

FDA Briefing Document

Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee

June 4, 2015

NDA 022526

Flibanserin

(Proposed trade name: Addyi)

Applicant: Sprout Pharmaceuticals

Proposed Indication:

Treatment of hypoactive sexual desire disorder in premenopausal women

Dosing regimen:

100 mg tablet orally once daily at bedtime

DISCLAIMER STATEMENT

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 are bringing the new drug application (NDA 022526) for flibanserin oral tablet (proposed trade name, Addyi) intended for the treatment of hypoactive active sexual disorder in premenopausal women to this Advisory Committee in order to gain the Committee's insights and opinions, and 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.

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I. Introductory Memorandum



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20093

INTRODUCTORY MEMORANDUM

Date: May 8, 2015

From: Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

To: Joint Members of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

Subject: Flibanserin New Drug Application (NDA) 022526
Joint Advisory Committee meeting
June 4, 2015

Introduction:

The FDA is convening this joint advisory committee meeting to obtain input on whether the benefits of flibanserin outweigh its risks and support approval. Flibanserin is a new molecular entity that is an agonist at the 5 hydroxytryptamine (5HT) type 1A receptor and an antagonist at the 5HT type 2A receptor. Flibanserin is not approved in any country. The Applicant, Sprout Pharmaceuticals, is seeking FDA approval for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The proposed dose is a 100 mg tablet taken by mouth every night at bedtime.

The following diagnostic criteria for HSDD are described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM):

- Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency or absence is made by the clinician taking into account factors that affect sexual functioning, such as age and the context of the person's life

- The disturbance causes marked distress and interpersonal difficulty
- The sexual dysfunction is not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

HSDD is no longer a stand-alone diagnosis in the current edition of the DSM (DSM-5), which was published in May 2013. DSM-5 describes a new condition, female sexual interest/arousal disorder (FSIAD), which combines features of both HSDD and another condition from DSM-IV known as female sexual arousal disorder.

There are no medications that are FDA approved for the treatment of HSDD or FSIAD. The FDA has recognized for a long time that there are women who have reduced sexual desire that causes distress, and who would benefit from safe and effective treatment. This condition is clearly an area of unmet medical need. However, for any product intended to treat an unmet medical need, the FDA is still required to base its regulatory decisions on an assessment of whether the benefits outweigh its risks. This has been the FDA's approach with flibanserin, which has a challenging benefit/risk assessment. To ensure that the FDA makes a fully informed decision based on the available data, the FDA is convening this joint advisory committee meeting to obtain outside, independent, expert advice from a multidisciplinary panel as to whether the benefits of flibanserin outweigh its risks. The advisory committee meeting will also provide an opportunity for the FDA to hear input from affected stakeholders such as patients with HSDD and patient safety advocates.

This introductory memorandum will provide a brief regulatory history and overview of the issues that will be presented to the advisory committee panel. More detailed information is included in the accompanying memoranda prepared by the FDA review team.

Regulatory History: This is the third review cycle for the flibanserin NDA. See Sections VII and VIII of the FDA Briefing Package for FDA's Complete Response letters, which describe the reasons why FDA did not approve flibanserin during the first two review cycles.

First Review Cycle: Boehringer Ingelheim, the previous Applicant, submitted the original NDA for flibanserin in 2009. The application was discussed at an advisory committee meeting in 2010. The advisory committee voted 10 to 1 that the Applicant had not provided sufficient evidence of efficacy. Of note, both pivotal phase 3 trials failed to show a statistically significant improvement compared to placebo in the pre-specified co-primary efficacy endpoint that assessed daily sexual desire using an electronic diary. These trials showed statistically significant improvement compared to placebo in a secondary endpoint that measured sexual desire using another instrument known as the Female Sexual Function Index (FSFI). The Applicant stated that the effect of flibanserin on sexual desire was better assessed with the FSFI, but most of the advisory committee members did not agree with altering the pre-specified method of assessing sexual desire. When asked whether the Applicant had shown an overall acceptable benefit/risk profile for flibanserin, the advisory committee unanimously voted no (11 vs. 0), stating that the

demonstrated efficacy with flibanserin was not sufficiently robust to justify the risks. Safety concerns expressed by committee members included adverse events such as fatigue and somnolence as well as drug-drug interactions (DDIs) and alcohol interactions with flibanserin.

The FDA agreed that the NDA could not be approved and issued a Complete Response letter in 2010, citing the following deficiencies:

- Lack of substantial evidence of efficacy because the phase 3 trials did not show a statistically significant change from baseline for one of the pre-specified co-primary efficacy endpoints.
- Overly restrictive entry criteria for the phase 3 trials, precluding a full assessment of efficacy and safety in the target population.
- The need for a DDI study to characterize the effects of a moderate CYP3A4 inducer and a moderate CYP3A4 inhibitor on flibanserin pharmacokinetics. The letter also asked the Applicant to submit results from a meta-analysis of phase 1 pharmacokinetic and safety data in women who concomitantly received flibanserin with an oral contraceptive (a weak CYP3A4 inhibitor).
- The need to complete the ongoing 12-week trial assessing the concomitant use of flibanserin with selective serotonin or norepinephrine reuptake inhibitors, with particular attention to possible exacerbation of depression.
- The need for a study assessing the effects of co-administered flibanserin and alcohol on tolerability, blood pressure and orthostatic vital signs.
- The need for a study assessing the effects of supra-therapeutic doses of flibanserin on orthostatic vital signs and risk of syncope in healthy premenopausal women.
- The need for an assessment of the risk of accidental injury with root cause analyses.
- The need for an assessment of the potential for human abuse because of central nervous system effects.

The Complete Response letter recommended that the Applicant conduct a new phase 3 trial with less restrictive entry criteria (e.g., allowing enrollment of patients with mild depression and anxiety and allowing commonly prescribed medications such as centrally-acting drugs). The letter also stated that the instrument used for assessing sexual desire should have adequate content validity, recall validity, and acceptable measurement properties consistent with recommendations in the 2009 guidance on Patient-Reported Outcomes.

Second Review Cycle: After FDA's first review cycle, Boehringer Ingelheim transferred ownership of the NDA to a new Applicant, Sprout Pharmaceuticals. Sprout responded to FDA's first cycle deficiencies and resubmitted the NDA for review in 2013. The resubmission included results from a third phase 3 trial and additional phase 1 studies. The FDA again determined that the NDA could not be approved and issued another Complete Response letter, citing the following concerns:

- Numerically small treatment differences compared to placebo, which do not clearly outweigh the safety concerns.

- Concerns with content validity of the FSFI sexual desire domain, used as the co-primary efficacy endpoint in the new phase 3 trial, and used as a secondary endpoint in the two prior phase 3 trials.
- Concerns about how healthcare providers would identify appropriate candidates for flibanserin, taking into account the change in DSM diagnostic criteria.
- A clinically significant interaction with alcohol causing syncope and hypotension.
- Increased exposures to flibanserin with moderate and strong CYP3A4 inhibitors, causing clinically significant hypotension in some cases.
- Events of central nervous system depression (e.g., somnolence), some of which appear temporally associated with accidental injury.

In the 2013 Complete Response letter, the FDA requested several new studies, including a driving study (to assess the impact of central nervous system depression on the ability to drive safely) and additional clinical pharmacology studies to better characterize the metabolism of flibanserin. In the Complete Response letter, the FDA stated that after the Applicant responded to these deficiencies, an advisory committee meeting would be warranted to seek advice on whether the benefits of flibanserin outweigh its risks.

Formal Dispute Resolution Request: Several months after the FDA issued the second Complete Response letter, Sprout appealed the Complete Response action to Dr. John Jenkins, the Director of FDA's Office of New Drugs. Sprout stated that the FDA had erred in its assessment of the benefit-risk profile of flibanserin and requested that the NDA be approved without requiring additional data or analyses. After reviewing the available data, Dr. Jenkins denied Sprout's appeal, stating that FDA's benefit-risk assessment was sound and did not deviate from precedent for similar decisions (see Section IX of the FDA Briefing Package). Dr. Jenkins recommended that Sprout address the issues raised in the Second Complete Response letter to better inform the benefit/risk assessment before resubmitting the NDA.

Third Review Cycle: After Dr. Jenkins denied the appeal, Sprout conducted additional studies and resubmitted the NDA. Below, I introduce the key efficacy and safety issues that the advisory committee panel will be asked to consider. These issues are discussed in detail in the accompanying memoranda in the FDA background package.

Efficacy Issues: Three pivotal phase 3 trials (Studies 511.71, 511.75, and 511.147) have been conducted to support the efficacy of flibanserin for the treatment of HSDD in premenopausal women. All three trials had two co-primary efficacy endpoints, one for satisfying sexual events (SSEs) and the other for sexual desire. All three trials also had a key secondary endpoint that measured distress related to sexual desire.

All three trials showed a statistically significant improvement with flibanserin compared to placebo in the number of satisfying sexual events and in distress related to sexual desire. The first two trials did not show a statistically significant improvement over placebo in the co-primary endpoint for sexual desire, which was assessed using a daily electronic diary, but did show a statistically significant improvement over placebo for a secondary endpoint that used

FSFI to assess sexual desire. The third trial used FSFI as the pre-specified co-primary endpoint for sexual desire and showed a statistically significant improvement over placebo, consistent with the FSFI findings in the two earlier trials.

The Applicant and FDA are not in full agreement that the FSFI is optimized for assessing sexual desire. Nonetheless, the Applicant and the FDA agree that statistically significant differences between flibanserin and placebo have been demonstrated in three phase 3 trials for SSEs, sexual desire measured by the FSFI, and distress related to sexual desire. The findings are consistent across the three phase 3 trials, demonstrating a pharmacologic effect of flibanserin in the patients studied. The results are summarized below:

- From a median baseline of about 2-3 SSEs per month, flibanserin resulted in a median placebo-corrected increase of about 0.5-1.0 SSEs per month.
- From a mean baseline of about 1.8-1.9 on the FSFI desire score, flibanserin resulted in a placebo-corrected mean increase of 0.3-0.4 (the FSFI desire score range is 1.2-6.0).
- From a mean baseline of 3.2-3.4 on the distress score, flibanserin resulted in a placebo-corrected mean improvement of 0.3-0.4 (on a scale of 0-4).

The fundamental question is whether these observed placebo-corrected treatment effects outweigh the risks associated with treatment.

Safety Issues: The accompanying Clinical Pharmacology and Clinical memoranda discuss flibanserin's safety findings in detail. Here, I focus the Advisory Committee panel on the serious risks of hypotension and syncope, because these are the most significant safety concerns with flibanserin. Hypotension and syncope can occur with flibanserin alone and the risk is amplified by drug interactions and with concomitant alcohol intake.

The most significant DDIs occur with moderate and strong CYP3A4 inhibitors. In our experience, utilization of the healthcare system's existing prospective drug utilization review at pharmacies and DDI screening technology are the most effective ways to identify and prevent serious DDIs. Therefore, the FDA does not currently foresee the need for additional risk management options beyond labeling to manage this risk.

In contrast, the clinically significant pharmacodynamic interaction between flibanserin and alcohol is more challenging to mitigate, particularly because flibanserin requires chronic administration and alcohol use, including binge drinking, is pervasive in our society. In the alcohol interaction study, 23 men and 2 women who were moderate drinkers consumed ethanol over 10 minutes with and without flibanserin. The ethanol doses were 0.4 g/kg (equivalent to about 2 drinks in a 70 kg person) and 0.8 g/kg (equivalent to about 4 drinks in a 70 kg person). In this study, the combination of ethanol and flibanserin precipitated concerning cases of hypotension and pre-syncope/syncope. The Advisory Committee should consider whether additional risk management strategies beyond labeling can effectively mitigate this risk.

The FDA can require a Risk Evaluation and Mitigation Strategy (REMS) if one is necessary to ensure that the benefits of a drug outweigh its risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The memorandum prepared by FDA's Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology describes the possible risk management options that are available to FDA together with a summary of the strengths and limitations of these options. After reading the background materials and hearing the presentations, the Advisory Committee panel will be asked whether it is possible to adequately mitigate the serious risks of concern and whether we can be assured that the benefits of flibanserin outweigh its risks.

Committee Expertise: To ensure sufficient expertise on the advisory committee panel, the FDA has convened a joint meeting involving the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee. In addition, the FDA has supplemented these standing committees with temporary voting members who have expertise in sexual medicine, patient reported outcome assessments, alcohol use, cardiology, emergency medicine, pharmacoepidemiology, and internal medicine.

Publicity and Claims of Gender Bias: Panel members may be aware of the extensive publicity surrounding flibanserin and treatments for female sexual dysfunction. Some have alleged that there is gender bias at the FDA, stating that there are many medications approved for treating male sexual dysfunction but none for treating female sexual dysfunction, and that the FDA is holding drugs intended to treat female sexual dysfunction to more stringent standards of approval. These claims are misleading and inaccurate. The FDA rejects claims of gender bias. The FDA's regulatory decision for each product is based on an assessment of whether the benefits outweigh the risks, and does not take gender into consideration.

The flibanserin NDA raises challenging scientific issues. The FDA welcomes science-based recommendations from the Advisory Committee panel as to whether the available data support a positive benefit/risk assessment for flibanserin. Thank you in advance for the vital public health contribution you are making through your participation in this meeting.

Draft Points to Consider:

The advisory committee members should consider the following while preparing for the meeting:

- The clinical significance of the observed placebo-corrected treatment effects of flibanserin on satisfying sexual events, sexual desire, and related distress
- Taking into account the generalizability of the clinical studies to the population of premenopausal women who would likely use flibanserin, if approved, your level of concern with the risks of hypotension and syncope when:
 - Flibanserin is used alone

- Flibanserin is used with alcohol
- With regard to the risks of hypotension and syncope, consider:
 - Whether the alcohol interaction study conducted mostly in men who were moderate alcohol drinkers adequately assesses risk in premenopausal women and in those who generally drink less alcohol than moderate drinkers
 - The feasibility of avoiding alcohol indefinitely while using flibanserin, taking into account the prevalence of alcohol use in the United States
 - Whether alcohol use should be contraindicated in patients using flibanserin
 - Whether a REMS is necessary and would be able to ensure that the benefits outweigh the risks of hypotension and syncope with flibanserin alone and with concomitant use of alcohol
 - If a REMS is appropriate, whether the Applicant's proposed REMS (consisting of a Medication Guide and communication plan) is sufficient to ensure safe use or whether additional elements such as elements to assure safe use (ETASU) with pharmacy certification or ETASU with pharmacy and provider certification, are needed
- Taking into account the generalizability of the clinical studies to the population of premenopausal women who would likely use flibanserin, if approved, your level of concern with any other safety findings
- Whether the overall benefit/risk profile of flibanserin is acceptable to support approval for HSDD in premenopausal women

**II. Clinical Background
Document – Division of Bone,
Reproductive and
Urologic Products,
Office of Drug Evaluation III,
Office of New Drugs**

**Clinical Background Document for the Joint Meeting of the Bone,
Reproductive and Urologic Drugs Advisory Committee (BRUDAC)
and
Drug Safety and Risk Management (DSaRM) Advisory Committee**

June 4, 2015

NDA 022526

Flibanserin

(Proposed trade name: Addyi)

Sprout Pharmaceuticals

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 Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration**

May 8, 2015

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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

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 benefit/risk 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.

Data in support of the efficacy of flibanserin treatment for the proposed indication is based primarily on three prospective, randomized, double-blind, North American clinical trials (Studies 511.71, 511.75, and 511.147) that compared flibanserin to placebo in premenopausal women with documented HSDD. Supportive efficacy and safety data were obtained from five phase 3, randomized, double-blind placebo-controlled trials – Studies 511.7 (evaluated doses lower than that proposed for marketing), 511.74 (randomized withdrawal trial), Study 511.77 (conducted in Europe), Study 511.84 (open-label, uncontrolled, safety extension trials enrolling women who participated in studies 511.71 and 511.75), and Study 511.114 [concomitant use of selective serotonin reuptake inhibitors or serotonin/norepinephrine reuptake inhibitors (SSRIs or SNRIs)].

For the discussion of efficacy, this Background Document will focus primarily on the three blinded 24-week trials (Studies 511.71, 511.75, and 511.147) that evaluated the 100 mg qhs flibanserin dose because 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

The original Applicant (Boehringer Ingelheim) studied flibanserin in men and women for the treatment of major depression. In phase 2a trials for depression, flibanserin failed to demonstrate efficacy; however, the subjects reported little sexual dysfunction. For this reason, in four phase 2b studies in the depression program, the Arizona Sexual Experiences Scale (ASEX) was used to compare the effect of flibanserin both to an approved antidepressant and to placebo 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.

1.3 Issues for Committee Consideration

The Division is seeking input from the advisory committee regarding whether flibanserin’s observed efficacy findings outweigh the risks and support approval for the treatment of HSDD in premenopausal women.

1.4 Hypoactive Sexual Desire Disorder

In the 4th edition of the Diagnostic and Statistical Manual-Text Revision (DSM-IV-TR), 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 generalized, as opposed to situational, HSDD. In the DSM-5, which was finalized in 2013, HSDD was combined with female sexual arousal disorder (FSAD) to form a new entity, female sexual interest/arousal disorder (FSIAD). Thus, HSDD no longer exists as a single clinical entity in DSM-5.

There are no drug products currently approved in the U.S. for the treatment of HSDD or FSIAD. A transdermal testosterone patch was previously approved for HSDD in several European countries, but has subsequently been withdrawn.¹

1.5 Flibanserin's Receptor Profile and Mechanism of Action

Flibanserin is a post-synaptic 5-hydroxytryptamine (5-HT) 1A receptor 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 D4 receptors. Flibanserin's mechanism of action in the treatment of HSDD is unknown.

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

The Division has advised sponsors of products intended to treat HSDD that the co-primary efficacy endpoints should include change from baseline in satisfying sexual events (SSEs) and sexual desire, and that change from baseline in personal distress due to low sexual desire should be assessed as a key secondary endpoint (or a co-primary endpoint). In addition, typical clinical development programs include, at a minimum, two randomized, double-blinded, placebo-controlled clinical trials to support a marketing application for HSDD. These trials are typically 6 months in duration, although additional long-term data are needed for products intended for chronic administration.

2 CLINICAL DEVELOPMENT OF FLIBANSERIN

2.1 Pharmacology/Toxicology

2.1.1 Carcinogenicity

Flibanserin was tested for its ability to induce cancer in animals with carcinogenicity studies in rats and mice. An increase in mammary tumors in female mice was the main carcinogenic signal.

¹ In 2006, Intrinsa TTS (testosterone transdermal system) was approved in Europe for the treatment of HSDD in surgically menopausal women on concomitant estrogen replacement. In 2012, the marketing authorization holder, Warner Chilcott, voluntarily withdrew the marketing authorization for "commercial reasons."

² The STRAW (Stages of Reproductive Aging Workshop, July 2001) criteria for pre-menopause are primarily women who have regular menstrual cycles that occur every 21 to 35 days for the previous 12 months and a normal FSH level.

Female mice (Charles River CD-1) were given flibanserin orally at doses of 0, 10, 80, 200, and 1000 mg/kg (raised to 1200 mg/kg on drug week 23 due to lack of toxicity) for two years. The two highest doses produced drug blood concentrations (area under the concentration-time curve or AUC) approximately 4 and 13 times higher than in women taking 100 mg of flibanserin (the recommended clinical dose).

Flibanserin treatment resulted in a highly significant dose-related increase in the incidence of mammary tumors in female mice. The incidence of malignant mammary tumors was 0.7% for the combined controls and 4%, 4%, 8.6% and 10% in low to high dose flibanserin groups, respectively (Table 1. Incidence of malignant mammary tumors in female mice)

Control CD-1 mice from the same supplier had an average incidence of malignant mammary tumors of 2.7% and a maximum incidence within any one group of 8.3%.

Table 1. Incidence of malignant mammary tumors in female mice

Dose (mg/kg)	0 (control)	0 (control)	10	80	200	1000/1200
Number of animals	70	70	70	70	70	70
Mammary gland adenocarcinoma, n (%)	0	1 (1.4%)	3 (4.3%)	3 (4.3%)	5 (7.1%)	5 (7.1%)
Mammary gland adenoacanthomas ^c , n (%)	0	0	0	0	1 (1.4%)	2 (2.8%)
Total, n	0	1 (1.4%)	3 (4.3%)	3 (4.3%)	6 ^a (8.6%)	7 ^b (10.0%)

^a p < 0.01 vs combined controls

^b p < 0.005 for trend compared to combined controls

^c adenoacanthomas also known as adenosquamous c

2.1.2 Genotoxicity

Flibanserin was not mutagenic in vitro in bacteria or Chinese hamster ovary cells. It was positive in the in vitro human lymphocyte assay but was negative in the Comet assay for DNA damage and in the in vivo rat micronucleus assay. Based on the weight of evidence, flibanserin can be considered non-genotoxic.

Division Comment:

Life-time administration of flibanserin to female mice resulted in a significant increase in the incidence of malignant mammary tumors at drug exposures approximately 4 and 13 times higher than those of women taking the recommended dose. Although this is clearly drug and dose related, the observed mammary tumor incidence was not much greater than the highest percent incidence in historical controls. Flibanserin is essentially non-genotoxic and does not increase serum prolactin concentrations in mice. The mechanism of tumor induction in mice is unknown.

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 administered flibanserin with total daily doses ranging from 60 mg to 300 mg. Steady state is achieved after approximately three days. The extent of exposure is increased 1.4-fold during once-daily administration of 100 mg flibanserin as compared to a single dose.

Flibanserin is rapidly absorbed, with 90% of the dose reaching the systemic circulation as flibanserin or metabolites. After oral administration, maximum observed plasma concentrations (C_{max}) 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.

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). The mean terminal half-life of flibanserin at steady state after oral administration is approximately 12 hours.

Co-administration with ketoconazole, a strong CYP3A4 inhibitor, increased flibanserin exposure 4.5-fold. Co-administration with fluconazole, a multi-CYP enzyme inhibitor and a moderate CYP3A4 inhibitor, increased flibanserin exposure 7-fold. For more detailed discussion of the pharmacokinetics and pharmacodynamics of flibanserin in specific populations and with concomitant use of CYP3A4 inhibitors, refer to the Clinical Pharmacology memorandum and Section 5.2.7 pertaining to safety information below. Whether CYP isoenzymes other than CYP3A4, such as CYP2C19, play a significant part in the metabolism of flibanserin is also discussed in the Clinical Pharmacology memorandum.

