pp 3025 – 88, Integrated Summary of Safety

Division Comment:
The Applicant acknowledges that alcohol use among women receiving flibanserin may increase the rate of AEs and proposes to label that users should "use alcohol with caution" while taking flibanserin. The Division is concerned that such labeling alone may be insufficient to protect flibanserin users against the risks of concomitant use of flibanserin and alcohol.

5.2.5 Use in Patients with Hepatic Impairment

5.2.5.1 Pharmacokinetics

Of the intrinsic factors evaluated by the Applicant, hepatic impairment had the most significant impact on exposure to flibanserin.

The effect of mild hepatic impairment (Child Pugh score of 6-8 points) and moderate hepatic impairment (Child Pugh score >8 points) on flibanserin pharmacokinetics was evaluated in a single-dose, open-label phase 1 clinical trial (Study 511.67). Twenty-eight subjects (ten with mild liver impairment, four with moderate impairment and 14 healthy gender, weight and age-matched controls) received a single oral dose of flibanserin 50 mg.

Flibanserin exposure increased 4.5-fold in subjects with mild hepatic impairment (AUC0-inf of flibanserin 3,310 ng·hr/mL) and 2.6 fold in those with moderate impairment (AUC0-inf 2,420 ng·hr/mL) compared to healthy controls (AUC0-inf range of 730-925 ng·hr/mL). The terminal half-life was longer in hepatically impaired subjects (26 hrs vs. 10 hrs in matching healthy controls). With data from only four subjects in the moderate group, meaningful interpretation of the results in women with moderate hepatic impairment is not possible.

Division Comment:
The Applicant recommends that flibanserin not be used in subjects with hepatic impairment.

5.2.5.2 Pharmacodynamics

In Study 511.67, five subjects reported a total of seven AEs after administration of a single dose of flibanserin 50 mg (Table 30). None were rated as severe intensity. There were no SAEs or deaths.

Table 30 AEs with a Single 50 mg Dose of Flibanserin in Study 511.67 (Hepatic Impairment)

Preferred Term	Healthy (N=14)	Mild impairment (N=10)	Moderate impairment (N=4)
Total with adverse events	3	2	0
Headache	1	0	0
Dizziness	1	1	0
Somnolence	1	1	0
Fatigue	1	0	
Rhinitis	1	0	0

Source: Study report for Study 511.67, Table 15.3.2: 3, p 149

There were no clinically relevant laboratory findings.

Division Comment:
There was no apparent difference in tolerability to flibanserin between normal subjects and subjects with hepatic impairment. However, the sample size in this single dose study was small.

Subjects with hepatic impairment (hepatic enzyme values $\geq$2 times the upper limit of normal [ULN]) were prohibited from enrollment in the phase 3 trials.

5.2.6 Exposure-Response Relationship for Adverse Events

In phase 1 studies in which supratherapeutic doses of flibanserin were investigated, dose-proportionality of common adverse events was also evident. Adverse event data from a multiple dose phase 1 pharmacokinetic study in healthy male and female volunteers (Study 511.2) is shown in Table 31 as an example.

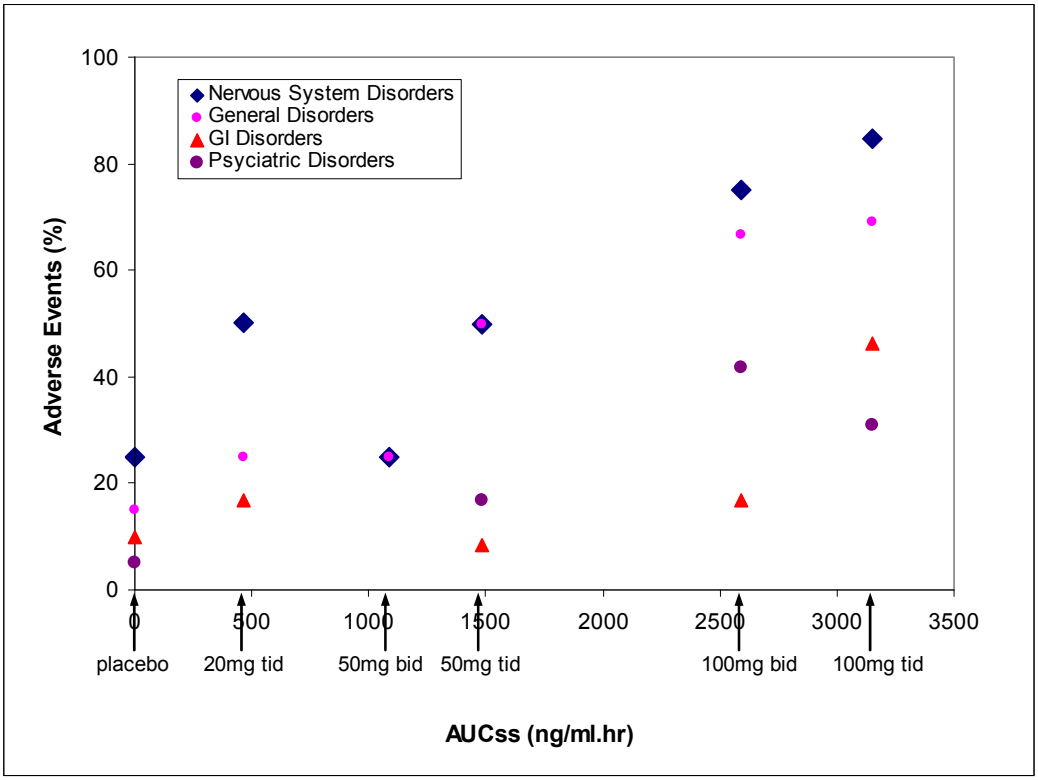
Table 31 Frequency of Treatment-Emergent Adverse Events - Study 511.2