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

The Division and Applicant had regular interactions throughout the development program for flibanserin for the treatment of HSDD. Key points and agreements conveyed to the Applicant regarding the phase 3 program are summarized below:

- Prior to the original NDA submission in 2009:
 - Following multiple meetings and reviews of Special Protocol Assessment requests, agreement was reached on the co-primary efficacy endpoints – the change from baseline in satisfying sexual events (SSEs) and sexual desire as measured by responses captured by the electronic diary (eDiary). Distress associated with reduced sexual desire would be assessed as a key secondary efficacy endpoint, using response to Question 13 in the Female Sexual Distress Scale-Revised (FSDS-R).
 - The Division agreed with 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) for use as the primary analysis population.
 - The Division agreed with using responder analyses to help understand the “clinical meaningfulness” of the treatment benefit with respect to the important endpoints – SSEs, desire, and distress.

- In a meeting held on January 8, 2009, the Applicant informed the Division that in both Studies 511.71 and 511.75, which had been completed in 2008, the desire endpoint based on the eDiary had failed to attain statistical significance. Citing “diary fatigue” due to decreased compliance with daily diary entry over time, the Applicant proposed instead to use the two questions from the desire domain of the Female Sexual Function Index (FSFI-desire, which uses a 28-day recall period) to assess the change in sexual desire; this post-hoc approach would elevate the FSFI-desire, previously a secondary efficacy endpoint, to a co-primary endpoint.
- The Division advised that failure to meet one of the two co-primary efficacy endpoints did not constitute an acceptable reason to alter a pre-specified and agreed-upon endpoint. Furthermore, the Division and the Study Endpoints and Label Development (SEALD) team had already shared with the Applicant concerns regarding limitations of FSFI-desire instrument, regarding 1) recall bias due to the use of a 28-day recall period, and 2) content validity of the two questions.
- On October 27, 2009, the Applicant submitted NDA 022526, seeking marketing authorization for flibanserin to treat HSDD in pre-menopausal women.
- On June 18, 2010, this application was presented at the Reproductive Health Drugs Advisory Committee Meeting. The Committee was asked to specifically comment on the appropriateness of altering a co-primary efficacy endpoint post-hoc. A majority (9 of 11) of the members did not agree with changing the co-primary endpoint. The Committee voted unanimously (11 vs. 0) not to recommend approval, noting that the Applicant had not demonstrated an acceptable overall benefit/risk profile for flibanserin in premenopausal women for the treatment of HSDD.
- At the July 22, 2010, post-Advisory Committee Meeting (prior to the Action Date) with the Applicant:
 - It was agreed that the FSFI-desire domain questions would not be accepted as the regulatory endpoint for sexual desire for the first review cycle. In addition to the issues related to the post-hoc use of the FSFI as a co-primary endpoint, the Applicant would need to address content validity, recall validity and measurement properties of the FSFI, especially as they relate to the desire domain. The Applicant informed the Division of an ongoing trial (Study 511.147, initiated in 2009) that was using the FSFI-desire items as a pre-specified co-primary endpoint.
 - The Division stated that additional efficacy data might better characterize safety in patients with co-morbid conditions and those taking concomitant medications as such patients were excluded from previous trials.
- On August 27, 2010, the application received a Complete Response (CR) letter, which cited safety, efficacy, and clinical pharmacology deficiencies.
 - In the CR letter, the Agency recommended that re-analysis of the studies using the FSFI-desire endpoint would be considered exploratory and hypothesis-generating, and an additional trial with the FSFI-desire items as a pre-specified co-primary efficacy endpoint would be required to demonstrate efficacy.
 - The Agency also requested additional studies to evaluate:

- The effect of co-administration of flibanserin 100 mg with moderate CYP3A4 inducers/inhibitors and alcohol
 - The risks for syncope-related events using supra-therapeutic doses of flibanserin
 - The abuse potential of flibanserin
- Sprout Pharmaceuticals, the current Applicant, acquired all rights to flibanserin from Boeringer Ingelheim in 2012. A pre-NDA meeting was held on April 26, 2012 between the Division and the new Applicant; the Division advised that the appropriateness of the FSFI-desire domain questions for evaluating sexual desire would be assessed during the review of their response to the CR letter.
 - On March 29, 2013, the Applicant submitted a Complete Response to the August 27, 2010 CR letter.
 - A second CR letter was issued on September 27, 2013. The Agency concluded that the observed treatment benefits, albeit statistically significant, were numerically small and as such, did not convincingly outweigh the substantial safety concerns identified, including adverse events related to CNS depression, syncope, hypotension, and accidental injury. The safety concerns were exacerbated when flibanserin was used concomitantly with alcohol and CYP3A4 inhibitors.
 - The letter noted residual concerns regarding the validity of the FSFI-desire domain, which may affect the interpretation of efficacy findings.
 - The Applicant was recommended to identify and assess efficacy of flibanserin in a premenopausal population in whom a larger treatment effect size may be demonstrated to maximize the benefit/risk calculation.
 - Given the concern for the long half-life and the sedative properties of flibanserin, the Agency requested a dedicated driving simulation study to evaluate the potential for residual (next-day) psychomotor impairment from night time administration of flibanserin.
 - The letter also requested that the Applicant propose plans to:
 - Assess rare safety signals such as appendicitis
 - Assess the clinical risk of breast cancer in light of the non-clinical findings of dose-related mammary tumors in mice.
 - Given the unexpected greater increase in flibanserin exposure with concomitant administration of fluconazole, a moderate CYP3A4 inhibitor (and an inhibitor of multiple CYP enzymes, including CYP2C9 and CYP2C19), additional drug-drug interaction studies were requested to fully characterize the metabolism of flibanserin.
 - In the CR letter, the Agency stated that after the Applicant addresses the deficiencies, an advisory committee meeting is warranted to determine whether the benefits of flibanserin outweigh the risks.

- On December 3, 2013, the Applicant submitted a formal dispute resolution request (FDRR), appealing the CR action to the Office of New Drugs (OND). The Applicant asked OND to approve flibanserin for the proposed use without requiring additional data or analyses.
- The Director of OND issued a denial of the FDRR on February 7, 2014. Dr. Jenkins agreed that the benefits of flibanserin in HSDD “do not outweigh the significant safety concerns that have been identified,” based on the available data. As a path forward, he advised that the Applicant fully address the issues raised by the second CR letter, in particular the request to “conduct a driving study to assess next-day impairment and assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin, before resubmitting the application.” Dr. Jenkins concurred with the Division’s plan to bring the complex issues to an advisory committee meeting on the next review cycle.
- The Applicant conducted these requested studies and met with the Division on January 15, 2015, informing the Division of the planned resubmission for a third review cycle.

2.4 Overview of Clinical Studies

Data from the following studies were submitted in the application to support the pre-menopausal HSDD indication:

- 7 bioavailability studies
- 21 pharmacokinetic (PK) studies
- 7 pharmacodynamic (PD) studies
- 3 combined PK/PD studies
- 7 non-drug studies to validate the diagnostic and patient recorded outcomes instruments
- 9 efficacy trials for major depression in men and women
- 11 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 – HSDD Studies

Study	Objective	Design	Flibanserin Doses (mg)	# Enrolled 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
511.147 US	Pivotal efficacy/safety	R, DB, PC	100 mg qhs	Flibanserin – 543 Placebo - 547	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
Phase 3 Special Studies					
511.74 Part 1	Long-term safety	Open-label, (24+ wk)	flexible regimen: 50 qhs 50 BID	Open-label, all on flibanserin – 749	24
511.74 Part 2 US/Can	Withdrawal effects	R, DB, PC (24 wk)	100 qhs	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 - 1,814 from Studies 511.70, 511.71 & 511.75	52
511.118 EU	Long-term safety and efficacy	Open-label, uncontrolled	flexible regimen: 50 or 100 qhs 25 or 50 BID	Flibanserin - 480 from Study 511.77	28
511.114 US	Safety , tolerability and withdrawal in patients taking concomitant SSRI or SNRI	DB, PC, parallel group, multiple dose increasing	50 mg plus placebo x 14 days, ↑ to 100 mg 100 mg qhs	Flibanserin – 73 - 45 @ 50 qhs, uptitrated to 100 qhs - 28 @ 100 qhs Placebo – 38	12
511.133 US	Safety and efficacy (extension from Study 147)	Open-label, uncontrolled	100 qhs	Flibanserin – 347	28

R = randomized, DB = double blind; PC = placebo-controlled

Source: NDA 22-526, ser 0062. 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

2.5 Dose Selection for Phase 3 HSDD Studies

From the phase 2 trials, the Applicant concluded that flibanserin at 50-100 mg bid showed improvement over placebo. The Applicant then studied lower doses and assessed whether up-titration to 50 mg bid or 100 mg qhs would result in improved tolerability. In the first phase 3 trials, doses ranging from 25 mg bid to 100 mg daily (given either as 50 mg bid or as 100 mg qhs) were studied. Ultimately, the 100 mg qhs dose was selected as the therapeutic dose because of better tolerability compared to 50 mg bid.

The dosing regimens evaluated in the phase 3 trials in the flibanserin clinical development program for HSDD are listed in Table 3.

Table 3. Flibanserin Dosing Regimens for Clinical Efficacy Phase 3 Trials

Trial No.	Placebo (N - Treated)	Flibanserin (N - Treated)			
		25 mg bid	50 mg qhs	50 mg bid	100 mg qhs
Pivotal Phase 3 Trials					
511.147	N=545	-	-	-	N=542
511.71	N=295	-	N=295	-	N=290
511.75	N=398	N=396	-	N=392 ^a	N=395 ^a
Non-pivotal Phase 3 Trials					
511.70	N=349	N=337	N=363	N=336	-
511.77 (EU)	N=318	-	-	N=311	N=316 ^a
511.74					
Open-label	-	-	N=738 ^b	-	-
Double-blind	N=170	-	N=35	N=13	N=115

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

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

^b 738 Patients started on FLI 50 mg qhs and could return to FLI 50 mg qhs after optional down-titration from FLI 50 mg bid or FLI 100 mg qhs.

Source: NDA 22526, ser 0039, Summary of Clinical Efficacy, Module 2.7.3, Table 2, p 18 of 139.

3 Efficacy of Flibanserin

3.1 Pivotal Efficacy Trials Used to Supporting Efficacy

As shown in Table 2, the Applicant conducted a total of seven phase 3 studies. The Division considers only three of these (Studies 511.71, 511.75 and 511.147) as primary efficacy support. The other trials are not considered pivotal because of less optimal study designs (open-label studies, not evaluating the proposed therapeutic dose/dosing regimen, or not evaluating all three efficacy endpoints).

3.1.1 Overall Study Design

The three trials were prospective, randomized, double-blind, North American (US and Canada) studies in premenopausal women with acquired HSDD. The total study duration was 28 weeks, consisting 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.

3.1.2 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.

In Study 511.147, subjects were randomized to receive either placebo or flibanserin 100 mg qhs.

3.1.3 Entry Criteria

Key eligibility criteria for studies 511.71, 511.75 and 511.147 are described below.

Inclusion Criteria

- 18 years of age and older at the Screening Visit; pre-menopausal status confirmed per the Stages of Reproductive Aging Workshop (STRAW) criteria²
- In a stable, monogamous, heterosexual relationship for at least one year prior to the Screening Visit. The partner was expected to be physically present at least 50% of each month during the screening period and the 24-week efficacy period of the trial.
- 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 the medically acceptable method of

² The STRAW (Stages of Reproductive Aging Workshop, July 2001) criteria for pre-menopause are primarily women who have regular menstrual cycles that occur every 21 to 35 days for the previous 12 months and a normal FSH level.

contraception during the trial. (If the use of a contraceptive was judged to be a contributing factor to the patient's HSDD, the patient was to be excluded from the trial.)

- At the Screening Visit:
 - Confirmed to have a primary diagnosis of HSDD, generalized acquired type according to DSM-IV-TR criteria. The current episode had to be at least 24 weeks in duration by the Baseline Visit. Secondary Female Sexual Arousal Disorder and/or Female Orgasmic Disorder were allowed if co-morbid with HSDD. This inclusion criterion was met only if the HSDD began prior to Female Sexual Arousal Disorder and/or Female Orgasmic Disorder and the HSDD was of more importance to the patient, in the investigator's judgment.
 - Has a score of 15 or higher on the Female Sexual Distress Scale-Revised (FSDS-R, score range from 0 to 52) at the Screening Visit. (The range of scores for this 13-item instrument is from 0 to 52; the higher the score, the greater the distress.)
 - Had a score of 0 or 1 on Item #2 of the Sexual Interest and Desire Inventory - Female (SIDI-F) instrument. 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).
 - Willingness to try to have sexual activity (e.g., any act involving direct genital stimulation) at least once monthly.
 - Willing and able to use an eDiary on a daily basis (e.g., had to have access to a working land line telephone for daily data transmissions).
- At the Baseline Visit, had demonstrated adequate compliance with eDiary use, entering data into the eDiary for at least 23 days during the 28-day Screening period.

Exclusion Criteria

- Prohibited medications included antiarrhythmics, anticoagulants, beta blockers, central nervous system (CNS) stimulants, dopamine-receptor agonists, fertility agents, progestins/estrogens/androgens or their antagonists for less than 6 months, over-the-counter "sexual enhancers," muscle relaxants, five broad subcategories of psychotherapeutics, anti-epileptics, controlled sedatives, respiratory agents and systemic corticosteroids (if used in high enough doses to cause CNS effects), narcotics (for frequent or as needed use), triptan antimigraine agents, and non-benzodiazepine sleep aids. Estrogen and progestin as a constituent of Hormone Therapy was acceptable as long as the patient had been on a stable dose for at least 6 months prior to the Screening Visit and it was not prescribed for treatment of low sexual desire
- Patients whose sexual function was affected (enhanced or worsened) by any medication within 30 days before the Screening Visit and any time prior to the Baseline Visit. This had to be determined by the investigator's judgment after performing a detailed review of the patient's sexual history and concomitant therapy.
- At the Screening Visit, patients who had a history of drug dependence or abuse (including alcohol, as defined in DSM-IV-TR or in the opinion of the investigator) within the past year.

- At the Screening Visit, patients who had a history of multiple severe reactions (i.e., allergic or oversensitivity to usual doses) to psychotropic drugs.
- Current (or within 14 days of study drug administration) use of a CYP3A4 inhibitor (including grapefruit juice) or CYP3A4 inducers.
- Current or past six month history of pregnancy or breast-feeding.
- Recent major depressive disorder, 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.
- Patients who had started psychotherapeutic (non-drug) treatment (e.g., sex therapy, behavior therapy, psychoanalytic therapy, interpersonal therapy, cognitive therapy, marital counseling, etc.) within 12 weeks before the Baseline Visit. Any patient who started psychotherapeutic treatment more than 12 weeks before the Baseline Visit could continue the psychotherapeutic treatment at the same frequency and duration provided that there had been no improvement in the patient's HSDD.
- At the Screening Visit:
 - Patients who met DSM-IV-TR criteria for Sexual Aversion Disorder, Substance-Induced Sexual Dysfunction, Dyspareunia (not caused by inadequate foreplay stimulation or alleviated by lubricants), Vaginismus, Gender Identity Disorder, Paraphilia, or Sexual Dysfunction Due to a General Medical Condition.
 - Patients who indicated that their sexual partner had inadequately treated organic or psychosexual dysfunction that could interfere with a patient's response to treatment.
 - Patients who entered the peri-menopause stage (menopausal transition) or the post-menopause stage, including those who have had a hysterectomy (without bilateral oophorectomy), bilateral oophorectomy, endometrial ablation, or chemical-induced menopause (e.g., chemotherapy), according to the STRAW criteria.
- Patients who had findings at the Screen Visit of pelvic inflammatory disease, urinary tract or vaginal infection/vaginitis, cervicitis, interstitial cystitis, vulvodynia, or significant vaginal atrophy.

Division Comments:

- **The women enrolled in the pivotal efficacy studies were generally healthy, without any significant medical conditions or concomitant medication use.**
- **There was an extensive list of medications and drug classes that were exclusionary of participation and prohibited during all three trials (5 pages in Studies 511.71 and 511.75 and 3 pages in Study 511.147, See Section 6.4). This may limit the generalizability of the trial results, particularly the safety findings. As discussed in Section 5, women who inadvertently took certain prohibited concomitant medications during the trial had higher rates of adverse events.**

3.2 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 to the 28 days prior to the final clinic visit (without spanning into the previous clinic visit). The eDiary sexual desire score over a 28-day period was calculated by summing the daily sexual desire scores.

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

As already discussed in Section 2.3, although the two co-primary endpoints (SSEs and sexual desire) remained the same in Study 511.147, the instrument used to assess sexual desire was changed. The electronic diary was not used to capture data for sexual desire in Study 511.147. Instead, the FSFI sexual desire domain questions (part of the 19-item questionnaire, FSFI) were used. The FSFI was assessed every 4 weeks at clinic visits (the baseline and final clinical visit data were used for the co-primary efficacy endpoint).

3.2.1 Satisfying Sexual Events (SSEs)

Women indicated daily if they had experienced a sexual event. Sexual events or encounters included sexual intercourse, oral sex, masturbation, or genital stimulation by the partner. If a sexual event occurred, the SSE primary endpoint was measured by the eDiary question: “Was the sex satisfying for you?” The woman (not the partner) judged whether or not the event was satisfying.

Subjects were instructed to complete the eDiary for SSEs every morning. In Studies 511.71 and 511.75, up to a 3-day window was allowed for recalling and reporting previous events. In Study 511.147, the lockout window was changed to 7 days. SSE data that were not entered within the protocol-specified lockout period were considered missing.

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. The daily average number of SSEs was standardized to a 28-days period (without spanning into the period preceding the previous clinic visit) by using the following formula:

$$\text{Total monthly count of SSEs} = 28 \times (\text{sum of the number of SSEs entered}) / (\text{sum of number of days entered})$$

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 $28 \times 6/24 = 7$.

3.2.2 eDiary Sexual Desire Score

This score was only collected in Studies 511.71 and 511.75; Study 511.147, which was conducted after Studies 511.71 and 511.75, did not assess desire with this measure.

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). The daily results were added together to achieve a monthly score ranging 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 a particular day and more than 24 hours had elapsed, the subject was locked out from entering data for that earlier day. As with SSEs, desire data were standardized to a 28-day period (without spanning into the period preceding the previous clinic visit). The monthly desire score was calculated as follows:

$$\text{Monthly sexual desire} = 28 \times (\text{sum of desire scores}) / (\text{sum of number of days entered})$$

3.2.3 FSFI Sexual Desire Score

The FSFI sexual desire domain includes the two following questions:

1. “Over the past 4 weeks, how often did you feel sexual desire or interest?” Response options range from 5 (almost always or always) to 1 (almost never or never).
2. “Over the past 4 weeks, how would you rate your level (degree) of sexual desire of interest?” Response options range from 5 (very high) to 1 (very low or none at all).

The FSFI sexual desire score was calculated by summing the score from items 1 and 2 (score of 1-5 per question) then multiplying the sum by a correction factor of 0.6. This total score for the desire domain had a range of 1.2 (lowest desire) to 6.0 (highest desire) (see Outcomes Assessment Instruments document, Item 1).

Among the three pivotal trials, the placement of the FSFI-desire domain in the endpoint hierarchy in the study protocols has varied. In Studies 511.71 and 511.75, the FSFI desire domain was pre-specified as a secondary endpoint. However, the Applicant proposed using FSFI-desire in place of the co-primary endpoint for these two studies after the studies were completed and results were known. The advisory committee panel in 2010 and the FDA did not agree with this proposal; as noted above, the Applicant’s ongoing study (511.147) pre-specified FSFI-desire as a co-primary efficacy endpoint.

For a subset of subjects (N =175), a 7-day recall version of the FSFI was administered at Visit 8 (Week 20) and 9 (Week 24) in Study 511.147. Because the co-primary endpoint in Study 511.147 uses the FSFI with the standard 28-day recall period, the FSFI assessment was considered missing for the subgroup of patients that used the 7-day recall, and LOCF using the previously available FSFI 28-day recall value was used instead. However, an exploratory analysis was conducted using the FSFI 7-day recall as a sensitivity analysis.

Division Comment:

The current SEALD review finds that while the FSFI-SD may not be optimal, it may provide interpretable findings of efficacy if there is a reasonably large magnitude of effect for a particular product development program. Of note, FDA held a two-day public meeting in October 2014 to discuss female sexual dysfunction, and low female sexual desire/arousal in particular.³ The first day of the meeting falls under the FDA's Patient-Focused Drug Development initiative and was devoted to obtaining input from patients. A scientific workshop was held on the second day for FDA to obtain input from experts. Many of the panelists expressed support for the use of the FSFI-desire domain in clinical trials to support regulatory approval.

3.2.4 Key Secondary Endpoint

To evaluate the change in distress, the Division and the Applicant have agreed to use each subject's response to Question 13 in the Female Sexual Distress Scale-Revised (FSDS-R). This question asks: "How often did you feel bothered by low sexual desire?"

The FSDS-R (refer to Outcomes Assessment Instruments, Item 3) 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 of "never," "rarely," "occasionally," "frequently," or "always," ranging from a score of 0 to 4. 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.

3.2.5 Other Secondary Endpoints

Other secondary efficacy endpoints include:

- SSE (count): a raw count of all SSEs since the previous visit without standardizing to a 28-day period. This endpoint was used in a sensitivity analysis for the co-primary endpoint "standardized SSE."
- FSFI total score: cumulative responses to all 19 items in the FSFI questionnaire, including those in domains other than sexual desire (domains of arousal, lubrication, orgasm, satisfaction, and pain).
- FSDS-R total score: cumulative responses to all 13 items in the FSDS-R questionnaire, which pertains to female personal distress associated with sexual dysfunction. Adjusted mean FSDS-R total scores were analyzed as well.
- Patient Global Impression of Improvement (PGI-I): evaluated the patient's impression of overall improvement of her HSDD condition, specifically with regard to the decreased desire and associated bother.