Preferred term	PLACEBO	FLI 20 mg tid	FLI 50 mg bid	FLI 50mg tid	FLI 100 mg bid	FLI 100 mg tid
N(%)	20 (100)	12 (100)	12 (100)	12 (100)	12 (100)	13 (100)
Headache	4 (20)	7 (58.3)	2 (16.7)	5 (41.7)	5 (41.7)	7 (53.9)
Dizziness	1 (5)	3 (25)	1 (8.3)	3 (25)	6 (50)	7 (53.9)
Fatigue	2 (10)	3 (25)	3 (25)	6 (50)	8 (66.7)	8 (61.5)
Nausea	0	0	0	1 (8.3)	1 (8.3)	3 (23.1)

Source: Study Report for Study 511.2, Table 10.2.1:1, pp 94-5

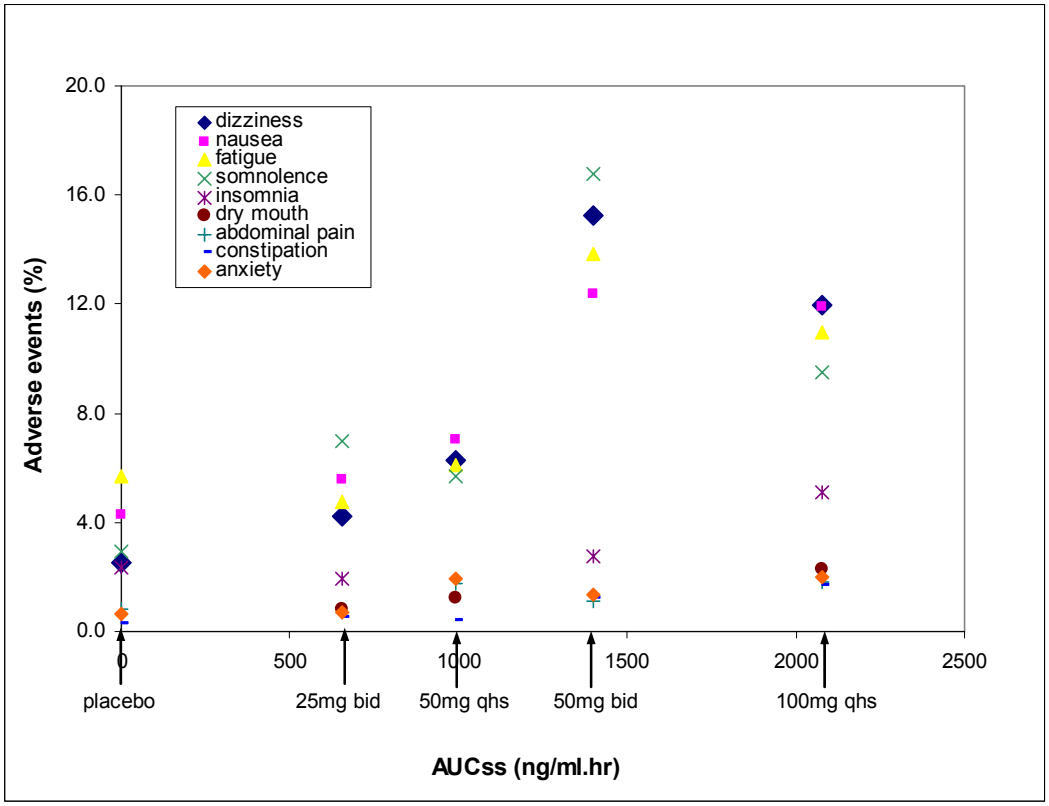
The frequency of AEs also exhibited a clear dose-response in Study 511.2 (Figure 1).