³ <http://www.fda.gov/Drugs/NewsEvents/ucm401167.htm>

3.3 Responder Analysis

If the co-primary efficacy endpoints were successful, the protocols stated that the Applicant could then perform a 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, desire, and distress.

A responder analysis of patient-reported outcomes is a descriptive technique used to help determine whether changes observed during the study are meaningful to the study participants, themselves. In the study, 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.

This scale, known as the Patient Global Impression-Improvement (PGI-I) (see Outcomes Assessment Instruments document, Item 4) is completed by the subject during each follow-up visit to assess her overall impression of the change in her HSDD condition following treatment. The question asks: “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”). A response of “4” designates “no change” and a response of “3” designates “minimal improvement.” A lower number represents improvement perceived by the subject. 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 methodology for the responder analyses for this NDA primarily entailed anchoring a subject’s individual assessment of her improvement on the PGI-I to her scores for SSEs, desire and distress.

Division Comment:

The FDA responder analysis was based on the receiver operating characteristic (ROC) method. The Applicant used a different method. Nevertheless, the results were similar. See Section 4 for results of FDA’s analysis.

3.4 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

Table 5. Study Flow Chart for Study 511.147

	Screen	Baseline	Treatment							Post-Treatment
Trial Periods:										
Clinic Visit (+/-7 days)	1	2		4	5		7		9 ¹ , 10	
Telephone Visit (+/-3 days)			3			6		8		10
Week	-4	0	1	4	8	12	16	20	24	25
Trial Evaluations:										
Informed Consent	X									
Medical and Sexual History	X									
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X
BDI® II ¹²	X									
C-SSRS® ²	X	X							X	
SIDI-F® Item 2	X	X								
FSDS-R® ¹²	X	X		X	X		X		X	
Clinical Interview for FSD	X									
DSM-IV-TR® Diagnosis ³	X									
Blood Pressure and Pulse ⁴	X	X		X	X		X		X	
Weight	X	X		X	X		X		X	
Physical Examination ⁵	X								X	
Pelvic Examination ⁶	X									
Laboratory Tests ⁷	X								X	
Pregnancy Test ⁸	X	X		X	X		X		X	
Inclusion/Exclusion Criteria	X	X								
BFLUTS-Sex ¹²	X									
Adverse Events ⁹	X	X	X	X	X	X	X	X	X	X
eDiary	Completed Daily by the Patient									
FSFI® ¹²	X	X		X	X		X		X	
IVRS/TWRS ¹¹	X	X		X	X		X		X	
Marital Adjustment Test ¹²	X	X							X	
Randomization		X								
SDDQ® ¹²		X		X	X		X		X	
PGI of Improvement ¹²				X	X		X		X	
Patient Benefit Evaluation ¹²									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. Whether a patient prematurely discontinues from or completes the trial, all Visit 9 (end of treatment) evaluations must be completed. All Visit 10 (post-treatment) evaluations must also be completed.

2. Administer Baseline version at Visit 1/Screening, Since Last Visit version at Visit 2/Baseline and Visit 9/End of Treatment.

3. Established after the Clinical Interview for Female Sexual Dysfunction has been completed.

4. Performed after sitting for five minutes.

5. Includes height, which will be assessed only at the Screening Visit.

6. Includes a Pap Smear, those patients who had a hysterectomy (without a cervix) and have at least one ovary must have a vaginal smear in lieu of a pap smear.

7. Taken between 6 a.m. and 10 a.m. Fasting is not necessary. Laboratory tests include urinalysis, routine blood tests, hormone assays, and a urine drug screen (Screening Visit only). See [Appendix 10.8](#)

8. Serum pregnancy test required at Visit 1. Urine pregnancy test required at Visits 2, 4, 5, 7, and 9.

9. 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.

10. Window for this visit is +/-3 days.
 11. Contact interactive voice/web randomization system (IVRS/IWRS) for registration (Visit 1), medication assignment (each visit: V2, V4, V5, and V7), and end of study completion (Visit 10).
 12. To be completed by the patient.
- BDI-II®: Beck Depression Inventory® II
 FSD: Female Sexual Dysfunction
 C-SSRS®: Columbia Suicide Severity Rating Scale®
 DSM-IV-TR®: Diagnostic and Statistical Manual, Fourth Edition, Text Revision
 SIDI-F©: Sexual Interest and Desire Inventory-Female
 BFLUTS-Sex©: Bristol-Female Lower Urinary Tract Symptoms©
 FSDS-R©: Female Sexual Distress Scale-Revised
 FSFI©: Female Sexual Functioning Index
 PGI of Improvement: Patient Global Impression of Improvement
 SDDQ©: Sexual Desire Distress Questionnaire

Source: Study Protocol Study 511.147, page 6

3.5 Statistical Methods

3.5.1 Analysis Populations

In all three studies, 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.

3.5.2 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

Missing efficacy data were estimated by the last-observation-carried-forward (LOCF) method. This analysis type imputes missing data by using a patient's data from their most recent previous visit. The underlying assumption of this approach is that the best estimate of the patient's response to an item on a visit is that patient's most recent previous response to that item. No data were carried forward from a baseline or pre-drug state to a post-drug state. In the case of a missing item of a multi-item scale, only the individual component was carried forward, not the overall total.

Another LOCF method was examined in a sensitivity analysis. The “LOCF zero” method employed the LOCF method mentioned above, but carried forward a zero change from baseline response (i.e., imputed the baseline value to the on-treatment visits) for patients who did not have any on-treatment efficacy data. As a sensitivity analysis, Mixed Model Repeated Measures (MMRM) was used for the primary and key secondary endpoints.

The eDiary SSE data were analyzed 2 ways, one used all available data and the other required at least 14 days of diary data from the 28-day periods. If less than 14 days of diary data were available for a given month, the most recent 28-day period with at least 14 days of available diary data was used for imputation for that month.

Division Comments:

- **The primary efficacy analyses were based on the Full Analysis Set (FAS), rather than the full ITT set, which would have used all randomized patients.**
- **The 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 greater rate than would have been needed if subjects had remained in the study.**

3.5.3 Efficacy Analysis Methods

In all three studies, statistical analyses were conducted using analysis of covariance (ANCOVA) and nonparametric methods (in case the normality assumption of ANCOVA was violated). For SSEs, results reported are based on nonparametric methods: Wilcoxon rank sum test and rank-transformed ANCOVA with treatment, pooled center (centers that entered fewer subjects than a complete block were pooled by country) and baseline SSEs as covariates.

In Studies 511.71 and 511.75, the eDiary sexual desire score was analyzed using 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. 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 LOCF method of data imputation.

In Study 511.147, where desire measured by the FSFI was pre-specified as a co-primary endpoint, an a priori ordered hierarchical model for the endpoints was implemented, ordered as FSFI desire, SSE and FSFS-R Question 13 score. For FSFI, treatments were compared using ANCOVA with treatment and pooled center as fixed effects, baseline score and hormonal contraceptive use as a covariate. For a subset of patients, a 7-day recall version of the FSFI was administered at Visit 8 (Week 20) and 9 (Week 24). Because the primary endpoint was the FSFI using the standard 28-day recall period, the FSFI assessment for these patients at these visits that used the 7-day recall was considered missing, and LOCF using the previously available FSFI 28-day recall value was used in the primary analyses. However, exploratory analyses were also conducted using the FSFI 7-day recall as a sensitivity analysis. To compare the FSFI-SD 28-day recall assessment to the 7-day recall assessment, the following analyses were performed:

1. An equivalence test approach using ANOVA to examine the mean differences between the 2 recall periods taking treatment, sequence and period effect into account in the model. The mean difference between the 7-day and 28-day recall periods was assessed using a value of 0.6 which is a 1 unit change on the FSFI-SD (also the smallest unit change on the FSFI desire).
2. Cohen's D was calculated to compare the 28-day to the 7-day recall assessment relative to the standard deviation.
3. Examination of the ratio of the within-patient assessment of the 2 different recall periods to determine whether the 95% confidence interval (CI) of the ratio was within 80-125%.

4. Examination of the correlation between the 2 different recall periods using the intraclass correlation coefficient (ICC).

For both co-primary efficacy endpoints, the comparison was made between the 4-week screening period and Week 21 to 24. Both co-primary endpoints had to be statistically significant in order for the trial to be positive.

Key secondary endpoint:

The key secondary endpoint was the change from baseline to Week 24 in the FSDS-R Question 13 score. Treatments were compared using an ANCOVA with treatment and center as fixed effects and baseline score as a covariate. In Studies 511.71 and 511.75, a Hochberg procedure was planned for the 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.

Other secondary analyses:

Several additional exploratory analyses were performed, including:

- Evaluation of the primary endpoints at each monthly time point to determine onset of treatment effect.
- Evaluation of the key secondary endpoint at each monthly time point to determine onset of treatment effect.

4 FINDINGS FROM THE PRIMARY PHASE 3 EFFICACY TRIALS

4.1 Subject Enrollment and Disposition

A total of 3,548 patients were randomized to treatment in the three pivotal trials. Of these, 2,310 were randomized to flibanserin and 1,238 were randomized to placebo.

In the three pivotal trials, the overall completion rate was 78% for placebo and 70% for flibanserin. Subject disposition for these three trials is summarized in Table 6.

Table 6. Subject Disposition in the Pivotal Phase 3 Trials

	511.147		511.71		511.75	
	Placebo N (%)	FLI N (%)	Placebo N (%)	FLI N (%)	Placebo N (%)	FLI N (%)
Randomized	547	543	295	585	399	1185
Treated	545 (100.0)	542 (100.0)	295 (100.0)	585 (100.0)	398 (100.0)	1183 (100.0)
Discontinued	99 (18.2)	134 (24.7)	61 (20.7)	156 (26.7)	111 (27.9)	399 (33.7)
Adverse event	20 (3.7)	53 (9.8)	10 (3.4)	56 (9.6)	43 (10.8)	159 (13.4)
Lack of efficacy	3 (0.6)	3 (0.6)	8 (2.7)	11 (1.9)	11 (2.8)	32 (2.7)
Noncompliance	12 (2.2)	15 (2.8)	3 (1.0)	14 (2.4)	7 (1.8)	31 (2.6)
Lost to follow up	28 (5.1)	31 (5.7)	14 (4.7)	23 (3.9)	13 (3.3)	62 (5.2)
Consent withdrawn	12 (2.2)	4 (0.7)	22 (7.5)	32 (5.5)	33 (8.3)	93 (8.0)
Other ^b	24 (4.4)	28 (5.2)	4 (1.4)	20 (3.4)	4 (1.0)	22 (1.9)
Completed	446 (81.8)	408 (75.3)	234 (79.3)	429 (73.3)	287 (72.1)	784 (66.3)

Notes: FLI = Flibanserin; N = Number of subjects.

^bOther: includes personal reasons, pregnancies, moving away, etc.

Source: NDA 22-526 ser 0039, Module 2.7.3, Summary of Clinical Efficacy, Table 49, p. 89.

Division Comment:

For Study 511.75, efficacy data from two sites were excluded from the FDA analyses due to data integrity issues at the study site. Table 6 above (from the Applicant) shows subject disposition including the 69 patients from these two sites.

4.2 Demographic Data

The demographic information for subjects enrolled in all three pivotal efficacy trials is displayed in Table 7 below.

Table 7. Subject Demographics for Pivotal Efficacy Trials (Treated Set)

	511.147		511.71		511.75		Total	
	Placebo N (%)	FLI N (%)	Placebo N (%)	FLI N (%)	Placebo N (%)	FLI N (%)	Placebo N (%)	FLI N (%)
Number of Patients	545	542	295	585	398	1183	1238	2310
Age Group, N (%)								
18-34 y	222 (40.7)	221 (40.8)	126 (42.7)	261 (44.6)	157 (39.4)	531 (44.9)	505 (40.8)	1013 (43.9)
35-44 y	225 (41.3)	223 (41.1)	136 (46.1)	243 (41.5)	195 (49.0)	529 (44.7)	556 (44.9)	995 (43.1)
≥45 y	98 (18.0)	98 (18.1)	33 (11.2)	81 (13.8)	46 (11.6)	123 (10.4)	177 (14.3)	302 (13.1)
Age, y								
Mean	36.6	36.5	35.5	36.0	36.2	35.3	36.1	35.9
SD	7.8	8.0	7.0	7.4	6.6	6.9	–	–
Race, N (%)								
White	463 (85.0)	466 (86.0)	256 (86.8)	511 (87.4)	370 (93.0)	1076 (91.0)	1089 (88.0)	2053 (88.9)
Black	64 (11.7)	66 (12.1)	33 (11.2)	66 (11.3)	22 (5.5)	90 (7.6)	119 (9.6)	222 (9.6)
Asian	9 (1.7)	7 (1.3)	6 (2.0)	7 (1.2)	6 (1.5)	17 (1.4)	21 (1.7)	31 (1.3)
Other ^a	9 (1.7)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.7)	3 (0.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Ethnic Origin – Hispanic								
No	485 (89.0)	470 (86.2)	272 (92.2)	536 (91.6)	370 (93.0)	1126 (95.2)	1127 (91.0)	2132 (92.3)
Yes	60 (11.0)	72 (13.2)	23 (7.8)	48 (8.2)	28 (7.0)	57 (4.8)	111 (9.0)	177 (7.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
How Long in Present Relationship, y								
Mean	10.8	11.0	10.4	10.8	11.4	10.5	10.9	10.8
SD	7.2	7.5	6.5	6.7	6.2	6.5	–	–
Hormonal Contraceptive Use								
HC non-users	291 (53.4)	309 (57.0)	181 (61.4)	346 (59.1)	239 (60.1)	726 (61.4)	711 (57.4)	1381 (59.8)
HC users	222 (40.7)	214 (39.5)	114 (38.6)	239 (40.9)	159 (39.9)	457 (38.6)	495 (40.0)	910 (39.4)
Missing	32 (5.9)	19 (3.5)	–	–	–	–	32 (2.6)	19 (0.8)
BMI								
Mean	27.31	27.33	26.35	26.97	26.28	26.57	26.65	26.96
SD	2.4	6.5	6.07	5.99	5.96	5.92	–	–
Smoking History								
Never smoked	372 (68.3)	375 (69.2)	200 (67.8)	408 (69.7)	258 (64.8)	769 (65.0)	830 (67.0)	1552 (67.2)
Ex-smoker	100 (18.3)	94 (17.3)	60 (20.3)	111 (19.0)	91 (22.9)	266 (22.5)	251 (20.3)	471 (20.4)
Current smoker	73 (13.4)	73 (13.5)	35 (11.9)	66 (11.3)	49 (12.3)	148 (12.5)	157 (12.7)	287 (12.4)

Notes: FLI = Flibanserin; N = Number of subjects; SD = Standard deviation; y = Years

Other (ethnic group): American Indian/Alaska native; Hawaiian/Pacific Islander

Source: NDA 22-526 ser 0039, Module 2.7.3, Summary of Clinical Efficacy, Table 50, p. 91-92.

4.3 Efficacy Results

4.2.1 Efficacy Findings for the Primary and Key Secondary Endpoints

The tables in this section display, by endpoint, the efficacy results for flibanserin 100 mg qhs vs. placebo in Studies 511.71, 511.75, and 511.147. Flibanserin's treatment effects were consistent across these three trials with respect to increasing overall satisfying sexual events and reducing

distress. Treatment benefit was also consistently demonstrated for sexual desire, but only when desire was measured by the FSFI-desire domain questions. Data presented in this section have excluded the two clinical sites from Study 511.75.

Satisfying Sexual Events:

As shown in Table 8. Summary Results for SSEs (FAS)#

treatment with flibanserin 100 mg qhs resulted in a statistically significant median increase of between 0.5 to 1.0 SSE per month from baseline over placebo.

Table 8. Summary Results for SSEs (FAS)#

	<u>Study 71</u>		<u>Study 75*</u>		<u>Study 147</u>	
	Flibanserin 100 mg	Placebo	Flibanserin 100 mg	Placebo	Flibanserin 100 mg	Placebo
N	275	285	358	365	500	521
Baseline	3.0	2.0	2.0	2.0	2.0	2.0
Week 24	4.0	2.8	3.0	2.8	4.0	3.0
Median Change	1.0	0.0	1.0	0.5	1.0	0.5
Treatment Difference	1.0		0.5		0.5	
p- value¹	< 0.05		< 0.05		< 0.05	

* Excluding two sites. ¹Wilcoxon rank sum tests. #FAS: Full Analysis Set. Median changes, instead of mean changes, are reported because of non-normal distribution.

FDA Analysis

Sexual Desire:

When sexual desire was measured by the eDiary method (using daily recall) – the pre-specified co-primary efficacy endpoint in Studies 511.71 and 511.75 – flibanserin treatment failed to separate from placebo. When desire was measured by the FSFI-desire domain questions (using a 28-day recall period) – a pre-specified secondary endpoint in those two studies, and the pre-specified co-primary endpoint in Study 511.147 – flibanserin consistently showed a statistically significant improvement over placebo in increasing sexual desire from baseline in all three trials. Summary results for sexual desire using FSFI are shown in Table 9. Because data on sexual desire as measured by eDiary in Studies 511.71 and 511.75 did not attain statistical significance, those results are not presented here.

Table 9. Summary Results for Sexual Desire Score by FSFI-Desire Domain (FAS)#

	<u>Study 71</u>		<u>Study 75*</u>		<u>Study 147</u>	
	Flibanserin 100 mg	Placebo	Flibanserin 100 mg	Placebo	Flibanserin 100 mg	Placebo
N	280	290	358	365	506	525
Baseline	1.9	1.9	1.8	1.8	1.9	1.9
Week 24	2.8	2.4	2.7	2.4	2.9	2.6
LS Mean Change	0.9	0.5	0.9	0.6	1.0	0.7
Treatment Difference (95% CI)	0.3 (0.2, 0.4)		0.4 (0.2, 0.5)		0.3 (0.2, 0.5)	
p- value²	< 0.05		< 0.05		< 0.05	

FSFI Desire score range: 1.2 to 6.0

* Excluding two sites. ² ANCOVA model: Change = Treatment + Baseline + Pooled Sites. #FAS: Full Analysis Population, FDA analysis**Division Comment:**

See the memorandum by FDA's Study Endpoints and Labeling Development (SEALD) team for a discussion of the FSFI-desire instrument.

Distress:

In all three pivotal phase 3 trials, patients treated with flibanserin had a statistically significant improvement in distress related to low sexual desire compared to placebo. Summary results are displayed in Table 10. Summary Results for Distress (using FSDS-R Q13), FAS# below.

Table 10. Summary Results for Distress (using FSDS-R Q13), FAS#

	<u>Study 71</u>		<u>Study 75*</u>		<u>Study 147</u>	
	Flibanserin 100 mg	Placebo	Flibanserin 100 mg	Placebo	Flibanserin 100 mg	Placebo
N	280	289	389	380	506	525
Baseline	3.2	3.2	3.3	3.2	3.4	3.4
Week 24	2.8	2.4	2.7	2.4	2.9	2.6
LS Mean Change	-0.8	-0.5	-0.7	-0.5	-1.0	-0.7
Treatment Difference (95% CI)	-0.3 (-0.4, -0.1)		-0.4 (-0.5,-0.2)		-0.3 (-0.4,-0.1)	
p- value²	< 0.05		< 0.05		< 0.05	

FSDS-R Q13 score range: 0 to 4

* Exclude two sites in study 75. ² ANCOVA model: Change = Treatment + Baseline + Pooled Sites. FDA analysis

4.3.1 FDA Responder Analysis

Both the Applicant and the FDA conducted responder analyses to explore the clinical meaningfulness of the observed changes in SSE, FSFI, and FSDS. FDA's approach used the receiver operating characteristic (ROC) method to relate the changes in SSE, FSFI and FSDS to the results of the PGI score. For this analysis, subjects in the FAS population, irrespective of treatment assignment, were categorized as "satisfied" vs. "unsatisfied" based on the PGI questionnaire results at the final visit. The "satisfied" subjects were defined as those whose PGI response was ≤ 3 (much improved to minimally improved), and "unsatisfied subjects" were defined as those whose PGI response was > 3 (no improvement/worse) or missing. Using this dichotomy, the ROC analysis was used to estimate a "cutoff" for the change in each of the three endpoints (SSEs, FSFI, and FSDS) to classify subjects as responders versus non-responders. The results of the FDA responder analyses are presented in Table 11. Percent Responders in the Pivotal Phase 3 Studies by Anchoring the Efficacy Endpoints to the Patient Global Impression of Improvement (PGI) – FDA Analysis below.

Table 11. Percent Responders in the Pivotal Phase 3 Studies by Anchoring the Efficacy Endpoints to the Patient Global Impression of Improvement (PGI) – FDA Analysis

Endpoints	Study 71			Study 75*			Study 147		
	FLI 100mg	Placebo	Trt. Diff	FLI 100mg	Placebo	Trt. Diff	FLI 100mg	Placebo	Trt. Diff
SSEs (standardized)	41%	29%	12%	43%	33%	10%	44%	34%	10%
FSFI desire domain	55%	40%	15%	54%	40%	14%	58%	48%	10%
FSDS-R Item 13	55%	43%	12%	49%	40%	9%	62%	49%	13%

SSEs (standardized): SSEs averaged over a 28-day period

Trt. Diff: treatment difference

*Excluded two sites.

Division Comments:

The difference in proportion of responders is quite consistent across all three studies, whichever definition of responder is used (PGI ≤ 3 , as shown above, which includes patients who are minimally improved or PGI ≤ 2 , not shown, which is based on patients with greater than minimally improved responses). Across all endpoints, more flibanserin-treated patients are classified as responders compared to placebo-treated patients, based on the ROC method anchored to the PGI. The absolute difference in the percentage of responders with flibanserin and the percentage of responders with placebo is about 9-15%. Placebo response rates are high, ranging from 29%-49%.

4.3.2 Exploratory Subgroup Analyses

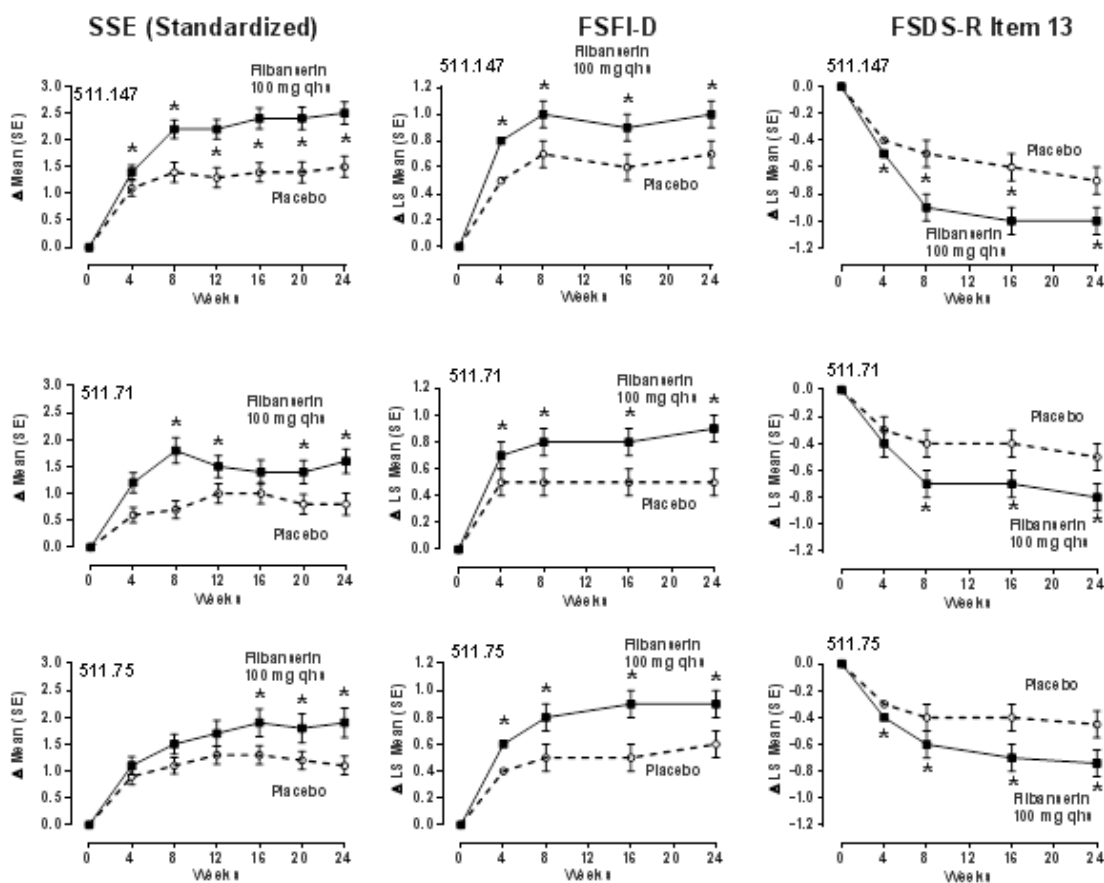
FDA conducted post hoc efficacy analyses to explore whether the treatment difference between flibanserin and placebo varies by severity of baseline SSEs, FSFI desire score, and FSDS-R 13 distress score. No notable differences were identified among any subgroups evaluated.

4.3.3 Onset of Efficacy

The Applicant provided the following graphs, which show treatment effects over time. These studies were not prospectively designed to assess onset of treatment (e.g., there was no control for multiplicity when testing for statistical significance at timepoints throughout the treatment period). Therefore, FDA views these as descriptive data only. Based on the information presented in Figure 1. Onset of Efficacy of Flibanserin for Each Endpoint for Studies 511.71, 511.75, and 511.147

below, it appears that there may be limited efficacy by Week 4 of treatment and that it may take up to 8-16 weeks (not all the endpoints were assessed at Week 12) until the treatment effect plateaus.

Figure 1. Onset of Efficacy of Flibanserin for Each Endpoint for Studies 511.71, 511.75, and 511.147



Source: NDA 22-526 ser 0039, Module 2.7.3, Summary of Clinical Efficacy, Figure 31, p. 106.

4.4 Efficacy Conclusion

The three pivotal trials conducted in North America of flibanserin 100 mg qhs showed a statistically significant difference between flibanserin and placebo on the endpoints of SSEs,

FSFI-desire score (but not daily desire measured by an eDiary) and FSDS-R Q13 distress score. These findings and the magnitude of the treatment effects are consistent across the three trials. However, the treatment differences are numerically small. The FDA is seeking expert advice from a multidisciplinary advisory committee panel as to whether these observed effects outweigh the safety concerns that will be described in the next section of this memorandum.

5 Overview of the Safety Database for Flibanserin

The assessment of the clinical safety of flibanserin is based on 31 phase 1 studies, 11 phase 2 studies in men and women with major depressive disorder (MDD), and 11 studies (two phase 2 and nine phase 3 studies) in premenopausal women with HSDD. Flibanserin has been tested in women with HSDD at doses ranging from 25 mg twice daily to 100 mg twice daily. A total of 6,439 women have received at least one dose of flibanserin in the HSDD clinical development program.

Exposure to each tested flibanserin dose in phase 3, placebo-controlled clinical trials in premenopausal women is shown in Table 12.

Table 12. Exposure (days) to Flibanserin (FLI) – phase 3, placebo-controlled HSDD trials in pre-menopausal women

	Placebo n (%)	FLI 25 mg bid n (%)	FLI 50 mg qhs n (%)	FLI 50 mg bid n (%)	FLI 100 mg qhs n (%)	All FLI n (%)
Number of subjects exposed to ≥1 dose	1905	733	969	728	1543	3973
Days						
≥28	1826 (96)	695 (95)	918	652 (90)	144 (94)	3709 (93)
≥56	1710 (90)	628 (86)	851 (88)	573 (79)	1311 (85)	3363 (85)
≥84	1614 (85)	587 (80)	797 (82)	520 (71)	1231 (80)	3135 (79)
≥182	166 (9)	62 (9)	103 (11)	43 (6)	99 (6)	307 (8)
≥365	0	0	0	0	0	0

Source: NDA 22-526 ser 0039, Clinical Overview, Module 2.5, Table 12, page 46 (includes trials 511.70, 511.71, 511.75, 511.77 and 511.147).

Long-term exposure to flibanserin in phase 3 double-blind and open-label HSDD trials in premenopausal and post-menopausal women is shown in Table 13.

Table 13: Exposure to Flibanserin, phase 3, placebo-controlled and open-label HSDD trials¹ in pre and post-menopausal women

	FLI 25 mg bid N=444 n (%)	FLI 50 mg qhs N=952 n (%)	FLI 50 mg bid N=619 n (%)	FLI 100 mg qhs N=3964 n (%)	FLI total N=5979 n (%)
≥84 days	291 (66)	731 (77)	400 (65)	3184 (80)	4606 (77)
≥182 days	51 (12)	397 (42)	137 (22)	1809 (46)	2394 (40)
≥365 days	10 (2)	145 (15)	60 (10)	851 (22)	1066 (18)
≥547 days	0	18 (2)	7 (1)	89 (2)	114 (2)

Source: NDA 22-526 ser 0039, Clinical Overview, Module 2.5, Table 1.5.9, p 589.

¹ includes trials .70, .71, .75, .77, .114, .130, .147, .156, .84, .118 and .133.

Division Comment:

The duration and extent of patient exposure to Flibanserin for the HSDD indication is adequate.

The safety review presented in this document is based on data pooled from the five phase 3 double-blind, placebo-controlled trials conducted in premenopausal women with HSDD, as well as data from select phase 1 studies in healthy volunteers. A range of doses were studied in the phase 3 trials, but flibanserin 100 mg qhs, the proposed therapeutic dose, is the primary focus of this review. Where applicable, the other flibanserin doses were examined to further investigate potential safety signals or explore dose-response relationships to adverse events of interest.

Trials involving post-menopausal women were not reviewed except for additional data relating to a safety signal identified in the pre-menopausal database.

It should be noted that routine inspection conducted by the Office of Scientific Investigations identified irregularities in trial conduct at two clinical sites involved in Study 511.75 that were sufficient to raise data integrity concerns. While the data from these two clinical sites were excluded from efficacy consideration, data from these sites were not excluded from this safety analysis because the number of subjects (69) relative to the total size of the safety database is small.

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)

On-treatment AEs were defined as AEs that occurred between the first day of treatment and the last day of treatment plus 1 day, inclusive.

5.1 Overall Safety Findings from the Flibanserin Clinical Development Program

Safety issues that formed the basis of the most recent CR action are summarized below and discussed in more detail in the following sub-sections. This review will also touch on areas that do not necessarily rise to the level of impacting approvability, but are included to give a broader perspective of flibanserin safety.

Clinical safety concerns identified in the September 27, 2013, CR letter:

- Flibanserin causes central nervous system depression (e.g., fatigue, somnolence, and sedation) which is more pronounced in settings where flibanserin exposure is increased and when flibanserin is administered during the daytime rather than at bedtime. In addition, the long half-life of flibanserin (~12 hours) raises concern for residual next-day impairment even if flibanserin is dosed at bedtime.
- Concomitant administration of centrally-acting medications (e.g., serotonin-norepinephrine reuptake inhibitors, alcohol, triptans) may adversely affect flibanserin tolerability.
- Concerns regarding the additive sedative and hypotensive effects of concomitant use of alcohol.
- Co-administration of flibanserin with drugs that are strong or moderate CYP3A4 inhibitors leads to a significant increase in flibanserin exposure, poor tolerability and a higher frequency of syncope and hypotension, which may be severe, compared to flibanserin used alone.
- Central nervous system (CNS) adverse effects such as dizziness and fatigue appear to be more pronounced when flibanserin is administered with hormonal contraceptives (which are mild CYP3A4 inhibitors). This interaction may compromise the safety of flibanserin in young women, many of whom will likely be chronic users of hormonal contraceptives.
- Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events.
- A greater incidence of appendicitis among flibanserin users compared to placebo may represent a class effect of drugs with 5HT_{2A} antagonism.
- It is unclear whether the increased incidence of mouse mammary tumors observed at flibanserin exposures approximately 4 and 13 times higher than those of women taking the recommended dose represents a clinical risk of breast cancer. The absence of a mammary tumor signal in rats does not completely exclude human risk.

The Agency recommended the Applicant do the following to address the safety issues:

- Clarify how CNS effects and risks of hypotension and accidental injury will be minimized in clinical practice.
- Propose strategies beyond labeling to ensure that flibanserin is not prescribed with moderate or strong CYP3A4 inhibitors, or taken with alcohol or other centrally acting medications.
- Propose a strategy to mitigate the risk to patients associated with concomitant use of flibanserin and hormonal contraceptive products (HCPs).
- Conduct a driving impairment study.
- Propose a plan to determine whether the excess incidence of appendicitis observed in the phase 3 placebo-controlled program is drug-related.
- Propose a plan to assess the clinical risk of breast cancer in light of the non-clinical findings of dose-dependent mammary tumors in mice at flibanserin exposures 4 and 13 times the proposed human dose.

The Applicant addressed the concerns identified in the 2013 CR letter in its most recent submission dated February 18, 2015. The Applicant's proposals are discussed in each relevant subsection of this review.

5.1.1 Deaths

Deaths that occurred on study or within 30 days of terminating flibanserin treatment were recorded. Across all HSDD trials (phase 1-3, including the open-label safety extensions), there was only one death, which 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 unrelated to study drug or procedures.

5.1.2 Serious Adverse Events

Serious adverse events (SAEs) were more common among flibanserin-treated subjects than in those taking placebo. SAEs which occurred in more than one flibanserin-treated subject (any dose) are shown in Table 14.

Table 14: Most Common Serious Adverse Events – phase 3, placebo-controlled HSDD trials in pre-menopausal women

	Placebo N=1905 n (%)	FLI 25mg bid N=733 n (%)	FLI 50 mg qhs N=969 n (%)	FLI 50 mg bid N=728 n (%)	FLI 100 mg qhs N=1543 n (%)	FLI Total n=3973 n (%)
Total with SAEs	10 (0.5)	4 (0.5)	10 (1.0)	5 (0.7)	14 (0.9)	33 (0.8)
Appendicitis	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.4)	0 (0.0)	6 (0.2)
Intervertebral disc protrusion	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (<0.1)	3 (<0.1)
Cholelithiasis	2 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	1 (<0.1)	3 (<0.1)
Concussion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	2 (<0.1)
Road traffic accident	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.2)

Source: NDA 22-526 ser 0039, Integrated Summary of Safety (ISS), Module Table 2.2.34, p. 4980-2.

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 0.07–0.15% or 6-month risk of 0.04-0.08%).⁴ A total of 0.2% of flibanserin-treated subjects (all doses) experienced appendicitis in the 6-month trials. The incidence is slightly greater than would be expected based on background risk. This issue is discussed further in Section 5.2.6.
- One event of concussion which occurred following *circulatory collapse* (investigator verbatim term) is discussed in Section 5.2.3.1.1. The second event of concussion was a result of a road traffic accident (accidental injuries are discussed in more detail in Section 5.2.4).
- 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.

5.1.3 Discontinuations Due to Adverse Events

The incidence of premature discontinuation due to an adverse event in the flibanserin 100 mg qhs group was more than twice that of placebo. The most common AEs leading to treatment discontinuation (i.e., occurring in $\geq 1.0\%$ of flibanserin-treated subjects) are shown in Table 15.

⁴ 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

Table 15: Most Common Adverse Events leading to discontinuation, phase 3, placebo-controlled HSDD trials in pre-menopausal women

	Placebo N=1905 n (%)	FLI 100 mg qhs N=1543 n (%)
AEs leading to discontinuation	112 (5.9)	198 (12.8)
Dizziness	3 (0.2)	26 (1.7)
Nausea	4 (0.2)	19 (1.2)
Somnolence	9 (0.5)	17 (1.1)
Anxiety	7 (0.4)	16 (1.0)
Insomnia	7 (0.4)	16 (1.0)

Source: NDA 22-256 ser 0039, Module 2.7.4, SCS, Table 63, p. 132.

5.1.4 Common Treatment-Emergent Adverse Events (AEs)

The most common treatment emergent adverse events (i.e., those occurring in > 1.0% of flibanserin subjects and more often than in placebo) are shown in Table 16.

Table 16: Most common treatment-emergent adverse events, phase 3, placebo-controlled HSDD trials in pre-menopausal women

Preferred term	Placebo N= 1905 n (%)	FLI 100 mg qhs N= 1543 n (%)
Dizziness	41 (2.2)	176 (11.4)
Somnolence	59 (3.1)	173 (11.2)
Nausea	71 (3.7)	161 (10.4)
Fatigue	95 (5.0)	142 (9.2)
Insomnia	46 (2.4)	75 (4.9)
Dry mouth	17 (0.9)	37 (2.4)
Anxiety	17 (0.9)	28 (1.8)
Constipation	9 (0.5)	25 (1.6)
Abdominal pain	15 (0.8)	23 (1.5)
Sedation	3 (0.2)	20 (1.3)
Somnolence or sedation or fatigue (i.e. CNS depression)	152 (7.9)	319 (20.6)

Source: NDA 22-526 ser 0039, Summary of Clinical Safety (SCS) Module 2.7.4, Table 36, p. 74.
Includes studies 511.70, .71, .75, .77, and .147.

Division Comments:

The majority of AEs were graded by the investigator as mild to moderate in severity.

5.2 Safety Issues of Particular Concern

5.2.1 Depression

Flibanserin was first assessed as a potential treatment for depression because of its central mechanism of action and affinity for 5-HT_{2B}, 5-HT_{2C}, and dopamine D4 receptors, but those trials failed to show efficacy and development was subsequently switched to HSDD. In the phase 3 placebo-controlled, pre-menopausal HSDD database, there was a dose-proportional increase in depression [identified by the MedDRA depression standard MedDRA Query (SMQ)] among subjects receiving flibanserin (see Table 17). Terms mapping to the MedDRA Depression SMQ are shown in Section 6.1.

Table 17. Incidence of Depression SMQ and Suicide/self-injury SMQ in phase 3, placebo-controlled HSDD trials in pre-menopausal women

	Placebo N=1905 n (%)	FLI 25 mg bid N=733 n (%)	FLI 50 mg qhs N=969 n (%)	FLI 50 mg bid N=728 n (%)	FLI 100 mg qhs N=1543 n (%)
Depression SMQ	55 (2.9)	20 (2.7)	37 (3.8)	31 (4.3)	71 (4.6)
Suicide/self-injury SMQ/preferred term	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.2)
Suicidal ideation	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.1)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Division Comment:

None of the adverse events of depression were serious, and the incidence of suicidal ideation and attempt was similar between placebo and flibanserin-treated patients.

The five double-blind, placebo-controlled phase 3 trials in pre-menopausal women with HSDD did not include a standardized evaluation of depressive symptoms during treatment. However, Study 511.114 of pre-menopausal women with HSDD who were also taking an SSRI/SNRI evaluated depression and anxiety symptoms with the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR16) and Beck Anxiety Inventory (BAI) questionnaires administered at baseline and end of treatment (Week 12). As shown in Table 18, depression and anxiety were more likely to improve among those subjects taking flibanserin than those receiving placebo.

Table 18. QIDS-SR16 and BAI score transition from baseline to Week 12 in Study 511.114 (LOCF)

Transition category	Placebo + SS/NRI	Flibanserin (all doses) + SS/NRI
N (%)	37 (100)	72 (100)
QIDS-SR16		
Remitted	4 (10.8)	14 (19.4)
No change	25 (67.6)	53 (73.6)
Worsened	8 (21.6)	5 (6.9)
Beck Anxiety Inventory		
Remitted	1 (2.7)	12 (16.4)
No change	35 (94.6)	60 (82.2)
Worsened	1 (2.7)	1 (1.4)

Source: NDA 22-526 ser 0039, Module 5.3.5.1.511-114, study report body, Table 15.3.4.3:4, p. 270 and Table 15.3.4.4: 4, p. 275.

Division Summary Comment:

- **Adverse events mapping to the MedDRA Depression SMQ were more common among flibanserin treated subjects compared to placebo, and the incidence of such events was dose-proportional. However, conclusions are limited by the fact that these trials were not prospectively designed to evaluate effects on mood and did not include a standardized evaluation of depressive symptoms during treatment.**
- **Among subjects taking concomitant SSRI's or SNRI's, flibanserin did not exacerbate depression or anxiety as measured by the QIDS-SR16 and BAI.**

5.2.2 Suicidality

Because of flibanserin's central activity at serotonin and dopamine receptors and its shared pharmacologic properties to some approved anti-depressants (e.g., nefazodone) which contain labeled boxed warnings regarding suicidality, DBRUP requested that the Applicant examine the potential for flibanserin to cause suicide/self-injury during clinical development. In the phase 3 placebo-controlled HSDD trials conducted for the original application (trials 511.70, 511.71, 511.75 and 511.77), the Applicant administered the Beck Scale of Suicide Ideation at screening, baseline, on-treatment and post-treatment visits. Review of the original submission found no signal of an increased risk of suicidality associated with flibanserin.

In the phase 3 trials (511.114 and 511.147) submitted with the complete response application in 2013, suicidality was assessed at baseline, during treatment and at the end of treatment using the Columbia-Suicide Severity Rating Scale (C-SSRS). There was no meaningful difference in the C-SSRS scores between flibanserin 100 mg qhs and placebo groups in either Study 511.147 or in Study 511.114 of patients taking concomitant SS/NRI's.

The incidence of adverse events of suicidality (i.e. events coding to the suicide/self-injury MedDRA version 11.1 SMQ, see Section 6.1 for preferred terms) in the phase 3 pre-menopausal HSDD database was low in both flibanserin 100 mg qhs and placebo groups (see Table 17) and not meaningfully different between the two groups.

Division summary comment:

DBRUP has concluded that there is no signal of an association between flibanserin treatment and suicidality.

In a memorandum of consultation from the Division of Psychiatry Products (DPP), DPP advised that, “Based on mechanism of action, we would not... recommend including [a] boxed warning [for suicidality] in the case that DBRUP decides to approve flibanserin for the treatment of HSDD.”

5.2.3 Syncope and Pre-Syncope

In the original submission, the Applicant searched the HSDD safety database (which included data from four phase 3 placebo-controlled safety and efficacy trials in pre-menopausal women with HSDD) for adverse events related to syncope and pre-syncope. It is not clear what prompted the concern for syncope. The first cycle review found that adverse events of pre-syncope and syncope were more common in flibanserin-treated subjects than with placebo, and the incidence was dose-proportional.

In the subsequent review cycles, the Agency reviewer searched phase 1 and phase 3 HSDD safety databases for adverse events of syncope. To date, with doses of flibanserin up to 100 mg qhs administered alone, there have been a total of:

- 6 reports of syncope in placebo-controlled, phase 3 HSDD trials, of which 4 were possibly drug-related (see Section 5.2.3.1.1 Phase 3 Data, and Appendix 6.6, Table 31)
- 5 reports of syncope in phase 1 studies, of which 4 were considered related to flibanserin see Section 5.2.3.1.2 Phase 1 Data, and Appendix 6.6, Table 32)

There has been one additional case of drug-related syncope in a phase 1 study involving doses of flibanserin greater than 100 mg qhs (see Appendix 6.6, Table 31). This patient (a male) received a dose of flibanserin 200 mg.

Finally, in phase 1 studies in which flibanserin up to 100 mg was administered with another product, there have been three cases of drug-related syncope – one each in the strong CYP3A4 strong inhibitor DDI study, the moderate CYP3A4 inhibitor study, and the ethanol DDI study. These cases are discussed in Sections 5.2.7.1.3 (adverse events in studies with moderate and strong CYP3A4 inhibitors) and 5.2.7.3.1 (dedicated alcohol DDI study) (See also Appendix 6.6, Table 32).

There are also some clinically significant cases of hypotension that did not result in syncope that are noted, where applicable, in the subsequent sections of this memorandum.

5.2.3.1 Flibanserin doses up to 100 mg qhs

5.2.3.1.1 Phase 3 Data

The Agency reviewer searched the updated phase 3 pre-menopausal HSDD database (now with data from five phase 3, placebo-controlled trials in pre-menopausal women) for adverse events of

syncope and pre-syncope and found the same results as during the previous review. This search strategy included preferred terms of *hypotension*, *syncope*, *blood pressure decreased*, *circulatory collapse*, *dizziness postural*, *loss of consciousness* and *syncope vasovagal*. This analysis yielded a slightly higher incidence of syncopal and pre-syncopal events with flibanserin compared to placebo (see Table 19). Similar results were seen when the search strategy was limited to events of syncope (based on a search using preferred terms of *syncope*, *circulatory collapse*, *syncope vasovagal* and *loss of consciousness*).