Figure 1 Exposure-Response for Adverse Events in Phase 1 Dose-Finding Study 511.2



Common adverse events exhibited a clear dose-response relationship in the four phase 3 placebo-controlled HSDD trials (Studies 511.70, 511.71, 511.75 and 511.77). Figure 2 shows the frequency of AEs by AUC at steady state.

Figure 2 Exposure-Response for AEs in Double-blind, Placebo-Controlled, Phase 3 HSDD Clinical Trials



Division Comments:

- **The AUC data for the various doses of flibanserin displayed in Figure 2 were obtained from a PK study performed in women with HSDD (Study 511.105), while the rates of AEs associated with various doses were obtained from the phase 3 placebo-controlled trials.**
- **Despite reducing the incidences of AEs by dosing qhs vs. bid, there remains a clear and possibly linear relationship between the frequency of adverse events and flibanserin exposure.**

Although flibanserin 100 mg qhs is the recommended dose, supratherapeutic exposure to flibanserin may be observed in the setting of concomitant administration with a CYP3A4 inhibitor or in patients with hepatic impairment. In these situations, systemic flibanserin exposure is several-fold greater than that obtained with a 100 mg per day dose (see Table 32). Therefore, the predicted frequency of adverse events would also be expected to increase.

The mean steady state systemic exposure of flibanserin (AUCτ, ss) in HSDD women following once daily dosing of 50 mg and 100 mg dose is 991 and 2,080 ng·hr/mL, respectively. Under conditions where the metabolism of flibanserin is altered, such as through the concomitant use of a strong CYP3A4 inhibitor or hepatic impairment, the systemic exposures following a single 50 mg dose flibanserin were increased to 5,260 and 3,310 ng·hr/mL, respectively. Based on the observed relationship between dose and adverse events, it is likely that patients using a CYP3A4

inhibitor or who have hepatic impairment will experience an increase in adverse events compared with healthy patients.

Table 32 Pharmacokinetics of flibanserin following different dosing regimens – Studies 511.105, 511.67 and 511.111

	25 mg flibanserin bid*	50 mg flibanserin qd*	50 mg flibanserin bid*	100 mg flibanserin qd*	50 mg flibanserin + mild hepatic impairment**	50 mg flibanserin + 400 mg ketoconazole***
AUCT, ss (ng.hr/ml)[a]	653 (60.1)	991 (47.7)	1400 (46.9)	2080 (46.6)	3310 (43.0)	5260 (56.5)
Cmax, ss (ng/ml)[a]	168 (50.9)	234 (41.2)	346 (34.4)	469 (42.7)	191 (53.9)	472 (24.6)
Tmax (hr)[b]	1.00 (0.50-3.00)	1.00 (0.42-4.00)	0.75 (0.50-3.00)	1.00 (0.50-3.00)	0.50 (0.25-4.00)	1.50 (0.75-4.00)

[a] geometric mean and gCV (%)
[b] median and range
* In the PK study 511.105, HSDD women in the once-a-day dosing regimen were given flibanserin in the morning as opposed to bedtime as done in the phase 3 studies 511.70, 511.71, 511.75, and 511.77.
** In study 511.67, the sponsor evaluated the pharmacokinetics of flibanserin following a single dose of 50 mg flibanserin in subjects with hepatic impairment. Systemic exposure of flibanserin is expressed as AUC0-inf.
**** In study 511.111, the sponsor evaluated the pharmacokinetics of flibanserin following a single dose of 50 mg flibanserin in subjects co-administered with multiple daily doses (400 mg) of the CYP3A4 inhibitor ketoconazole. Systemic exposure of flibanserin is expressed as AUC0-inf.

5.2.7 Withdrawal Effects

Because flibanserin is centrally acting, the Applicant examined the safety database for evidence of withdrawal phenomena. Post-treatment adverse events were assessed for:

- The four weeks following treatment discontinuation in Phase 3 studies 511.70, 511.71, 511.75 and 511.77
- The first four weeks of double-blind treatment in the randomized withdrawal study 511.74 (the first 24 weeks of this trial involved open-label flibanserin treatment; subsequently, flibanserin responders participated in a 24-week double-blind placebo-controlled phase)

Adverse events that occurred more frequently following flibanserin discontinuation are shown in Table 33.