Table 19. N (%) of subjects experiencing adverse events consistent with syncope or pre-syncope, phase 3 placebo-controlled, HSDD trials in pre-menopausal women

	Placebo n (%)	FLI 25 mg bid n (%)	FLI 50 mg qhs n (%)	FLI 50 mg bid n (%)	FLI 100 mg qhs n (%)
Total N	1905	733	969	728	1543
Syncope and pre-syncope	6 (0.3)	0 (0.0)	4 (0.4)	4 (0.5)	8 (0.5)
Syncope only	4 (0.2)	0 (0.0)	1 (0.1)	3 (0.4)	6 (0.4)

Individual case reports for subjects experiencing syncope were reviewed and the following was noted:

- Timing – The timing of syncope relative to treatment initiation was unpredictable – in the flibanserin 100 mg qhs dose group, 50% of subjects experienced syncope within the first 28 days and the remaining events occurred after 28 days. Syncopal events typically coincided with t_{max} (i.e., one hour after dosing).
- Risk Factors (medical history) – Two subjects assigned to flibanserin 100 mg qhs had a previous history of vasovagal syncope. In the remaining subjects, no past medical history was identified that would predispose to syncope.
- Concomitant medications – Among these subjects who experienced syncope, hormonal contraceptives were used by 2 of the 4 subjects on placebo, 1 on flibanserin 50 mg qhs, 1 of 3 subjects on flibanserin 50 mg bid, and 4 of 6 subjects on flibanserin 100 mg qhs. Hormonal contraceptives are noted to increase flibanserin exposure by approximately 40%.
- Alcohol use – Among the subjects in Table 19, 3 of 4 placebo subjects, 1 subject on flibanserin 50 mg qhs, all 3 subjects on flibanserin 50 mg bid, and 3 of 6 subjects on flibanserin 100 mg qhs identified themselves as “drinkers” at baseline.

In the phase 3 placebo-controlled pre-menopausal HSDD database, there was a single serious adverse event of syncope which occurred in a subject assigned to flibanserin 100 mg qhs. The five remaining events of syncope in the flibanserin 100 mg qhs dose group were not coded by the investigators as serious because they did not meet the regulatory definition of “serious,” (i.e. any event resulting in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect.)

However, all syncopal events were considered by the Agency to be clinically significant regardless of whether they met the regulatory definition of serious.

The narrative for the case coded as serious 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. Vital signs at the time of circulatory collapse are not available. 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 and resumed flibanserin

Division Comment:

It is difficult to determine what role, if any, flibanserin played in this event given that the subject had a history of hypotension and orthostatic dysregulation. The same conclusion may be drawn for a second syncope case (case 511.75-032050) that was not coded as serious (summarized in Table 31). Of the remaining four cases coded as non-serious, all were deemed possibly related to flibanserin because there were no confounding medical conditions or concomitant medications that may have contributed.

5.2.3.1.2 Phase 1 Data

A total of five healthy subjects in phase 1 studies experienced syncope after receiving standard therapeutic doses of flibanserin; four are considered by the Division to be causally related to flibanserin. Reports of syncope occurring in the setting of concomitant use of ethanol or CYP3A4 inhibitors are discussed in sections 5.1.5.7.3 and 5.1.5.7.1, respectively. The case narratives of the four phase 1 subjects are provided below:

1. *Study 511.158 – subject #5*: A significant adverse event of syncope occurred in one of 13 female subjects enrolled in a phase 1 drug/drug-interaction (DDI) study of digoxin (trial 511.158). Subject #5 was a healthy 33 year-old women on no concomitant medications who suffered “circulatory collapse” (investigator’s verbatim term) and vomiting of severe intensity following the first dose of flibanserin 100 mg on Day 1 (prior to any administration of digoxin). This AE necessitated discontinuation from the study. The circulatory collapse, which started with syncope, occurred 29 minutes after flibanserin administration and continued for 2 hours. Vital signs at the time of the event were not recorded, but prior to the event supine blood pressure was 104/54 mmHg and heart rate was 71 beats per minute (bpm). The subject required medical treatment consisting of 500 mL intravenous (IV) fluids. Severe vomiting was reported 54 min after flibanserin

administration and occurred twice in a period of 15 min and was treated with IV diphenhydramine.

Division comment:

This event in Study 511.158 appears to be drug-related as the event coincided with flibanserin T_{max}.

2. *Study SPR-14-06-Subject # 1014:* A single subject experienced unresponsiveness in Study SPR-14-06, which evaluated the single-dose pharmacokinetics of a 100 mg oral dose of flibanserin in healthy premenopausal female volunteers who are poor metabolizers (PM) of either CYP2C9 or CYP2C19. Healthy premenopausal female volunteers who are extensive metabolizers (EM) of both CYP2C9 and CYP2C19 were included as controls to determine the extent to which these two isoenzymes are involved with flibanserin's metabolism.

Subject 1014, a 47-year-old Asian woman in the CYP2C19 PM group (weight, 50.4 kg; BMI, 19.2 kg/m²) received a single 100 mg dose of flibanserin, after an overnight fast. The subject reported the sudden onset of sleepiness 28 minutes after dosing. Shortly thereafter, she exhibited pallor, experienced nausea, and had retching for about 5 minutes, without emesis. While she was in a semi-recumbent position, she became unresponsive for about 1 minute. A blood pressure cuff was applied, and before the machine finished cycling, the subject had aroused with stimulation by a study nurse. She did not exhibit hypotension before or during the event (see Figure 2 below for supine blood pressure readings). The subject was unable to stand for measurement of orthostatic vital signs at 1 hour post-dose even with the assistance of the site staff. She was placed in bed, had recovered by 20 minutes later, and was able to stand for the orthostatic blood pressure measurement at 2 hours post-dose.

Figure 2. Vital Signs for Subject 1014 around time of loss of consciousness, Study SPR-14-06

Time Point	Time	Blood Pressure (mmHg)	Pulse Rate (bpm)
Predose	08:35	104/65	55
Unscheduled ^[a]	09:37	137/83	58
Unscheduled ^[a]	09:48	114/71	63
1 Hour Postdose	09:53	120/76	60
Unscheduled	09:57	119/73	55
Unscheduled	10:20	123/74	57
2 Hours Postdose	10:50	107/69	54

^[a] The event of unresponsive to stimuli had a start time of 09:45 and a stop time of 09:46.

Source: NDA 22-526 ser 0062, module 5.3.3.3 SPR-14-06 study report, p. 58.

Division Comment:

Given the CNS-related symptoms and signs in the absence of abnormalities in the vital signs, the investigator considered the events to represent a primary drug effect in the CNS, not

symptoms secondary to cardiovascular insufficiency. However, in this case, the patient was unable to stand so orthostatic hypotension cannot be excluded.

3. Study 511.88-subject #4: In this phase 1 study, a 41-year-old woman (of 14 women in the flibanserin treatment arm) received 100 mg of flibanserin daily for three days and was discontinued from the study due to syncope. The event occurred one hour after administration of 100 mg flibanserin on Day 3 of dosing, and lasted twenty seconds. No treatment was required for the event and she recovered. Vital signs at the time of syncope were not provided in the case report form.
4. Study 511.111-subject 11: A 40 year old white female experienced “circulatory collapse” (investigator verbatim term) and “fainting” approximately 20 minutes after administration of flibanserin 50 mg alone. The event lasted 40 minutes. Supine vital signs, obtained 25 minutes after the onset of symptoms, showed a blood pressure of 92/64 mmHg and pulse of 76 bpm. Standing vital signs were not recorded. Baseline vital signs were BP of 109/75 mmHg and pulse of 72 bpm. No medical therapy was initiated for the adverse event and the patient recovered. The event was coded as not serious, but causally related to study drug.
5. Study 511.87-subject 0013: An event of syncope occurred in a healthy 30-year-old woman experienced two episodes of vasovagal syncope of 5 minutes and 6 minutes duration, separated by an interval of 10 minutes. These syncope episodes occurred 96 hours after flibanserin 50 mg administration. The subject recovered with no sequelae and discontinued the study.

Division comment:

The large interval between flibanserin administration and syncope suggests etiologies other than drug for the event in this case.

5.2.3.2 Supra-therapeutic doses of flibanserin

5.2.3.2.1 Dedicated Study of supra-therapeutic doses of flibanserin

To assess the risk of syncope and hypotension associated with supra-therapeutic doses of flibanserin as might occur in the setting of inadvertent overdose or concomitant CYP3A4 inhibitor administration (refer to section 5.2.7.1 for discussion of CYP3A4 inhibitor interaction), the Applicant conducted a PK study of standard and supra-therapeutic single oral doses of flibanserin in twelve healthy pre-menopausal adult female subjects aged 18 through 50 years (Study SPR-12-04). The study was a single-center, two-stage investigation. In Stage one, 12 subjects were randomized to receive single doses of placebo, flibanserin 100 mg and flibanserin 200 mg in one of three treatment sequences (N=4 per cohort). Stage two involved two sequential ascending dose cohorts. Eight subjects were randomized in a 3:1 ratio to receive either flibanserin 250 mg or placebo (cohort 4), followed by flibanserin 300 mg or placebo (cohort 5).

Dose escalation was stopped after cohort 4 (flibanserin 250 mg) because a review of the blinded safety results showed that the protocol-specified stopping criteria had been met (i.e., 3 of 8 subjects experienced moderate or severe adverse events that were considered possibly or probably

related to study medication). The events in the three subjects were fatigue, severe somnolence and severe disorientation. Therefore, the planned testing of 300 mg flibanserin in Cohort 5 was not performed.

In this study, there were no deaths, serious adverse events or adverse events of syncope in any dose group. No subject discontinued because of an adverse event.

The percentage of individual subjects experiencing orthostatic changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse and clinically significant orthostatic vital signs (defined by this reviewer as SBP <90 mmHg or pulse >100 bpm) was greater among flibanserin-treated subjects than placebo (see Table 20). Only the incidence of pulse >100 bpm after changing posture appeared dose-proportional, although the incidence of pulse increase >20 bpm after changing posture was comparable across all tested flibanserin doses.

Division comment:

Orthostatic blood pressure and pulse were measured after subjects had remained standing for two minutes.

Table 20. Number of subjects meeting orthostatic criteria for SBP, DBP or pulse at any single post-dose time point, Study SPR-12-04

Parameter	Stage 1				Stage 2	
	100 mg	150 mg	200 mg	Placebo	250 mg	Placebo
N	8	8	7	12	6	2
SBP ↓>20 mmHg, N (%)	1 (13)	0	1 (14.3)	0	1 (17)	0
DBP ↓>20 mmHg, N (%)	1 (13)	0	0	0	0	0
Pulse, ↑ >20 bpm, N (%)	5 (63)	4 (50)	3 (43)	3 (24)	3 (50)	1 (50)
SBP <90 mmHg, N (%)	2 (25)	3 (38)	0	0	0	0
Pulse> 100 bpm, N (%)	2 (25)	2 (25)	3 (43)	0	3 (50)	0

The incidence of adverse events of dizziness and nausea increased in a dose proportional manner (see Table 21). Somnolence was common with all tested doses. The 250 mg flibanserin was the maximum tolerated dose.

Table 21. Incidence of adverse events by treatment administered, Study SPR-12-04

Preferred term	FLI 100 mg	FLI 150 mg	FLI 200 mg	Placebo	FLI 250 mg	Placebo
N	8	8	7	12	6	2
Any AE, N (%)	8 (100)	8 (100)	7 (100)	5 (42)	6 (100)	0 (0)
Somnolence, N (%)	6 (75)	5 (63)	6 (86)	5 (42)	5 (83)	0 (0)
Dizziness, N (%)	1 (13)	3 (38)	6 (86)	1 (8)	5 (83)	0 (0)
Nausea, N(%)	1 (13)	1 (13)	4 (57)	1 (8)	4 (67)	0 (0)

5.2.3.2.2 Other Phase 1 Data

There was one report of syncope in Study SPR-12-05, a study that compared the abuse potential of single doses of flibanserin administered at 100 mg (therapeutic dose) to supra-therapeutic doses (200 mg and 250 mg), a positive comparator (zolpidem at doses of 15 mg and 30 mg), and placebo. Syncope occurred in 1 of 35 subjects dosed with flibanserin 200 mg compared to 0 of 35 subjects receiving placebo. Subject #1048, experienced syncope one hour after dosing with flibanserin 200 mg. Semi-recumbent vital signs at the time of the event showed blood pressure of 120/71 mmHg and pulse of 84 bpm. Standing vital signs were not obtained.

In addition, 1 of 36 subjects receiving flibanserin 250 mg experienced an accidental fall resulting in right shoulder dislocation. The event occurred on the third day after treatment (i.e. during the washout period between doses). It is not clear whether the fall was preceded by syncope. The event was not considered by the investigator to be related to study drug.

Division Summary Comment:

- The updated pre-menopausal HSDD database shows a numerical imbalance in events of syncope, including serious events, associated with therapeutic doses of flibanserin. Event rates are low and differences between groups are small, but the observed findings are noteworthy and cannot be dismissed given the concerning cases of syncope seen with flibanserin in other settings, such as with alcohol and drug interactions.
- Tolerance to syncope does not appear to develop with continued therapy.
- Factors such as concomitant medication use or medical conditions that might increase the risk of syncope in flibanserin users have not yet been identified. In some affected subjects, there was no obvious risk factor.
- Alcohol use may increase the risk of syncope in both placebo and flibanserin-treated patients as the majority of subjects experiencing syncope were classified as “drinkers” at baseline. Data regarding alcohol use at the time of the events were not provided.
- The safety margin for flibanserin appears to be narrow, with flibanserin 250 mg being the maximum tolerated dose.
- The mechanism of syncope appears to be in some cases associated with a decrease in blood pressure (without an appropriate compensatory increase in heart rate), but may be due to central effects in other cases (i.e. profound CNS depression without associated hypotension).
- The Applicant’s risk mitigation proposal for syncope: The flibanserin package insert and Risk Evaluation Mitigation Strategy (REMS) documents (i.e., medication guide, communication plan, Dear Healthcare Professional Letters) caution that taking flibanserin in the morning, taking doses higher than recommended, or taking flibanserin with CYP3A4 inhibitors or with CNS depressants such as ethanol can result in potentially dangerous incidents of hypotension or syncope.

5.2.4 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; however, the sedative effects were mostly reversed by six hours post-dose. For this reason, in the initial submission, the Applicant examined safety data for adverse events (specifically, accidental injury) that could be related to an impairment in coordination or mental ability.

Review of the first submission found that the incidence of accidental injury was greater in the flibanserin 100 mg qhs dose group than in placebo in both HSDD safety databases analyzed – the phase 2/3, placebo-controlled, pre-menopausal HSDD trials and the double-blind portion of the randomized withdrawal trial 511.74 (see Table 22). The risk of accidental injury was a safety concern noted in both CR letters.

Table 22. Incidence of Accidental Injury*, First Cycle Review of NDA 22-526

User-defined AE category	Placebo	FLI 100 qhs
Phase 2/3 placebo-controlled HSDD trials		
Total N	1508	978
Accidental injury, N (%)	21 (1.4)	19 (1.9)
Double-blind portion of study 511.74 (randomized withdrawal trial)		
Total N	170	115
Accidental injury, N (%)	4 (2.3)	5 (4.3)

*Based on preferred terms identified by the Applicant as representing accidental injury

During the second cycle review, the updated pre-menopausal HSDD placebo-controlled safety database, which included data from a fifth phase 3 trial, was examined again for adverse events consistent with accidental injury using the MedDRA version 11.1 *Accidents and Injury* SMQ (see Section 6.1 for search terms). Events occurring prior to initiation of drug treatment were excluded. As found during the first cycle review, the incidence of accidental injury was slightly greater in the flibanserin 100 mg qhs group than with placebo, although the difference between flibanserin and placebo had narrowed. Serious accidental injury was also more common with flibanserin (see Table 23).

Table 23. Treatment emergent Accidental Injury (MedDRA 11.1 SMQ), phase 3 placebo-controlled HSDD trials in pre-menopausal women

	Placebo	FLI 100 mg qhs
Total N (%)	1905	1543
SMQ accidental injury	47 (2.5)	42 (2.7)
Serious accidental injury	1 (<0.1)	4 (0.3)

Division comment:

By the sponsor's analysis, the incidence of accidental injury was 2.1% for flibanserin 100 mg qhs vs. 2.0% for placebo. However, the sponsor's search did not include all terms contained in the MedDRA 11.1 Accidental Injury SMQ – specifically excluded were preferred terms of *animal bite, burns second degree, corneal abrasion, retinal tear, sunburn, thermal burn, tympanic membrane perforation and wound*. DBRUP's analysis considered all terms in the MedDRA 11.1 Accidental Injury SMQ.

The most common side effect of flibanserin is CNS depression (i.e. sedation, somnolence, fatigue). Syncope and hypotension are also possible risks of flibanserin. To determine whether accidental injury might be related to these risks, the Agency reviewer searched the phase 3 placebo-controlled pre-menopausal HSDD database for events of accidental injury then determined the proportion of these patients who reported an adverse event within 24 hours of the accident that coded to a MedDRA preferred term of *dizziness, somnolence, fatigue, hypotension, circulatory collapse, or sedation*. As shown in Table 24 of the patients who reported accidental injury, nearly three times as many reported corresponding CNS depression with flibanserin compared to placebo.

Table 24. Proportion of subjects experiencing concomitant accidental injury and CNS depression, phase 3, placebo-controlled pre-menopausal HSDD trials*

	Placebo	FLI 100 mg qhs
Total N (%)	1905	1543
N (%) with accidental injury	47 (2.5)	42 (2.7)
N (%) Accidental injury + CNS depression	4/47 (9.0)	10/42 (24.0)

*CNS depression identified based on preferred terms of dizziness, somnolence, fatigue, hypotension, circulatory collapse, and sedation

Division Summary Comment:

The updated pre-menopausal HSDD safety database of phase 3, placebo-controlled, pre-menopausal HSDD trials continues to show a slightly greater incidence of accidental injury that appears temporally associated with adverse events of CNS depression in the flibanserin 100 mg qhs dose group compared to placebo. The absolute difference is small (0.2% based on the FDA analysis). An imbalance not favoring flibanserin is also seen in the randomized withdrawal trial but the small number of events in this trial limits conclusions. It is not possible to exclude a small increase in the risk of accidental injury with the use of flibanserin in the phase 3 trials.

5.2.5 Next Day Driving Impairment

Because of flibanserin's sedative effects and long half-life, as well as concerns about an association between accidental injury and concomitant CNS depression in some patients, the Agency recommended that the Applicant conduct a next-day driving impairment study; the protocol was reviewed by the Division with input from the Division of Neurology Products. Results of Study SPR-14-01 are included in the current resubmission. The study was a randomized, multiple-dose, double-blind, placebo-controlled, 4-way, 4-period crossover study to evaluate pair-wise comparisons of the positive control, zopiclone 7.5 mg, placebo, flibanserin 100 mg and flibanserin 200 mg on simulated driving performance. Healthy pre-menopausal women not on any psychoactive medications were enrolled.

During each Treatment Period, subjects were dosed at bedtime with flibanserin, zopiclone or matching placebo the evening prior to testing (night 1). Cognitive testing and driving simulation began approximately 8.5 and 9 hours post dosing, respectively. Subjects then continued their assigned study dosing at home for approximately 5 days (nights 2 to 6). Prior to the Day 7 dose for each Treatment Period, subjects returned to the clinic to be dosed and remained in the clinic overnight. Subjects performed cognitive testing and driving simulation the morning after dosing.

Next-day simulated driving performance was assessed primarily by the standard deviation of lateral position (SDLP) using the Cognitive Research Center driving simulator (the CRCDS-MiniSim). Other measures included number of lane exceedances; speed deviation; incidence of speeding; ratio of speeds above the speed limit; average speed; a self-perceived safety to drive question; and a visual analog scale (VAS) to assess the subject's self-appraisal of their driving performance.

Results demonstrated that therapeutic and supra-therapeutic doses of flibanserin had no negative effect on the measures of next-day simulated driving performance that were evaluated.

Division comment:

The negative findings of the next-day driving impairment study are reassuring with regard to patients who take flibanserin at night without alcohol, who have exposures to flibanserin that approximate up to the 200 mg dose, and who drive 8.5 hours or later after the last dose.

5.2.6 Gastrointestinal AEs related to Altered Intestinal Motility

In the safety database reviewed during the first cycle, there were six adverse event reports of appendicitis occurring in flibanserin-treated subjects compared to none in the placebo group. At the time, the reason for this excess was unclear. There were no excess reports of intestinal obstruction in the flibanserin treatment groups, and none of the patients with appendicitis experienced adverse events of intestinal obstruction or constipation.

Since the first cycle review, DBRUP has become aware of the possibility that appendicitis may represent a class effect of drugs that are antagonists at the 5HT_{2A} receptor. The 5HT_{2A} receptor is prevalent in the smooth muscle cells of the GI tract.

The Agency reviewer searched the updated pre-menopausal HSDD phase 3 safety database and the post-menopausal HSDD phase 3 safety database for adverse events of diverticulitis (preferred terms containing *diverticulitis*), appendicitis (preferred terms containing *appendicitis*), gastrointestinal obstruction [using the *gastrointestinal obstruction* and the *gastrointestinal perforation* MedDRA version 11.1 standard MedDRA query (SMQ)] and gallbladder disorders (preferred terms within the *gallbladder related disorders* MedDRA version 11.1 SMQ). Results of this search are shown in Table 25.