Table 33 Frequency of Subjects with Adverse Events Following Treatment Discontinuation — Phase 3 Placebo-Controlled HSDD Trials

AE category (SMQ) or Preferred Term (PT)	Post-Placebo	Post-25 bid	Post-50 qhs	Post-50 bid	Post-100 qhs	Flibanserin to flibanserin (all doses)[1]
Phase 3 placebo-controlled HSDD trials						
Total N (%)	1360 (100)	733 (100)	969 (100)	728 (100)	1001 (100)	NA
Vomiting	3 (0.2)	0	2 (0.2)	1 (0.1)	5 (0.5)	NA
Depression (SMQ)*	6 (0.4)	4 (0.5)	7 (0.7)	4 (0.5)	7 (0.7)	NA
Insomnia	4 (0.3)	0	3 (0.3)	1 (0.1)	4 (0.4)	NA
Anxiety	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)	NA
Double-blind portion of study 511.74 (randomized withdrawal)						
Total N (%)	NA	NA	38 (100)	16 (100)	116 (100)	163 (100)
Anxiety	NA	NA	1 (2.6)	1 (6.3)	0	0
Dizziness	NA	NA	0	0	3 (2.6)	1 (0.6)
Nausea	NA	NA	1 (2.6)	2 (12.5)	2 (1.7)	2 (1.5)
Irritability	NA	NA	1 (2.6)	1 (6.3)	2 (1.7)	1 (0.6)
Depression (SMQ)	NA	NA	1 (2.6)	1 (6.3)	2 (1.7)	1 (0.6)

* includes preferred terms of *disturbance in attention, depression, middle insomnia, depressed mood, mood altered, mood swings, poor quality sleep, affect lability, dysphoria, tearfulness, apathy, crying, early morning awakening, major depression, memory impairment, blunted affect, decreased interest, depressive symptom, dyssomnia, emotional distress, hypersomnia, initial insomnia, psychomotor hyperactivity, and listless.*

1 - in study 511.74, subjects who entered the double-blind phase were switched from flibanserin to placebo or to flibanserin (in a randomized, double-blind fashion). This column represents the frequency of adverse events in subjects who remained on flibanserin.

Source: Tables 5.7.1 and 5.7.2, pp 3095-3110, Integrated Summary of Safety

Division summary:

The data suggest that adverse events of depression, anxiety, irritability and dizziness occur with slightly greater frequency in the 4 weeks following discontinuation of flibanserin 100 mg qhs. If the drug is approved, the Division recommends that this information be included in labeling.

5.3 Safety Conclusions

The important safety findings regarding flibanserin use in premenopausal females with HSDD are:

- Dizziness and nausea were the most frequently reported adverse events and occurred in nearly 12% of subjects treated with flibanserin 100 mg qhs during the phase 3 placebo-controlled HSDD trials.
- Sedating adverse events (i.e., fatigue, somnolence, sedation) were also commonly reported and were proportional to flibanserin dose; the frequency of sedative effects was very high with supratherapeutic exposure to flibanserin (e.g., with doses >100 mg qhs).
- The tolerability of flibanserin was only moderate, with nearly 15% of subjects who received 100 mg qhs discontinuing treatment prematurely due to an adverse event (compared to 6.8% of placebo subjects).

- The only serious adverse event that occurred more commonly among flibanserin treated subjects compared to those on placebo was appendicitis.
- An increased frequency of depression, syncope and accidental injury was observed among flibanserin-treated subjects when compared to placebo in the HSDD clinical trials database; syncope and depression appeared to be dose-proportional.
- Tolerability of flibanserin was adversely affected when it was administered with commonly used prescription drugs such as SSRIs, triptans, and hormonal contraceptives, or when taken with alcohol.
- Concomitant administration of potent CYP3A4 inhibitors with flibanserin (at 50 mg qhs) leads to at least a 4.5-fold increase in systemic exposure to flibanserin. In addition, the frequency of adverse events of dizziness, nausea and vomiting increased significantly with concomitant administration of flibanserin and a CYP3A4 inhibitor.
- The effect of flibanserin on orthostatic blood pressure and pulse is not known.

The Division has the following concerns regarding the safety of flibanserin:

- The population studied in the phase 2 and 3 HSDD trials was generally healthy and taking few, if any, concomitant medications (the list of prohibited medications per protocol was extensive, as discussed in Section 3.2.4 and listed in Section 6.3). The safety of flibanserin in the general population on concomitant prescription drugs or with significant medical or psychiatric histories is unknown.
- It is not clear if labeling alone will be sufficient to alert women to the numerous drug interactions that exist with flibanserin.
- The risk of significant adverse events of accidental injury, syncope and depression associated with flibanserin may increase further in the setting of supratherapeutic exposure to flibanserin (as may occur with concomitant CYP3A4 inhibitors), or when given with drugs with a similar adverse event profile (e.g., SSRIs, other centrally acting drugs).