Table 25. Incidence of Adverse Events related to Altered Intestinal Motility in Flibanserin pre-menopausal and Post-menopausal safety databases

	Placebo	FLI 25 mg bid	FLI 50 mg qhs	FLI 50 mg bid	FLI 100 mg qhs	FLI total
Pre-menopausal HSDD phase 3 placebo-controlled database (studies 511.70, .71, .75, .77 and .147)						
Total N	1905	733	969	728	1543	3973
Appendicitis	0	1 (0.1)	3 (0.3)	2 (0.3)	0	6 (0.2)
Diverticulitis	0	0	0	0	0	0
SMQ gastrointestinal obstruction	0	0	0	0	2 (0.1)	2 (0.1)
SMQ gallbladder related disorders	0	0	0	0	0	0 (0.0)
Post-menopausal HSDD phase 3 placebo-controlled database (studies 511.130, .156)						
Total N	849				843	843
Appendicitis	0				0	0
Diverticulitis	3 (0.4)				2 (0.2)	2 (0.2)
SMQ gastrointestinal obstruction	0				0	0
SMQ gallbladder related disorders	4 (0.5)				2 (0.2)	2 (0.2)

Division summary comment:

Of all gastrointestinal adverse events related to altered intestinal motility, only appendicitis and gastrointestinal obstruction occurred more frequently in flibanserin-treated subjects than in those receiving placebo. This discrepancy was observed in the phase 3, placebo-controlled, pre-menopausal HSDD database, but not in the phase 3 placebo-controlled trials in post-menopausal women.

The etiology of the increased incidence of appendicitis in pre-menopausal flibanserin-treated subjects remains unclear and could be due to chance alone or may represent a class effect of drugs that are antagonists at the 5HT_{2A} receptor.

The Applicant has proposed to conduct a post-approval observational pharmacoepidemiologic safety study using administrative healthcare claims data to assess any risk for less common adverse events such as appendicitis. Their proposal is under consideration.

5.2.7 Prescription and non-prescription drug interactions

5.2.7.1 CYP3A4 inhibitors

Flibanserin is metabolized primarily by the CYP3A4 enzyme. The original application contained results of a DDI study (study 511.111) of flibanserin 50 mg qhs administered alone or following

pre-treatment with the strong CYP3A4 inhibitor, ketoconazole. Exposure to flibanserin increased significantly following ketoconazole administration (AUC increased 4.5 times and C_{max} increased 1.9 times). The combination was also poorly tolerated by subjects.

In response to the first CR letter, the Applicant conducted a DDI study (Study SPR-12-01) of flibanserin 100 mg with a moderate CYP3A4 inhibitor. The study was an open-label, sequential-dose investigation of the effect of a single dose of grapefruit juice and multiple doses of fluconazole on the pharmacokinetics and tolerability of flibanserin 100 mg in healthy adult females. A total of 26 subjects were enrolled and were divided into two groups (15 in Group 1, 11 in Group 2), with dosing of Group 2 to begin three days after the first dose administration in Group 1. Each group was to receive flibanserin 100 mg alone, flibanserin 100 mg with 240 ml of grapefruit juice, fluconazole 400 mg alone, and flibanserin 100 mg plus fluconazole 200 mg (fluconazole had been administered for 4 days previously so was at steady state).

5.2.7.1.1 Pharmacokinetic results (DDI study with moderate CYP3A4 inhibitor)

Total and peak exposures of flibanserin increased significantly when administered with fluconazole at steady state. Flibanserin C_{max} increased 2.2-fold, and AUC increased 7.0-fold in the presence of steady-state concentrations of fluconazole. Mean flibanserin terminal half-life increased from 10 hours to 25 hours in the presence of fluconazole.

Administration of flibanserin with grapefruit juice had a modest effect on flibanserin AUC (38% increase) and no significant effect on C_{max} (10% increase).

Division comment:

The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.6-fold increase with ketoconazole, a strong CYP3A4 inhibitor. The exposure change with fluconazole was not anticipated because flibanserin was considered to be metabolized primarily by CYP3A4. Fluconazole is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor. According to the clinical pharmacology review team, these results suggest other enzymes may be involved in the metabolism of flibanserin. (Please review to clinical pharmacology briefing document for additional discussion of the metabolism of flibanserin).

5.2.7.1.2 Vital Signs (DDI study with moderate CYP3A4 inhibitor)

Seated vital signs (heart rate, blood pressure, respiratory rate, oral body temperature) were measured at Screening; Day -1; and Day 1, Day 3, and Day 10 at pre-dose, 1, 3, and 48 hours after dosing; at the follow-up visit, and once daily during outpatient clinic visits. Subjects on the combination of flibanserin + fluconazole were more likely to experience hypotension, defined as systolic blood pressure (SBP) < 90 mmHg, at any post-dose time point than subjects taking either drug alone (Table 26).

Orthostatic vital signs were not monitored during the trial.

Table 26. N (%) of hypotension or tachycardia at any post-dosing time point according to treatment administered, Study SPR-12-01

	FLI 100 mg alone	FLI 100 mg + GF juice	FLU alone	FLI 100 mg + FLU 200 mg (steady state)
Total N (%)	26 (100.0)	26 (100.0)	15 (100.0)	15 (100.0)
SBP < 90 mm Hg	0 (0.0)	1 (4.2)	0 (0.0)	4 (25.0)
Pulse > 100 bpm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

5.2.7.1.3 Adverse Events (DDI studies with moderate and strong CYP3A4 inhibitors)

There were no deaths in Study SPR-12-01 (moderate CYP3A4 inhibitor).

The study was terminated early because of hypotension-related AEs observed in three subjects in Group 1 following concomitant administration of fluconazole and flibanserin. All 15 subjects in the first group completed all treatments. However, the 11 subjects in the second group completed dosing only with flibanserin alone and with grapefruit juice.

Three adverse events of hypotension are notable and the narratives are provided below. All three events occurred within one hour following dosing with flibanserin 100 mg and fluconazole 200 mg (at steady state since this was the fifth day of fluconazole dosing).

Subject 1001: was a healthy 41-year-old white female who became unresponsive one hour after administration of flibanserin 100 mg with fluconazole 200 mg. Blood pressure at the time of the event was 64/41 mmHg and heart rate was 50 bpm. Oxygen saturation was 88%. Intravenous normal saline was administered and the patient was transported to the emergency department (ED).

Upon evaluation in the ED, the subject was resting but was unable to speak and was responsive only to painful stimuli and ammonia inhalant. The airway remained open and breathing was unlabored. ECG and clinical laboratory tests were normal. The patient improved over the next 3 hours and was then awake, alert, and oriented. Blood pressure subsequently stabilized at 97/53 mmHg and heart rate was 75 beats per minute.

Subject 1004: was a healthy 38 year-old female experienced hypotension (lowest blood pressure 80/49 mmHg) with pallor, nausea, and fatigue, beginning 36 minutes following dosing with flibanserin and fluconazole. The subject was placed supine with her feet elevated and she recovered. Duration of symptoms was approximately one hour.

Subject 1013: was a healthy 42 year-old female who became hypotensive (minimum blood pressure 73/41 mmHg) with associated fatigue and “feeling drugged” 45 minutes after dosing with flibanserin and fluconazole. She was placed supine with feet elevated and recovered. Duration of the event was 8 minutes.

In addition, some adverse events were more common when flibanserin was combined with fluconazole or grapefruit juice than when used alone, as shown in Figure 3. Fatigue was

exacerbated by the combination of flibanserin and grapefruit juice compared to flibanserin alone. Fatigue, nausea, hypotension and pallor are some of the adverse events that occurred more frequently with flibanserin+fluconazole compared to flibanserin alone or fluconazole alone.

Figure 3. Most common adverse events (i.e. >1 subject in any treatment group) according to treatment administered, Study SPR-12-01

Preferred term	FLI alone	FLI + GF juice	FLU alone	FLI+FLU
Total N	26	26	15	15
N with any AE	22 (84.6)	24 (92.3)	4 (26.7)	15 (100)
Fatigue	18 (69.2)	22 (84.6)	0	14 (93.3)
Dizziness	9 (34.6)	7 (26.9)	0	3 (20)
Nausea	7 (26.9)	5 (19.2)	0	11 (73.3)
Hiccups	2 (7.7)	0	0	4 (26.7)
Euphoric mood	4 (15.4)	1 (3.8)	0	4 (26.7)
Hypotension	2 (7.7)	0	0	3 (20)
Pallor	2 (7.7)	0	0	3 (20)

Source: NDA 22-526 ser 0039, Module 5.3.3.1, study report body-12-01, Table 9, p. 43.

In Study 511.111, a DDI study conducted to evaluate the effect of flibanserin when co-administered with ketoconazole, there were two cases of syncope, both occurring one hour following flibanserin administration. The first case, subject 11 who experienced syncope, was discussed previously in Section 5.2.3.1.2. The narrative of the second case follows:

Subject 13: was a 19 year old white female who experienced orthostatic hypotension (investigator verbatim term), followed immediately by orthostatic syncope (investigator verbatim term), one hour after administration of flibanserin 50 mg (she had already received multiple doses of ketoconazole 400 mg). The patient had reported dizziness and fatigue five minutes before the orthostatic hypotension. The duration of orthostatic hypotension was 15 minutes and syncope lasted one minute. Supine vital signs immediately prior to the event showed a blood pressure of 113/70 mmHg and pulse of 84 bpm. Vital signs were not recorded during the event. No therapy was administered for the adverse event and the subject recovered. The investigator considered the events to be drug-related.

Division comment:

Presumably the event was defined as “orthostatic hypotension” because the patient was lightheaded and dizzy while standing, although this is not explicitly stated in the case report form.

Division’s Summary Comment:

- Strong CYP3A4 inhibitors (e.g., ketoconazole) increase systemic exposure to flibanserin over 4-fold, and the combination of flibanserin with strong CYP3A4 inhibitors is poorly tolerated.
- Fluconazole, which is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor, increases systemic exposure to flibanserin 7-fold. The combination of flibanserin with fluconazole is associated with an increased risk of syncope and hypotension which may result in serious injuries. The interaction with fluconazole suggested that other enzymes were involved in flibanserin metabolism. A subsequent phase 1 study of the pharmacokinetics of flibanserin in relation to CYP2C19 and CYP2C9 genotypes demonstrated that flibanserin is partially metabolized by CYP2C19 but not by

CYP2C9 (please refer to the clinical pharmacology briefing document for further discussion of this issue).

- The Applicant proposes a labeled contraindication against combined use of flibanserin with moderate or strong CYP3A4 inhibitors.

5.2.7.2 Selective Serotonin Reuptake Inhibitors and Selective Norepinephrine Reuptake Inhibitors (SSRI/SNRI)

5.2.7.2.1 *Dedicated study of flibanserin with SSRI/SNRI's*

The original Applicant, Boehringer Ingelheim, initiated a dedicated, double-blind, placebo-controlled study to assess the safety of concomitant use of flibanserin 100 mg daily in patients taking an SSRI or SNRI. The trial was terminated early by BI and prior to reaching the intended number of randomized patients when the decision was made to divest the product. Subjects who had already enrolled however were followed through study completion.

This trial was a prospective, multi-center, 12-week, randomized, double-blind, placebo-controlled, parallel group study that compared the effects of flibanserin to placebo in premenopausal women, 18 to 50 years of age, who were taking an SSRI or SNRI for mild depression, and who had symptoms of decreased sexual desire and related distress as determined by the Clinical Interview of FSD- Depression and criteria in the DSM-IV text revision (DSM-IV-TR) for at least four weeks prior to the screen visit.

Division comment:

Approximately 24% of subjects in the study had HSDD as their primary sexual dysfunction diagnosis.

In addition to their existing SSRI/SNRI medications, eligible subjects were to be randomized in a 1:1:1 ratio to receive:

- Flibanserin 50 mg qhs x 2 weeks with up-titration to 100 mg qhs
- Flibanserin 100 mg qhs x 12 weeks
- Placebo qhs x 12 weeks

Following the 12-week double-blind treatment period, subjects completed a one week, post-treatment assessment for adverse events occurring upon abrupt withdrawal of flibanserin.

No deaths or serious adverse events occurred during the study.

The frequency of any adverse event was similar across treatment groups. Flibanserin slightly increased the incidence of dizziness (3/72, 4.2%), and insomnia (4/72, 5.5%) compared to an SSRI/SNRI alone (dizziness 0/38; insomnia 1/38, 2.6%). Suicidal ideation and suicidal behavior were assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) at each clinic visit throughout the trial. No patients indicated a positive response on the C-SSRS for suicide behavior or suicidal ideation during the double-blind treatment and post-treatment periods.

Depression and anxiety symptoms were evaluated by the Quick Inventory of Depressive

Symptomatology Self-Report (QIDS-SR16) and the Beck Anxiety Inventory (BAI), respectively, at each clinic visit throughout the trial. Addition of flibanserin to SSRI/SNRI therapy did not appear to exacerbate depression or anxiety symptoms.

5.2.7.2.2 *Placebo-controlled Phase 3 trial data*

Concomitant use of SS/NRIs was prohibited per protocol in the phase 3 placebo-controlled trials in the original NDA and in study 511.147. Still, a small portion of subjects used these medications. The most common adverse events (i.e., occurring in > 3 subjects) in the FLI+SS/NRI group are shown in Figure 4.

Figure 4. N (%) of treatment-emergent adverse events in phase 3, placebo-controlled HSDD trials in premenopausal women according to baseline concomitant use of SSRI or SNRI medications

	FLI 100 qhs + SS/NRI	FLI 100 qhs	Placebo + SS/NRI	Placebo
Total N	38	1486	32	1841
Any adverse event	34 (89.5)	990 (66.6)	28 (87.5)	1026 (55.7)
Depression	7 (18.4)	8 (0.5)	6 (18.8)	10 (0.5)
Somnolence	6 (15.8)	167 (11.2)	3 (9.4)	56 (3.0)
Anxiety	6 (15.8)	20 (1.3)	1 (3.1)	16 (0.9)
Fatigue	5 (13.2)	135 (9.1)	3 (9.4)	90 (4.9)
Insomnia	5 (13.2)	70 (4.7)	3 (9.4)	43 (2.3)
Dizziness	5 (13.2)	169 (11.4)	1 (3.1)	40 (2.2)
Headache	4 (10.5)	141 (9.5)	4 (12.5)	140 (7.6)
UTI	3 (7.9)	32 (2.2)	0	44 (2.4)

Source: NDA 22-526 ser 0039, Module 5.3.5.3, ISS, Table 5.5.3, p. 18766.

Division comment:

Adverse events exacerbated by concomitant use of flibanserin with an SS/NRI were anxiety, somnolence, fatigue, insomnia, and dizziness. These results are consistent with those observed in the trial dedicated to study the combination of flibanserin with an SS/NRI.

The findings presented in Section 5.2.7.2 should not preclude concomitant use but consideration should be given to incorporating the key findings into labeling should flibanserin be approved.

5.2.7.3 Alcohol

5.2.7.3.1 Dedicated DDI Study

Review of phase 3, pre-menopausal HSDD safety data included in the first submission found that combined use of alcohol with flibanserin increased the frequency of adverse events related to CNS depression. The Agency recommended that the Applicant conduct a dedicated DDI study of flibanserin with ethanol.

The first Complete Response submission contained results of Study SPR-12-03, a single-center, randomized, double-blind, single-dose, crossover study of the effect of concomitant alcohol intake on flibanserin tolerability and safety in healthy adult subjects with a history of moderate alcohol intake (average of approximately 5 to 21 units of alcohol per week). Twenty-five subjects (23 males and 2 females) were randomly assigned to 1 of 5 sequence groups (5 subjects per sequence) and subjects within each sequence group received the following treatments:

- **Treatment A:** 0.8 g/kg ethanol (95%) diluted in 240 mL (total volume) with orange juice and administered orally with 1 over-encapsulated Flibanserin tablet 100 mg.
- **Treatment B:** 0.8 g/kg ethanol (95%) diluted in 240 mL (total volume) with orange juice and administered orally with 1 matching placebo capsule.
- **Treatment C:** 0.4 g/kg ethanol (95%) diluted in 240 mL (total volume) with orange juice and administered orally with 1 over-encapsulated Flibanserin tablet 100 mg.
- **Treatment D:** 0.4 g/kg ethanol (95%) diluted in 240 mL (total volume) with orange juice and administered orally with 1 matching placebo capsule.
- **Treatment E:** 240 mL of orange juice administered orally with 1 over-encapsulated Flibanserin tablet 100 mg.

Alcohol (or orange juice) was to be consumed over 10 minutes.

Division comments:

One unit of alcohol is equivalent to 14 gm of alcohol, or the amount of alcohol contained in 12 oz beer, 5 oz wine or 1.5 oz of 80-proof spirits. Therefore, eligible subjects should report consumption of 5 to 21 drinks per week or $\frac{3}{4}$ to 3 drinks per day. A dose of 0.8 g/kg ethanol in a 70 kg adult would approximately equal 4 drinks (i.e., 56 grams of alcohol).

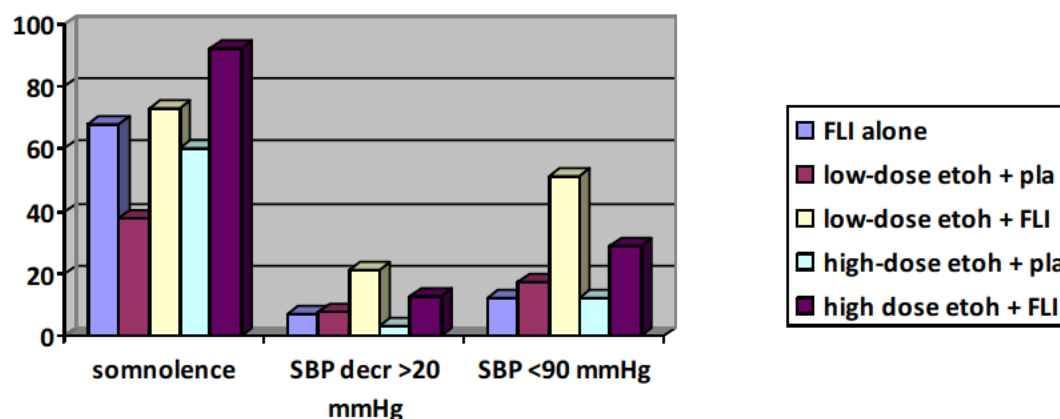
The Applicant reportedly had difficulty recruiting female subjects who were moderate drinkers, which accounts for the trial enrolling mostly males.

Subjects remained in the study clinic for the duration of each dosing period. Seated vital signs (blood pressure, pulse and respiration rate after sitting for at least 5 minutes), orthostatic vital signs (blood pressure and pulse after standing for 2 minutes) and oxygen saturation were measured at screening, pre-dose and at multiple time points up to 24 hours post-dosing. To assess for sedation, subjects completed a visual analog scale (VAS) on Day 1 of each period at pre-dose and at 0.5, 1, 1.5, 2 and 4 hours post-dose.

As shown in Figure 5, somnolence and clinically significant decreases in systolic blood pressure were exacerbated by concomitant administration of flibanserin and alcohol. Notably, the

incidence of somnolence was greater with flibanserin alone than with either low or high dose alcohol alone.

Figure 5. Percentage of subjects experiencing select adverse events according to treatment group, Flibanserin-Etoh DDI study, SPR-12-03



Four subjects experienced symptomatic hypotension, all following administration of flibanserin with low-dose alcohol. Key details for each event are shown in Table 27.

Table 27. Individual Adverse Events of Symptomatic Hypotension, Flibanserin-ETOH DDI Study, SPR-12-03

Subject ID/age, race, gender	Time post-dose	AE preferred term	Baseline vital signs	Vital signs at time of event	Treatment given
1030/52 yo WM	2 hours	Orthostatic hypotension	108/79 mmHg, 74 bpm	72/44 mmHg, 68 bpm (standing)	Trendelenberg position
1009/22 yo WM	1.5 hours	Hypotension, somnolence	142/91 mmHg, 75 bpm	85/43 mmHg, 68 bpm (standing) 92/60, 60 bpm (semi-recumbent)	Placed supine
1020/26 yo BM	2 hours	Syncope	133/77 mmHg, 77 bpm	162/64 mmHg, 60 bpm	Placed supine, legs elevated, ammonia inhalant
	3 hours	Syncope		83/49 mmHg, 53 bpm	
1013/22yo WM	4 hours	Dizziness	109/74 mmHg, 70 bpm	82/64 mm Hg, 81 bpm (standing), 114/74 mmHg, 62 bpm (semi-recumbent)	Placed supine

5.2.7.3.2 Phase 3 Clinical Trials Database

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 or quantified during the treatment phase of the studies.

The updated pre-menopausal HSDD phase 3 safety database was analyzed for any difference in adverse event rates based on baseline reported drinking status. As shown in Table 28, CNS adverse events (bolded in the table below) were most frequent among drinkers assigned to flibanserin 100 mg qhs than among any other sub-group. Syncope and pre-syncope was also most common in that group. Alcohol use status did not impact the incidence of accidental injury.

Table 28 Most Common treatment emergent Adverse Events (i.e., incidence >3% in flibanserin drinker treatment groups) and incidence of syncope and accidental injury SMQ according to baseline drinking status, phase 3, placebo-controlled HSDD trials in pre-menopausal women

	FLI 100 mg qhs		Placebo	
	Drinker n (%)	Non-drinker n (%)	Drinker n (%)	Non-drinker n (%)
Total N	898	645	1212	693
Any adverse event	695 (57.3)	357 (53.0)	637 (70.9)	396 (61.4)
Fatigue	97 (10.8)	45 (7.0)	69 (5.7)	26 (3.8)
Dizziness	115 (12.8)	61 (9.5)	26 (2.1)	15 (2.2)
Somnolence	98 (10.9)	75 (11.6)	33 (2.7)	26 (3.8)
Insomnia	52 (5.8)	23 (3.6)	29 (2.4)	17 (2.5)
Syncope/pre-syncope	7 (0.8)	1 (0.2)	4 (0.3)	2 (0.2)
Accidental injury SMQ	25 (2.8)	17 (2.6)	25 (2.1)	21 (3.0)

Division’s Summary Comments Regarding Concomitant Administration of Flibanserin and Alcohol:

- In the phase 1 DDI study, alcohol, consumed over 10 minutes and combined with flibanserin, increased the incidence of somnolence, orthostatic hypotension and syncope.
- In the phase 3 pre-menopausal HSDD database, patients were classified as drinkers or non-drinkers based on self-reported alcohol use at baseline. In this database, the incidence of syncope/pre-syncope and dizziness was similar among placebo drinkers and non-drinkers but greater among flibanserin drinkers compared to flibanserin non-drinkers.
- Patients who, in general, drink less alcohol than moderate drinkers may have a more dramatic response if flibanserin and alcohol are used together because the liver in these patients will be less efficient at metabolizing alcohol.
- The dedicated DDI study population was predominantly male (23 of 25 subjects). The effect of the combination of flibanserin and ethanol may be more pronounced in females.
- The Applicant’s proposed draft label includes a warning regarding the risks of CNS depression, hypotension and syncope associated with co-administration of flibanserin with alcohol. The Committee will be asked to discuss whether the use of alcohol should be contraindicated in product labeling, and whether a risk mitigation and management strategy (REMS) is required to ensure safe use of flibanserin, if approved.

5.2.7.4 Hormonal Contraceptives (mild CYP3A4 inhibitors)

Hormonal contraceptive products (HCP's) are known to be weak CYP3A4 inhibitors.⁵ During the first cycle review it was noted that women taking both flibanserin and hormonal contraceptives tended to have higher rates of adverse events than those taking HCP's and placebo.

In the first complete response submission, adverse event data were stratified by concomitant use of hormonal contraceptives (includes all methods of delivery, including oral 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 which 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 Figure 6.

Figure 6. N (%) of most common treatment emergent adverse events (i.e., >3%) in FLI + HCP combination group and comparative incidence in other treatment groups, phase 3, placebo-controlled HSDD trials in premenopausal women

	FLI 100 qhs	FLI 100 qhs + HC	Placebo	Placebo + HC
Total N	865	659	1066	807
Any adverse event	566 (65.4)	458 (69.5)	597 (56.0)	457 (56.6)
Nausea	86 (9.9)	75 (11.4)	35 (3.3)	35 (4.3)
Dizziness	86 (9.9)	88 (13.4)	22 (2.1)	19 (2.4)
Somnolence	92 (10.6)	81 (12.3)	32 (3.0)	27 (3.3)
Fatigue	55 (7.5)	75 (11.4)	52 (4.9)	41 (5.1)
Headache	78 (9.0)	67 (10.2)	84 (7.9)	60 (7.4)
Nasopharyngitis	39 (4.5)	39 (5.9)	50 (4.7)	50 (6.2)
URI	34 (3.9)	36 (5.5)	32 (3.0)	26 (3.2)
Insomnia	40 (5.6)	35 (5.3)	29 (2.7)	17 (2.1)
Sinusitis	20 (2.3)	25 (3.8)	35 (3.3)	29 (3.6)

Source: NDA 22-526 ser 0062, Module 5.3.5.3, ISS, Table 5.2.1, p. 17903.

Division comment:

- The incidences of somnolence, dizziness and fatigue were greater among flibanserin treated patients who were on HCs than those who were not (whereas placebo treated patients on HCs and those not on HCs had comparable incidences of somnolence, dizziness and fatigue).

⁵ Retrieved on July 9, 2013, from <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>

This interaction between flibanserin and HCs may be due to HC's weak inhibition of the CYP3A4 enzyme, which increases flibanserin exposures by about 40%. Should the application be approved, the label should caution providers regarding the increased incidence of certain adverse events in the setting of combined use of flibanserin with hormonal contraceptives.

- The Applicant's proposed label for flibanserin contains a statement in Section 7, Drug Interactions, that "Patients taking mild CYP3A4 inhibitors (e.g., oral contraceptives) should be advised of the increased risk of dizziness, somnolence, and fatigue. "

5.2.7.5 Triptans

Triptans are 5HT_{1B} and 5HT_{1D} receptor agonists that are used for treating migraine headaches. Because of their serotonergic activity, there was some concern that co-administration of flibanserin with a triptan could exacerbate serotonergic adverse events.

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 3.3% of placebo treated subjects used triptans during the studies. Treatment-emergent adverse events that are exacerbated when flibanserin was taken concomitantly with triptans identified from the placebo-controlled, HSDD phase 3 database are shown in Table 29.

Table 29. Treatment-emergent adverse events exacerbated by reported triptan use—phase 3, placebo-Controlled HSDD Trials in pre-menopausal women

	FLI 100 qhs N = 1469	FLI 100 qhs + triptan N = 55	PLACEBO N = 1812	PLACEBO + triptan N = 61
	n (%)	n (%)	n (%)	n (%)
Any Adverse Event	978 (66.6)	46 (83.6)	1012 (55.8)	42 (68.9)
Somnolence	164 (11.2)	9 (16.4)	56 (3.1)	3 (4.9)
URI	65 (4.4)	5 (9.1)	57 (3.1)	1 (1.6)

Source: NDA 22-526 ser 0039, Module 5.3.5.3, ISS Update, Table 5.6.1, p. 19203.

Division Comment:

Concomitant use of flibanserin with a triptan increased the incidence of somnolence and URI over use of either drug alone.

Division's Summary Comments Regarding Drug-Drug Interactions: CYP3A4 inhibitors

- Concomitant administration of strong CYP3A4 inhibitors with flibanserin (at 50 mg qhs) led 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 when the drugs were combined.
- Fluconazole, which is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor, increases systemic exposure to flibanserin 7-fold. In addition, the combination of flibanserin with fluconazole increased the risk of syncope and

hypotension and resulted in one serious adverse event of loss of consciousness and two events of symptomatic hypotension requiring intervention.

- The Applicant is proposing a contraindication for concomitant use of flibanserin with a strong or moderate CYP3A4 inhibitor.
- A dedicated DDI study of flibanserin with a mild CYP3A4 inhibitor has not been done. Data on the combination of flibanserin with hormonal contraceptives, which are known to be mild CYP3A4 inhibitors, suggest that mild inhibitors may increase common adverse events by virtue of increasing systemic exposure. A meta-analysis conducted by the Applicant suggests that flibanserin exposure increases with concomitant hormonal contraceptive use by approximately 40%.

Ethanol

Ethanol combined with flibanserin increases the risk of somnolence and fatigue, orthostatic hypotension and syncope. Patients who, in general, drink less alcohol than moderate drinkers may have a more dramatic response if flibanserin and alcohol are used together because the liver in these patients will be less efficient at metabolizing alcohol. Because of the risk of injury associated with these adverse events, the Committee will be asked to discuss whether the use of alcohol should be contraindicated in product labeling, and whether a risk evaluation and mitigation strategy (REMS) is required to ensure safe use of flibanserin, if approved.

SS/NRIs

- The combination of flibanserin with an SS/NRI exacerbated dizziness and insomnia but does not appear to worsen psychiatric symptoms based on data obtained from the phase 3 study of flibanserin in women taking an SSRI or SNRI.
- In the phase 3 placebo-controlled trials, adverse events exacerbated by concomitant use of flibanserin with an SS/NRI were anxiety, somnolence, fatigue, insomnia, and dizziness.
- These findings should not preclude concomitant use but consideration should be given to incorporating the key findings into labeling if flibanserin is approved.

Hormonal Contraceptives

The incidences of somnolence, dizziness and fatigue were greater among flibanserin treated patients who were on HCs than those who were not (whereas placebo treated patients on HCs and those not on HCs had comparable incidences of somnolence, dizziness and fatigue). This interaction between flibanserin and HCs may be due to HC's weak inhibition of the CYP3A4 enzyme, which increases flibanserin exposures by about 40%. Should the application be approved, the label should caution providers regarding the increased incidence of certain adverse events in the setting of combined use of flibanserin with hormonal contraceptives.

Triptans

Concomitant use of flibanserin with a triptan increased the frequency of somnolence and URI over use of either drug alone. This finding does not preclude concomitant use of the drugs, but consideration should be given to including this information in labeling should flibanserin be approved.

5.3 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. Adverse events that occurred more frequently following flibanserin 100 mg qhs discontinuation are shown in Table 30.

Table 30. Frequency of Subjects with Adverse Events Following Treatment Discontinuation – phase 3, placebo-controlled HSDD Trials in pre-menopausal women

AE category (SMQ) or Preferred Term (PT)	Post-Placebo	Post-100 qhs
Phase 3 placebo-controlled HSDD trials		
Total N (%)	1360 (100)	1001 (100)
Vomiting	3 (0.2)	5 (0.5)
Depression (SMQ)	6 (0.4)	7 (0.7)
Insomnia	4 (0.3)	4 (0.4)
Anxiety	1 (0.1)	2 (0.2)

Source: NDA 22526 ser 0039, ISS update, Tables 5.7.1 and 5.7.2, pp 3095-3110

Division comment:

The data suggest that adverse events of vomiting, depression, insomnia and anxiety, occur at slightly greater frequency in the 4 weeks following discontinuation of flibanserin 100 mg qhs than placebo, although event rates are low. If the drug is approved, consideration should be given to including this information in labeling.

5.4 Human Carcinogenicity

Findings from the 2-year mouse carcinogenicity study are discussed in Section 2.1.1. Although there were no events of breast cancer in the pre-menopausal phase 3 controlled clinical trials, the duration of the trials (up to 6 months) is insufficient to characterize the incidence of neoplasms related to chronic use of flibanserin.

Division comments:

The mechanism of mammary tumor development in mice is not known. Absence of tumorigenicity in rats is reassuring but cannot completely exclude a clinical risk. The pharmacology/toxicology review team does not envision any additional nonclinical studies that would clarify the risk.

It has been estimated that 12.4% of U.S. women will be diagnosed with breast cancer in their lifetime. Even if the drug were labeled to exclude use in women with a personal or family history of breast cancer, a large population of women may be exposed at uncertain risk.

The Applicant proposes to conduct a post-approval observational pharmacoepidemiologic safety study using administrative healthcare claims data to assess any risk for less common adverse events such as breast cancer. Their proposal is under consideration.

5.5 Safety Conclusions

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

- Dizziness, somnolence and nausea were the most frequently reported adverse events and each occurred in approximately 11% of subjects treated with flibanserin 100 mg qhs compared to 2-3% treated with placebo during the phase 3 placebo-controlled pre-menopausal HSDD trials.
- Events consistent with CNS depression (i.e., fatigue, somnolence, sedation) occurred in nearly 21% of subjects receiving flibanserin 100 mg qhs and at a rate three times greater than placebo.
- There is an increased risk of syncope, including serious events, associated with therapeutic doses of flibanserin. Tolerance to syncope does not appear to develop with continued therapy. The risk of syncope increases in the setting of supra-therapeutic exposure to flibanserin (e.g., when administered with fluconazole or with a strong CYP3A4 inhibitors) or with alcohol use.
- There is a slightly greater incidence of accidental injury in the flibanserin 100 mg qhs dose group compared to placebo across pre-menopausal HSDD safety databases. The negative findings of the next-day driving impairment study are reassuring with regard to patients who take flibanserin at night without alcohol, who have exposures to flibanserin that approximate up to the 200 mg dose, and who drive 8.5 hours or later after the last dose.
- Flibanserin is poorly tolerated when administered with fluconazole and with strong CYP3A4 inhibitors and the combination increases the risk of syncope and symptomatic hypotension.
- Ethanol combined with flibanserin significantly increases the risk of somnolence, fatigue, orthostatic hypotension and syncope.
- Adverse events mapping to the MedDRA Depression SMQ were more common among flibanserin treated subjects than placebo, and the incidence is dose-proportional. However, there is no signal of an association between flibanserin treatment and suicidality. Flibanserin also did not exacerbate depression or anxiety in patients taking SSRI or SNRI medication.
- Tolerability of flibanserin was adversely affected when it was administered with commonly used prescription drugs such as SSRIs, triptans, and hormonal contraceptives.
- Serious adverse events of appendicitis occurred more commonly among flibanserin treated subjects than placebo and may represent a class effect of 5HT_{2A} antagonism.

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 the protocols prohibited an extensive list of concomitant medications, as listed in Section 6.2. Generalizability of existing safety findings to the general population taking these concomitant prescription drugs or with significant medical histories is unknown.
- There exists a risk of clinically significant adverse events of accidental injury and syncope associated with therapeutic doses of flibanserin. Those risks increase further in the setting

of supra-therapeutic exposure to flibanserin (as may occur with drug-drug interactions), or when the product is taken with alcohol.

- In the pivotal Phase 3 trials, the efficacy for flibanserin appeared to plateau at 8-16 weeks for the key endpoints evaluated. However, the risks of CNS depression appear highest in the first month after initiating therapy based on Phase 3 data.

6 Appendices

6.1 Preferred Terms in MedDRA version 11.1 Accidental Injury SMQ

Abdomen crushing,	Joint dislocation	Rib fracture
Burns third degree,	Penis reattachment	Diffuse axonal injury
Burns first degree,	Atrial rupture	Flail chest
Nerve root injury lumbar,	Comminuted fracture	Liver injury
Abdominal injury	Joint hyperextension	Road traffic accident
Bursa injury	Peripheral nerve injury	Dislocation of sternum
Burns fourth degree	Avulsion fracture	Foot fracture
Nerve root injury sacral	Complicated fracture	Lower limb fracture
Accident	Joint injury	Scapula fracture
Buttock crushing	Peroneal nerve injury	Dislocation of vertebra
Burns second degree	Axillary nerve injury	Decapitation
Nerve root injury thoracic	Compression fracture	Lumbar vertebral fracture
Accident at home	Joint sprain	Sciatic nerve injury
Cartilage injury	Pharyngeal injury	Drowning
Humerus fracture	Back crushing	Diaphragmatic injury
Oesophageal injury	Concussion	Lumbosacral plexus injury
Accident at work	Kidney rupture	Scratch
Cataract traumatic	Photoelectric conjunctivitis	Dural tear
Hyphaema	Back injury	Diaphragmatic rupture
Oesophageal rupture	Conjunctival abrasion	Lung injury
Accidental death	Laceration	Severed digit reimplantation
Caustic injury	Pneumothorax traumatic	Ear abrasion
IIIrd nerve injury	Bile duct stenosis traumatic	Forearm fracture
Open fracture	Contusion	Lymphatic duct rupture
Accidental needle stick	Laryngeal injury	Sinus tarsi syndrome
Cerebral haemorrhage traumatic	Posterior capsule rupture	Ear canal abrasion
Ilium fracture	Bladder injury	Foreign body in eye
Optic nerve injury	Corneal abrasion	Median nerve injury
Acetabulum fracture	Ligament injury	Skeletal injury
Cervical vertebral fracture	Posterior tibial nerve injury	Ear canal injury
Impacted fracture	Bladder perforation	Foreign body trauma
Optic pathway injury	Cranial nerve injury	Mouth injury
Acoustic shock	Ligament rupture	Skin injury
Chemical burn of skin	Post-traumatic headache	Ear canal stenosis traumatic
Injury	Blast injury	Fracture
Pancreatic injury	Crush injury	Multiple fractures
Adrenal gland injury	Ligament sprain	Skin laceration
Chemical burns of eye	Pubic rami fracture	Ear injury
Injury corneal	Blindness traumatic	Fracture displacement
Patella fracture	Jaw fracture	Multiple injuries
Anal injury	Penis injury	Skull fracture
Chemical eye injury	Arterial rupture	Electric shock
Internal injury	Colon injury	Fracture of penis
Pelvic fracture	Crush syndrome	Muscle injury
Ankle fracture	Limb crushing injury	Skull fractured base
Chemical injury	Radial nerve injury	Electrocution
Intervertebral disc injury	Brachial plexus injury	Fractured coccyx
Pelvic organ injury	Crushing injury of trunk	Muscle reattachment
Aortic injury	Limb injury	Soft tissue injury

Accidental Injury SMQ Preferred Terms, continued.

Chest crushing	Radius fracture	Enophthalmos traumatic
Iris injury	Brain contusion	Fractured ischium
Penetrating abdominal trauma	Deafness traumatic	Muscle rupture
Aortic rupture	Limb reattachment surgery	Spinal compression fracture
Chest injury	Retinal injury	Epiphyseal fracture
IVth nerve injury	Breast injury	Fractured sacrum
Penetrating eye injury repair	Fibula fracture	Muscle strain
Arterial injury	Limb traumatic amputation	Spinal cord injury
Clavicle fracture	Traumatic shock	External genitalia crushing
Nerve injury	Urinary tract injury	Fractured skull depressed
Splenic injury	Tibia fracture	Musculocutaneous nerve injury
Facial bones fracture	Traumatic arthropathy	Spinal cord injury cauda equina
Haematuria traumatic	Traumatic spinal cord compression	Eye burns
Nerve root injury	Vaginal laceration	Gallbladder injury
Splenic rupture	Tongue injury	Myocardial rupture
Fall	Traumatic brain injury	Spinal cord injury cervical
Hand fracture	Traumatic torticollis	Eye injury
Nerve root injury cervical	Vascular injury	Gastrointestinal injury
Splinter	Tooth avulsion	Nail avulsion
Femoral neck fracture	Acrotrophodynia	Spinal cord injury lumbar
Head injury	Traumatic ulcer	Eye penetration
Spondylopathy traumatic	Vascular rupture	Genital injury
Sternal fracture	Wrist fracture	Nail injury
Femoral nerve injury	Animal bite	Spinal cord injury sacral
Hepatic rupture	Ulna fracture	Eyeball avulsion
Sports injury	Traumatic coma	Gingival injury
Sternal injury	Stress fracture	Near drowning
Femur fracture	Tendon injury	Spinal cord injury thoracic
Hip fracture	Tooth injury	Eyeball rupture
Tooth fracture	Traumatic fracture	Glaucoma traumatic
Struck by lightning	Testicular injury	Neck crushing
Tendon rupture	Tracheal injury	Spinal fracture
Torus fracture	Traumatic haemorrhage	Face crushing
Traumatic haematoma	Superficial injury of eye	Greenstick fracture
Sunburn	Thermal burn	Neck injury
Sympathetic nerve injury	Traumatic amputation	Spinal shock
Thermal burns of eye	Traumatic intracranial haemorrhage	Face injury
Traumatic anuria		Gun shot wound
Traumatic liver injury		Tympanic membrane perforation
Urinary bladder rupture		Synovial rupture
Thoracic vertebral fracture		
Traumatic arthritis		

Source: Standardized MedDRA Query (SMQ) Version 11.1, Accidental Injury SMQ, MedDRA Web-based Browser at www.meddra.org

6.2 Preferred Terms in MedDRA version 11.1 Suicide/Self-Injury SMQ

Completed suicide	Multiple drug overdose	Suicidal behaviour
Depression suicidal	intentional	Suicidal ideation
Intentional overdose	Poisoning deliberate	Suicide attempt
Intentional self-injury	Self injurious behaviour	
	Self-injurious ideation	

Source: Standardized MedDRA Query (SMQ) Version 11.1, Depression and Suicide/Self-Injury, MedDRA Web-based Browser at www.meddra.org

6.3 Preferred Terms in MedDRA version 11.1 Depression SMQ

Depression	Dysphoria	Drug abuser
Depression postoperative	Dysthymic disorder	Drug dependence
Depressive symptom	Electroconvulsive therapy	Drug dependence, antepartum
Constricted affect	Feeling guilty	Drug dependence, postpartum
Alcoholism	Feeling of despair	Dyssomnia
Apathy	Feelings of worthlessness	Early morning awakening
Blunted affect	Major depression	Emotional distress
Middle insomnia	Menopausal depression	Hypersomnia
Mood swings	Postpartum depression	Hyposomnia
Negative thoughts	Affect lability	Impaired self-care
Polysubstance dependence	Alcohol abuse	Initial insomnia
Psychomotor hyperactivity	Alcohol problem	Intentional drug misuse
	Alcohol rehabilitation	Listless
	Crying	Maternal use of illicit drugs
	Disturbance in attention	Memory impairment
	Drug abuse	Psychosocial support
	Mood altered	Psychotherapy
	Morose	Self esteem decreased
	Neglect of personal appearance	Substance abuse
	Poor quality sleep	Substance abuser
	Psychomotor retardation	Tearfulness

Source: Standardized MedDRA Query (SMQ) Version 11.1, Depression and Suicide/Self-Injury SMQ, MedDRA Web-based Browser at www.meddra.org

6.4 List of Prohibited Medications

6.4.1 Medications prohibited in phase 3 study 511.147

- **CYP 3A4 inducers, including, but not limited to:**
- *Aminoglutethimide, dexamethasone, modafinil, nafcillin, rifampin, rifabutin, rifapentine*
- **opamine-receptor agonists and other anti-parkinsonian drugs, including but not limited to:**
- **All anti-epileptic drugs**
- **All hormonal agonists/antagonists** (*androgens; anti-androgens; anti-estrogens; estrogens; progestins; GnRH analogues, hormones and inhibitors*) *
- **All benzodiazepines**
- **All antidepressants**
- **All antipsychotics**
- **St John's wort**
- **All mood stabilizers**
- **All controlled sedatives and hypnotics**
- **Metoclopramide**
- **Narcotics** (*opioids and opioid combinations*) (*exception -- these drugs are permitted for short-term use in acute situations*)
- **Non-benzodiazepine prescription sleep aids**

- **Vaginal lubricants moisturizers containing warming and/or enhancing agents, including but not limited to: *KY Intense, Zestra***

*Estrogen and progestin as a constituent of Hormone Therapy is acceptable as long as the patient has been on a stable dose for at least 6 months prior to the Screening Visit and it was not prescribed for treatment of low sexual desire.

6.4.2 Medications prohibited in phase 3 studies 511.70, 511.71, 511.75, 511.77

Include all medication classes that were prohibited in study 511.147 (section 6.2.1) as well as the following:

- All antiarrhythmics
- All anticoagulants
- All beta blockers
- All CNS stimulants, including but not limited to amphetamines, Ephedra, Ma-Huang, methamphetamine, methylphenidate
- All fertility agents
- The following over the counter pro-sexual agents: Yohimbe, yohimbine
- All muscle relaxants
- 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
- Triptan anti-migraine agents
- CYP3A4 inhibitors and inducers (excluded unless all of the following conditions are met:
 - The patient has been taking study medication for at least 7 days
 - The patient is having no adverse events that are related to study medication in the investigator's judgment
 - The proposed concomitant medication will be used for no more than 14 days

6.5 Risk Management Plan Proposed by the Applicant

The goals of the Applicant's risk management plan are to inform patients about the serious risks and appropriate use of flibanserin, and to inform healthcare professionals about the serious risks and appropriate use of flibanserin, the importance of appropriate patient selection, and to discontinue flibanserin in patients with an inadequate clinical response.

To accomplish these goals, the Applicant proposes the following components of their risk management strategy:

- Medication guide to be dispensed with each prescription of flibanserin
- Implementation of a communication plan to healthcare professionals (gynecologists, psychiatrists, general practitioners, internists and nurse practitioners/physician assistants), pharmacists and professional organizations. The communication plan includes a Dear Healthcare Provider Letter, the Decreased Sexual Desire Screener (DSDS), an appropriate use checklist, and a Dear Professional Organization Letter. The Applicant will ensure that

these materials are available through the product's Risk Evaluation and Mitigation Strategy (REMS) website.