6. APPENDICES

6.1 Instruments Used in Pivotal Trials

6.1.1 Instruments Used for Co-Primary Efficacy Endpoints

eDiary: (Used for SSEs and desire co-primary endpoints)
The eDiary was interactive. The precise question(s) which appeared (and the wording of those questions) was dependent upon the responses entered by the subject and the time of the last eDiary entry (e.g., if a subject entered a response indicating that she had not had sexual activity since the last entry, questions that ask for descriptions of sexual activity since the last entry would not appear). The first eDiary entry asked about the previous 24-hour period only.

l. Indicate your most intense level of sexual desire...
["in the last 24 hours" for first assessment or if last entry > 24 hours ago] OR
["since your last entry DAY DATE TIME" if last entry < 24 hours ago]

No desire
Low desire
Moderate desire
Strong desire

2. How distressed have you felt about your level of sexual desire...
["over the past 24 hours" for first assessment or if last entry >24 hours ago] OR
["since your last entry DAY DATE TIME" if last entry <24 hours ago]

Not at all
A little bit
Moderately
Quite a bit
Extremely

3. Did you have sex...
[" in the last 24 hours" for first assessment] OR
["since your last entry" if last entry < 72 hours ago] OR
[“in the last 3 days” if last entry > 72 hours ago]

□ NO
□ YES

Sex is defined as sexual intercourse, oral sex, masturbation, or genital stimulation by your partner.

The following questions are asked only if the subject answers “yes” to the previous question.

4. How many times did you have sex...
[" in the last 24 hours" for first assessment] OR
["since your last entry" if last entry < 72 hours ago] OR
[“in the last 3 days” if last entry > 72 hours ago]

<Number spinner to increase by increments of 1 >

The following questions are asked for each sexual event indicated in the previous question.

4a. Select the day of your sexual activity.

5. Was the sex satisfying for you?

□ NO
□ YES

6. Did you have an orgasm?

□ NO
□ YES

----

sex = includes sexual intercourse, oral sex, masturbation and/or stimulation of your genitals by your partner.
satisfying for you = gratifying, fulfilling, satisfactory, and/or successful for you. Your partner's satisfaction is not the subject of this question.

6.1.2 Instruments used for key secondary efficacy endpoints

FSDS-R: FSDS-R Item 13 was considered the appropriate key secondary endpoint for distress by the Division; the Applicant used the FSDS-R total score. The instrument is copyrighted and not included here (refer to Section 7).

6.1.3 Instruments used for secondary efficacy endpoints

6.1.3.1 FSFI Desire Items:

There were two items from the FSFI instrument that asked about sexual desire or interest. The complete instrument is copyrighted and is not included here (refer to Section 7). It can be accessed at:

http://www.fsfiquestionnaire.com/FSFI%20questionnaire2000.pdf

6.1.3.2 Patient Global Impression of Improvement (PGI-I):

1. How is your condition – meaning decreased sexual desire and feeling bothered by it - today compared to when you started study medication?

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

Guidance for Industry

Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. Copies of this draft guidance are available on the Internet at http://www.fda.gov/cder/guidance/index.htm. For questions on the content of the draft document contact Lana L. Pauls, 301-827-4260.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2000
Clin.

Guidance for Industry

Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment

Additional copies are available from:
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Draft – Not for Implementation

Guidance for Industry[1]

Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment

I. INTRODUCTION

This guidance is intended to provide recommendations for sponsors on the design of clinical trials in support of new drug applications (NDAs) for the treatment of female sexual dysfunction (FSD).

II. DEFINITION OF FEMALE SEXUAL DYSFUNCTION

Although the definition of FSD continues to evolve, it currently consists of four recognized components:

- decreased sexual desire;
- decreased sexual arousal;
- dyspareunia; and
- persistent difficulty in achieving or inability to achieve orgasm.

To establish a diagnosis of FSD, these components must be associated with personal distress, as determined by the affected woman.

Appropriate definition of the patient population to be studied is an important component of drug development for the treatment of FSD. If the indication for which drug approval is sought is based on a comprehensive definition of FSD that incorporates all four recognized components and any associated subtypes of the disorder, sufficient numbers of women having each component and associated subtype should be enrolled in clinical trials. A sponsor can choose one or any combination of the four components to study. In order to obtain approval for the desired indication (i.e., one or more components), safety and effectiveness should be demonstrated in each component group chosen.

III. APPROPRIATE STUDY POPULATIONS FOR CLINICAL TRIALS INTENDED TO DEMONSTRATE EFFICACY

[1] This guidance has been prepared by the Division of Reproductive and Urologic Drug Products (DRUDP) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the development of drug products to treat female sexual dysfunction. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statues, regulations, or both.

Clinical trials intended to demonstrate efficacy for the treatment of FSD should enroll women who are sexually active and who have a valid and reliable diagnosis of FSD. Study populations for such trials may focus on or be limited to one of the following subgroups if it is anticipated that response to therapy may differ across these subgroups:

- premenopausal women
- naturally menopausal women
- surgically menopausal women
- women taking hormone-containing products for hormone replacement therapy (e.g., estrogen and/or estrogen-progestin containing products)
- women taking hormone-containing products for contraception

Inclusion and exclusion criteria for clinical trials of drug products to treat FSD should be based on the specific research question being posed for the trial and should be chosen to protect volunteer safety. To increase the likelihood of demonstrating a treatment effect in clinical trials of FSD, it may be appropriate in some trials to exclude subjects with the following:

- relationship difficulties with a sexual partner
- use of concomitant medications that could affect sexual function (e.g., certain antidepressant medications)
- the presence of medical conditions that could affect sexual function (e.g., depression, anxiety, the first few weeks of the postpartum period)
- sexual dysfunction on the part of the woman's partner

IV. OTHER STUDY CONSIDERATIONS

Appropriate patient selection should include identification and enrollment of women for whom sexual dysfunction causes personal distress. *Personal distress* should be measured to ensure appropriate patient selection for trial participation but should not serve as the primary endpoint for establishing effectiveness.

Study populations can be stratified by or limited to one or more of the subgroups listed in section III of this guidance.

Objective data based on sexual events or encounters can be collected by having each enrolled subject record the number of events she experiences during a pretreatment baseline period and

throughout each month of trial participation. The pretreatment baseline period should be a minimum of 4 weeks, and preferably 8 weeks, in duration. To minimize recall bias, this data should be recorded daily by the study subjects, using diaries. This data should be collected from the study subjects every 1 or 2 weeks.

Drug development should include appropriate dose-finding studies and determination of the lowest effective dose for the indication sought. Generally, two adequate and well-controlled, phase 3 trials are recommended for approval of drug products for FSD indications. The trials should typically be 6 months in duration, excluding the baseline period.

V. USE OF SCALES, QUESTIONNAIRES AND OTHER INSTRUMENTS DURING DRUG DEVELOPMENT

New scales, questionnaires, and other instruments to diagnose FSD and/or particular components or to measure response to treatment over time should be developed, tested, and validated in women with FSD. The validation process for the scale should demonstrate its reliability, validity, responsiveness, and ability to measure minimal meaningful differences.

Diagnostic scales and questionnaires should be able to distinguish patients with FSD from those without the disorder. If a scale is meant to detect a specific component of FSD, such as decreased sexual desire or decreased sexual arousal, the scale should also attempt to differentiate between women who have the component for which approval is sought and women having a different component of the disorder.

To minimize the risk that an instrument or scale may prove inadequate in post-trial analysis for identifying women with FSD or for detecting response to treatment, instrument validation should precede initiation of phase 3 efficacy studies.

VI. CLINICAL TRIAL ENDPOINTS

Primary endpoints for trials of drug products to treat FSD should be clinically meaningful and specifically related to the component or components of FSD being studied in the trials. These endpoints should be based on the number of successful and satisfactory sexual events or encounters over time. The determination of *successful* and *satisfactory* should be made by the woman participating in the trial, as opposed to her partner. Such *events* or *encounters* include:

- satisfactory sexual intercourse;
- sexual intercourse resulting in orgasm;
- oral sex resulting in orgasm; and
- partner-initiated or self masturbation resulting in orgasm.

In addition to the daily records kept by study participants, partners can also complete diaries, but the information obtained from those diaries should not constitute primary endpoints in phase 3 studies.

If physical genital changes (such as increased vaginal blood flow, increased clitoral blood flow, clitoral engorgement, or vaginal lubrication) are measured, they should be linked to clinically significant changes in the number of successful and satisfying sexual events experienced by the woman during the trial.

Effectiveness should be demonstrated by statistically and clinically significant improvements in these event-endpoints over time in the active treatment arms when compared to the placebo treatment arms. These demonstrations should be based on between-group differences in the change in the number of successful and satisfactory events from baseline to end of treatment.

The primary efficacy endpoints and statistical analysis plans for phase 3 trials should be specified in detail prior to initiating the studies. Selection of efficacy endpoints after completion of any trial should be considered exploratory. Results from these exploratory post-trial analyses should not be considered to establish effectiveness.

Many of the diagnostic and treatment response instruments being developed for FSD are based on health-related quality of life (HRQL) claims. Although these instruments can be useful in providing supportive information, they most likely should not serve as primary endpoints for phase 3 trials. Endpoints based on HRQL claims should be linked to clinically meaningful objective endpoints as described above.

6.3 List of Prohibited Medications[2]

10.3 MEDICATIONS

These lists (Part I and Part II) are not meant to be exhaustive; the lists contain only the common agents in each class.

10.3.1 Part I – List of prohibited medications

Use of any of the following medications 30 days before the Screen Visit and anytime after the Screen Visit will exclude the patient from participation and randomization into the trial.

All antiarrhythmics, including but not limited to:

amiodarone	*encainide*	*procainamide*
bretylium	*flexainide*	*propafenone*
digoxin.	*lidocaine*	*quinidine*
disopyramide	*mexilitine*	*sotalol*
dofetilide	*moricizine*	*tocainamide*

All anticoagulants, including but not limited to:

abciximab	*dipyridamol*	*ticlopidine*
acenocoupramol	*enoxaparin*	*tirofiban.*
clopidogrel	*eptifibatide*	*warfarin*
dalteparin	*heparin*	
danaparoid	*phenprocoumon*	

All beta blockers, including but not limited to:

acebutolol	*celiprolol*	*nebivolol*
alprenolol	*esmolol*	*oxprenolol*
atenolol	*labetalol*	*penbutolol*
betaxolol	*levobunolol*	*pindolol*
bisoprolol	*mepindolol*	*propranolol*
butoxamine	*metipranolol*	*timolol*
carteolol	*metoprolol*	
carvedilol	*nadolol*	

All CNS stimulants, including but not limited to:

amphetamines (dextroamphetamine, atomoxetine, ephedrine)
Ephedra
Ma-Huang
methamphetamine
methylphenidate

All dopamine-receptor agonists and other antiparkinsonian drugs, including but not limited to:

bromocriptine	*pergolide*	*rogitotine*
levodopa	*pramipexole*	*ropinirole*
lisuride	*rasagiline*	

All fertility agents

(continued on the next 4 pages)

[2] Copied directly from the protocol for Study 511.75. The list is virtually identical for study 511.71

All hormonal agonists/antagonists, including but not limited to:

All androgens, including but not limited to:

androstenediol	*dehydroandrosterone*	*dehydroisoandrosterone*
androstenedione	*dehydroepiandrosterone (DHEA)*	*dihydrotestosterone (DHT)*
androsterone		*testosterone*

All antiandrogens, including but not limited to:

bicalutamide	*dutasteride*	*nilutamide*
bicalutamide	*finasteride*	*spironolactone*
cyproterone acetate	*flutamide*	

All antiestrogens, including but not limited to:

aminoglutethimide	*exemestane*	*raloxifene*
anastrozole	*formestane*	*tamotifen*
bazedoxefine	*fulvestrant*	*toremifine*
clomifene	*letrozole*	*vorazole*

All estrogens[1], including but not limited to:

chlorotrianisene	*estrone*	*polyestradiol phosphate*
dienestrol	*ethinylestradiol*	
estradiol	*fosfestrol*	
estriol	*mestranol*	

[1]Oral contraceptive use is acceptable as long as the patient has been on a stable dose for at least 1 month before baseline (Visit 2) and it is not affecting sexual functioning

All progestins[2], including but not limited to:

desogestrel	*gestonorone*	*norethisterone*
drospirenone	*levonorgestrel*	*norethynodrel*
dydrogesterone	*lynestrenol*	*norgestimate*
ethisterone	*medroxyprogesterone*	*norgestrel*
ethynodiol	*megestrol*	*norgestrione*
etonogestrel	*mifeprostone*	*progesterone*
gestodene	*norelgestromin*	*tibolone*

[2]Oral contraceptive use is acceptable as long as the patient has been on a stable dose for at least 1 month before baseline (Visit 2) and it is not affecting sexual functioning

All gonadotropin-releasing hormone (GnRH) analogues, hormones and inhibitors including but not limited to:

abarelix	*ganirelix*	*nafarelin*
buserelin	*gestrinone*	*triptorelin*
cetrorelix	*goserelin*	*urofollitropin*
clomifene	*histrelin*	
danazol	*leuprorelin*	

The following over the counter pro-sexual agents:

Yohimbe
Yohimbine

All muscle relaxants, including but not limited to:

baclofen	*cyclobenzaprine*	*orphenadrine*
carisoprodol	*dantrolene*	*tizanidine*
chlorzoxazone	*metaxalone*	

Psychotherapeutics

All benzodiazepines, including but not limited to:

alprazolam	*flunitrazepam*	*oxazepam*
chlordiazepoxide	*flurazepam*	*temazepam*
clonazepam	*lorazepam*	*triazolam*
diazepam	*nitrazepam*	

All antidepressants, including but not limited to:

bupropion	*mirtazepine*	*toloxatone*
citalopram	*moclobemide*	*tranylcypromine*
duloxetine	*nefazodone*	*selegiline*
escitalopram	*nialamide*	*trazodone*
fluoxetine	*paroxetine*	*venlafaxine*
iproclozide	*phenelzine*	
isocarboxazid	*sertraline*	

All anti-psychotics, including but not limited to:

aripiprazole	*olanzapine*	*thioridazine*
chlorpromazine	*perphazine*	*trifluoperazide*
droperidol	*pimozide*	*ziprasidone*
fluphenazine	*quetiapine*	
haloperidol	*risperidone*	

St. John's wort

All mood stabilizers, including but not limited to:

carbamazepine	*lithium*	*valproic acid*
gabapentin	*oxycarbazine*	
lamotrigine	*topiramate*	

All anti-epileptic drugs, including but not limited to:

acetazolamide	*mephenytoin*	*selectracetam*
beclamide	*mesuximide*	*tiagabine*
brivaracetam	*phensuximide*	*valpromide*
ethosuximide	*phenytoin*	*vigabitrin*
ethotoin	*pregabalin*	*zonisamide*
fosphenytoin	*primidone*	
levaracetam	*progabide*	

All controlled (abusable) sedatives and hypnotics, including but not limited to:

all barbiturates including but not limited to:

butabarbital (note : a barbiturate is a component of agents including but not limited to: Donnatal, Fiorinal, and Fioricet)

phenobarbital

secobarbital

Metoclopramide

Respiratory agents

Bronchodilators if used in high enough doses to be causing CNS effects
Systemic corticosteroids if used in high enough doses to be causing CNS effects
(inhaled corticosteroids are not prohibited)

The following drugs are also prohibited for frequent or "p.r.n." use. Call the medical monitor if a patient has been prescribed one of the following for occasional use only:

Narcotics:
opioids and opioid combinations including but not limited to:

codeine	*hydrocodone*	*propoxyphene*
extended release	*hydromorphone*	
morphine	*oxycodone*	

Triptan antimigraine agents, including but not limited to:

eletriptan	*naratriptan*	*sumatriptan*
frovatriptan	*rizatriptan*	*zolmitriptan*

Non-benzodiazepine prescription sleep aids, including but not limited to:

chloral hydrate	*doxylamine*	*zaleplon*
chlormethiazole	*eszopiclone*	*zolpidem*
diphenhydramine	*promethazine*	*zopiclone*

(continues on the next page)

10.3.2 Part II – List of medications of possible relevance

In Part II, a separate list of medications that may interfere with flibanserin metabolism are included. These medications must be avoided except under special conditions, which are noted.

CYP 3A inhibitors and inducers

These medications if taken systemically rather than topically may interfere with flibanserin metabolism and thus must be avoided for an adequate period (five half-lives of the drug or 7 days, whichever is longer) before Baseline, and should not be taken during the study medication period unless all of the following conditions are met:

- The patient must have been taking study medication for at least 7 days.
- The patient is having no AEs that are related to study medication in the investigator's judgment.
- The proposed concomitant medication will be used for no more than 14 days.
- The investigator agrees to warn the patient about possible new or worsening AEs and/or loss of efficacy during the use of the proposed concomitant medication.

CYP 3A inducers: (e.g.)

aminoglutethimide
dexamethasone
modafinil
nafcillin
rifampin
rifabutin
rifapentine

CYP 3A inhibitors: (e.g.)

aprepitant
clarithromycin
cimetidine (Tagamet®)
diltiazem
erythromycin
fluconazole
grapefruit juice
itraconazole
ketoconazole
telithromycin
verapamil
voriconazole

7. References

1. Derogatis L, et al. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sexual Medicine 2008 Feb; 5(2): 357-64.

2. Rosen R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sexual Marital Therapy 2000 Apr – Jun; 26 (2): 191-208.