Division comment:

See the memorandum from the Division of Risk Management for further discussion of risk management options for flibanserin-associated hypotension and syncope.

6.6 Summary of Syncope Cases occurring in phase 1 studies and phase 3 placebo-controlled pre-menopausal HSDD trials conducted in support of the HSDD marketing application

Table 31 contains summary clinical and demographic information for all cases of syncope that occurred in the flibanserin 100 mg qhs dose group in the phase 3, placebo-controlled HSDD trials in pre-menopausal women.

Table 31. Cases of Syncope occurring in the flibanserin 100 mg qhs dose group in phase 3, placebo-controlled HSDD trials in pre-menopausal women

Study#/Subject ID #	Age, race, alcohol use status, BMI, and relevant past medical history	Investigator adverse event preferred term	Onset day (relative to initiation of flibanserin)	Concomitant medication at time of event	Relationship to study drug (Agency reviewer consideration)
511.71 025702	40 yo white female, Etoh user, BMI 19 kg/m ²	Syncope	14	Macrochantin (for UTI prophylaxis), (intranasal corticosteroid)	Possibly
511.75 030689	24 yo white female, non-drinker, BMI 27 kg/m ²	Syncope	34	Lessina OCP	possibly
511.75 032050	28 yo white female Etoh user, BMI 24kg/m ² , PMHx of "fainting" episodes	Syncope	93	Tricyclen OCP	Confounded by PMHx of "fainting" episodes
511.75 033348	32 yo white female, Etoh user, BMI 30 kg/m ²	Loss of consciousness	34	Mirena IUD	Possibly
511.77 037779	34 yo white female, Etoh user, BMI 21 kg/m ² , PMHx of recurrent orthostatic dysregulation and circulatory collapse	circulatory collapse	11	Yasmin OCP Nexium 40 mg qd	Confounded by PMHx of circulatory collapse
511.147 040060	37 yo, Hispanic, non-drinker, BMI 20.4 kg/m ²	Syncope	23	None	Possibly

yo = year-old; BMI = body mass index; UTI = urinary tract infection; OCP = oral contraceptive product; IUD = intrauterine device; PMHx = past medical history
FDA analysis

Characteristics of subjects experiencing syncope in the phase 1 studies are shown in Table 32.

Table 32. Cases of syncope experiencing syncope in the phase 1 studies

Study #/ Subject #/	Demographic information	Flibanserin dose/ concomitant medication/ time relative to dosing	AE preferred term, time relative to dosing	Baseline vital signs	Vitals at time of event (position if provided)	Treatment and outcome	Agency reviewer assessment of relatedness to study drug
511.158 Subject #5	33 yo white female, 53 kg, 19 kg/m ²	100 mg alone	Circulatory collapse, 29 minutes	104/54 mm Hg, 71 bpm	Not recorded	500 cc IV fluids, recovered after 2 hours	Yes
SPR-14-06 Subject #1014	47 yo Asian female, 50 kg, 19 kg/m ²	100 mg alone	Unresponsive to stimuli, 28 minutes	104/65 mmHg, 55 bpm	137/83 mmHg, 58 bpm (supine)	Placed supine, recovered after 20 minutes	Yes
511.88 subject #4	41 yo white female, 61 kg; 25 kg/m ²	100 mg (on 3 rd dose of dosing)	Syncope, 1 hour	116/69 mmHg, 76 bpm	Not recorded	None, recovered within 20 seconds	Yes
511.87 subject13	30 yo white female	50 mg alone	Vasovagal syncope (two episodes separated by 10 minutes), 96 hours after flibanserin	115/70 mmHg, 68 bpm	Not recorded	None; lasted 5 minutes and 6 minutes, respectively	No
511.111 Subject 11	40 yo white female, 23 kg/m ²	50 mg alone	Circulatory collapse and fainting, 20 minutes	104/70 mmHg, 65 bpm	Not recorded	No medical therapy initiated	Yes
SPR-12-01 (fluconazole) Subject #1001	41 yo white female, 75 kg; 28 kg/m ²	Flibanserin 100 mg + fluconazole 200 mg	Unresponsive, 1 hour	92/65 mmHg, 70 bpm	64/41 mmHg, 50 bpm	ER transport, IV fluids, ammonia inhalant	Yes
511.111 (ketoconazole)/ Subject 13	19 yo white female, 70 kg/ 24 kg/m ²	Flibanserin 50 mg + ketoconazole 400 mg	Orthostatic hypotension, orthostatic syncope	113/70 mmHg, 84 bpm	Not recorded	No medical therapy initiated	Yes
SPR-12-03 (alcohol)/ subject #123 (1020)	26 yo black male, 22 kg/m ²	Flibanserin 100 mg + 0.4 g/kg Etoh	Syncope x 2 (2 hours and 3 hours)	120/75 mmHg, 68 bpm (standing)	162/64 mm Hg, 50 bpm (event 1), 83/49 mmHg, 53 bpm (event 2) (semi- recumbent)	Placed supine, legs elevated, ammonia inhalant	Yes
SPR-12-05 (abuse potential)/ Subject 1048	28 yo black male,* 23 kg/m ²	Flibanserin 200 mg alone	Syncope, one hour	138/81 mmHg, 61 bpm (semi- recumbent)	120/71 mmHg, 84 bpm (semi- recumbent)	None reported	Yes

yo = year-old; Etoh= alcohol; IV = intravenous; ER = emergency room

*This male subject is included to account for all syncope cases in the phase 1 studies for the flibanserin HSDD program.

FDA analysis

**III. Clinical Pharmacology
Memorandum – Division of
Clinical Pharmacology 3, Office of
Clinical Pharmacology, Office of
Translational Sciences**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Clinical Pharmacology Memorandum

Date: May 7, 2015

To: Members of the Joint Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

From: Division of Clinical Pharmacology 3
Office of Clinical Pharmacology
Office of Translational Sciences

Subject: Flibanserin (NDA 22526)

PHARMACOKINETIC CHARACTERISTICS

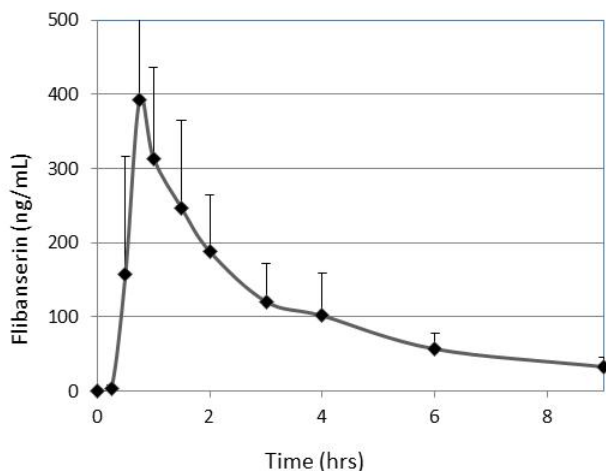
Following oral administration of a single 100 mg dose of flibanserin in healthy premenopausal women:

- Mean C_{max} was 419 (standard deviation 206) ng/mL
- Mean AUC_{0-inf} was 1543 (standard deviation 511) ng*hr/mL
- Median T_{max} was 0.75 (range 0.75 – 4.0) hours
- Mean t_{1/2} was 11.7 (standard deviation 1.9) hours

Following single dose administration of flibanserin tablets, C_{max} appears to be dose proportional and AUC_{0-inf} appears to be greater than dose proportional from 100 to 250 mg.

The accumulation ratio is in the range of 1.05 to 1.34, based on once daily doses of 25 mg and 50 mg. Following once daily administration of 100 mg flibanserin for 8 days in premenopausal women with HSDD, the mean t_{1/2} at steady state was 11.8 (standard deviation 3.1) hours.

Figure 1. Flibanserin Concentration-Time Profile in Healthy Premenopausal Women (N=8) Following a Single 100 mg Oral Tablet of Flibanserin.



Source: FDA analysis

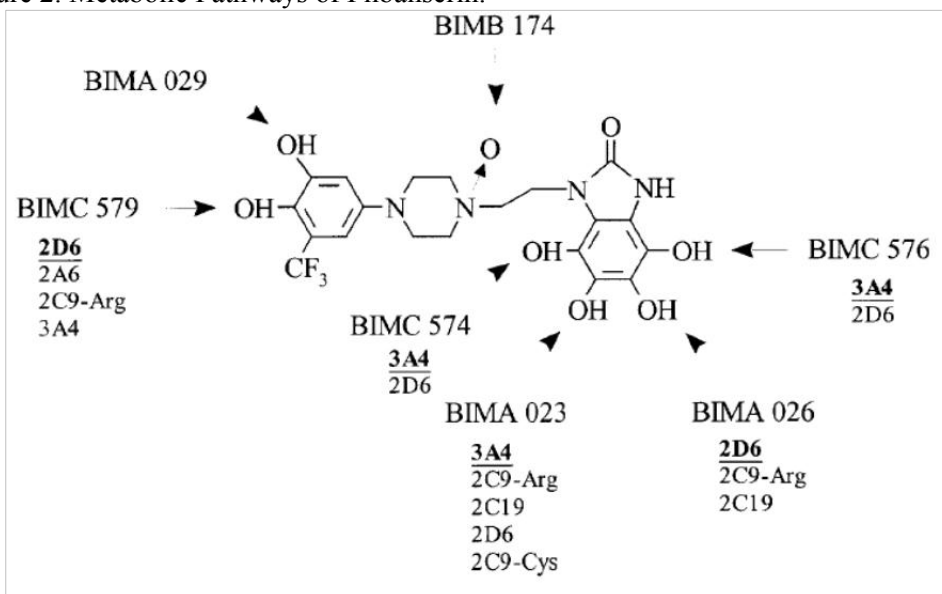
Food Effect

The effect of different food types on the pharmacokinetics (PK) of flibanserin after a single 50 mg dose was evaluated in an open-label, four-way, crossover study in 16 healthy subjects. Compared to the fasted condition, the exposure (AUC_{0-inf}) of flibanserin was 17%, 41%, and 53% higher after administration of a light, medium, and high fat/caloric breakfast, respectively.

Flibanserin Metabolism Pathway

Based on in vitro studies, the sponsor identified multiple enzymes that may be responsible for the metabolism of flibanserin, which primarily include CYP3A4, CYP2D6, CYP2C9, and CYP2C19. In vivo clinical data has shown that CYP3A4 is the primary enzyme for flibanserin metabolism. Additional in vivo data have shown CYP2C19 as a contributing enzyme.

Figure 2. Metabolic Pathways of Flibanserin.



BIMA, BIMB, and BIMC are possible metabolites of flibanserin. The arrows indicate possible sites of hydroxylation. The CYP enzymes involved in the formation of a specific metabolite are listed below each metabolite.

Source: study report B-859, NDA 22526

DRUG-DRUG INTERACTION

1. Pharmacokinetic-based

a. Effect of Other Drugs on Flibanserin

1) Strong CYP3A4 Inhibitors

i. Itraconazole

The sponsor evaluated the effect of multiple doses of itraconazole, a strong CYP3A4 inhibitor, on the PK of a single 50 mg dose of flibanserin. The study was a randomized, open label, two-way crossover study in healthy subjects who received once daily oral administration of 200 mg itraconazole for 8 days followed by a single tablet administration of 50 mg flibanserin with water.

Itraconazole co-administered with flibanserin increased flibanserin AUC_{0-inf} by 2.6-fold and C_{max} by 1.7-fold. t_{1/2} was extended by 4.2 hrs from 7.4 to 11.6 hrs in the presence of itraconazole.

Table 1. Flibanserin Pharmacokinetic Parameters in Healthy Male and Female Subjects Following a Single 50 mg dose of Flibanserin Given Alone and Given After Multiple doses of 200 mg Itraconazole.

PK parameter*	Flibanserin	
	Without co-administration of itraconazole	With co-administration of itraconazole
AUC _{0-inf} (ng*hr/mL)	1090 (58)	2810 (76)
C _{max} (ng/mL)	201 (50)	341 (33)
T _{max} (hr) ¹	1.25 (0.50 – 3.00)	1.25 (1.00 – 4.00)
t _{1/2} (hr)	7.4 (27.0)	11.6 (46.5)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Division Comment:

- Although itraconazole is a suitable drug to evaluate potential CYP3A4 inhibition, the 200 mg dose selected for the study is lower than the recommended 400 mg dose and, therefore, the degree of CYP3A4 inhibition by itraconazole was not maximized.
- The results from this suboptimally designed study using itraconazole 200 mg, not 400 mg, did not provide a maximal inhibition effect of CYP3A4 inhibition on flibanserin metabolism.
- Therefore, the sponsor conducted another drug-drug interaction study using ketoconazole 400 mg daily to evaluate the effect of a strong CYP3A4 inhibitor on flibanserin exposure.

ii. Ketoconazole

The sponsor evaluated the influence of multiple doses of the strong CYP3A4 inhibitor ketoconazole on the PK of a single oral dose of 50 mg flibanserin. The study was an open-label, randomized, two-period, crossover study in healthy young female subjects. Flibanserin was administered with 240 mL of water in the morning about 1 hour after ketoconazole and light breakfast.

Ketoconazole 400 mg daily for 5 days inhibited flibanserin metabolism leading to a 4.6-fold increase in flibanserin AUC_{0-inf}. C_{max} increased 1.8-fold. T_{max} increased slightly from 1.25 to 1.50 hours and t_{1/2} was significantly prolonged from 8.5 to 15.9 hrs.

Table 2. Flibanserin Pharmacokinetic Parameters in Healthy Male and Female Subjects Following a Single 50 mg dose of Flibanserin Given Alone and Given After Multiple doses of 400 mg Ketoconazole.

	Flibanserin	
PK parameter*	Without co-administration of ketoconazole	With co-administration of ketoconazole
AUC _{0-inf} (ng*hr/mL)	1140 (44)	5260 (57)
C _{max} (ng/mL)	256 (27)	472 (25)
T _{max} (hr) ¹	1.25 (0.75 – 2.00)	1.50 (0.75 – 4.00)
t _{1/2} (hr)	8.5 (29.8)	15.9 (41.7)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Safety Finding:

- Subject #11 lost consciousness approximately 40 minutes after receiving flibanserin 50 mg (no concomitant medication). Blood pressure at the time of the event is unavailable. Blood pressure was 92/64 mmHg approximately 1 hour after flibanserin dosing and 91/59 mmHg approximately 3 hours after flibanserin dosing.
- Subject #13 experienced orthostatic hypotension lasting 15 min and syncope lasting 1 minute approximately 1 hour post administration of flibanserin and ketoconazole. Moderate orthostatic hypotension and syncope were also reported 17 days after ketoconazole and flibanserin co-administration.

Division Comment:

- Due to the high degree of inhibition of flibanserin metabolism in the presence of ketoconazole, a strong CYP3A4 inhibitor, and the likely incidence of increased adverse events with increases in flibanserin exposure, the Division requested that the sponsor address whether and to what degree flibanserin metabolism will be inhibited by mild and moderate CYP3A4 enzymes.
- An extensive list of prescription drugs and dietary supplements including mild and moderate CYP3A4 inhibitors were prohibited during the pivotal Phase 3 trials.

2) Moderate CYP3A4 Inhibitors

i. Grapefruit juice

Due to concerns that grapefruit juice, a moderate CYP3A4 inhibitor, can affect the metabolism of flibanserin, the sponsor evaluated the effect of a single administration of grapefruit juice on flibanserin PK. Co-administration of a single 100 mg dose of flibanserin and 240 mL of regular strength grapefruit juice resulted in an increase of 10% in C_{max} and an increase of 38% in AUC_{0-inf}, compared to flibanserin alone. Median T_{max} of flibanserin was delayed by 0.7 hrs (0.8 to 1.5 hrs) when flibanserin was taken with grapefruit juice. Mean half-life of flibanserin

was similar for flibanserin alone (10.6 hours) and flibanserin + grapefruit juice (9.9 hours).

Table 3. Flibanserin Pharmacokinetic Parameters in Healthy Young Female Subjects (N=26) Following a Single 100 mg dose of Flibanserin Alone and a Single 100 mg dose of Flibanserin + 240 mL of Grapefruit Juice.

PK parameter*	Flibanserin	
	Without co-administration of grapefruit juice	With co-administration of grapefruit juice
AUC _{0-inf} (ng.hr/mL)	1869 (42)	2508 (46)
C _{max} (ng/mL)	405 (48)	433 (38)
T _{max} (hr) ¹	0.8 (0.75 – 6.00)	1.5 (1.0 – 4.0)
t _{1/2} (hr)	10.6 (32)	9.9 (31)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Division Comment:

- Effect of grapefruit juice on CYP3A4 could be variable and depends on the source and strength of the grapefruit juice.
- Regular strength grapefruit juice is considered a moderate CYP3A4 inhibitor according to the FDA drug interaction guidance; however, this study, designed with a single administration of grapefruit juice, does not adequately assess the CYP3A4 inhibition potential of grapefruit juice used chronically on flibanserin exposure.

ii. Fluconazole

Co-administration of flibanserin 50 mg with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 4.6-fold increase in flibanserin exposure and increased the incidence of adverse events (AEs). To address the effect of a moderate CYP3A4 inhibitor on flibanserin exposure, the sponsor conducted a drug-drug interaction study with multiple doses of fluconazole. Fifteen healthy young women received one 400 mg loading dose of fluconazole, 200 mg doses of fluconazole daily for three days, then a single 100 mg dose of flibanserin co-administered with 200 mg fluconazole on Day 5.

Multiple doses of fluconazole resulted in a 2.2-fold increase in C_{max} and 7.0-fold increase in AUC_{0-inf} of flibanserin. Mean terminal half-life of flibanserin increased from 10 to 23 hours.

Table 4. Flibanserin Pharmacokinetic Parameters in Healthy Young Female Subjects (N=15) Following a Single 100 mg Dose of Flibanserin Alone and a Single 100 mg Dose of Flibanserin After Multiple Doses of Fluconazole.

PK parameter*	Flibanserin	
	Without co-administration of fluconazole	With co-administration of fluconazole
AUC _{0-inf} (ng*hr/mL)	1756 (52)	11249 (30)
C _{max} (ng/mL)	421 (52)	889 (41)
T _{max} (hr) ¹	0.8 (0.75 – 6.00)	1.0 (0.75 – 4.00)
t _{1/2} (hr)	10.0 (37)	25.3 (43)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Safety Findings:

- Overall, co-administration of flibanserin and multiple doses of fluconazole resulted in more frequent and profound AEs, compared to flibanserin alone. All 15 subjects who were co-administered flibanserin and fluconazole experienced at least 1 AE.
- Hypotension was observed in 3 of 15 subjects (20%) co-treated with flibanserin and fluconazole. The following provides details on these hypotensive events:
 - Subject #1001 became unresponsive and hypotensive approximately 1 hour post-dose when flibanserin was administered with fluconazole on Day 10. The investigator classified this event as a severe drug-related adverse reaction. Her blood pressure was 64/41 mmHg, her heart rate was 50 beats/minute and she was unable to speak. She required emergency attention, ammonia inhalant, oxygen and intravenous saline administration. The subject was otherwise healthy and eventually improved with time and became awake and alert.
 - Subject #1004 experienced hypotension that lasted approximately 1 hour. The subject had a blood pressure of 80/49 mmHg at approximately 1 hour following co-administration of flibanserin and fluconazole. The investigator classified this event as mild in severity. Her hypotension was accompanied by pallor, nausea, and fatigue, without loss of consciousness.
 - Subject #1013 experienced hypotension that lasted approximately 8 minutes after her feet were elevated. The subject had a blood pressure of 73/41 mmHg at approximately 1 hour following co-administration of flibanserin and fluconazole. The investigator classified this event as moderate in severity. The hypotension was accompanied by fatigue.

Division Comment:

- Hypotension occurred approximately 1 hour following co-administration of flibanserin and fluconazole (i.e., at about T_{max} for flibanserin).
- Due to the hypotensive-related AEs experienced in the three subjects described above, the sponsor stopped the study early and did not enroll the additional 15 subjects as initially planned.
- The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.6-fold increase with ketoconazole, a strong CYP3A4

inhibitor. The exposure change with fluconazole was not anticipated based on the presumed metabolism pathway of flibanserin of mainly through CYP3A4.

- Fluconazole is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor. The in vivo study results with fluconazole suggest other enzymes may be involved in the metabolism of flibanserin.
- Based on subsequent studies, CYP2C19 appears to also contribute towards the metabolism of flibanserin.

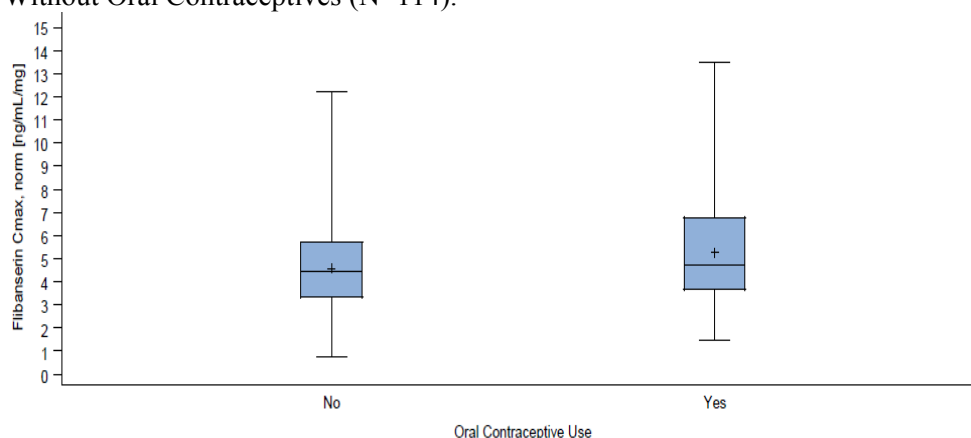
3) Weak CYP3A4 Inhibitors

i. Oral contraceptives (meta-analysis)

Oral contraceptives are weak CYP3A4 inhibitors. The sponsor conducted a meta-analysis of phase 1 PK data in women who received oral contraceptives and various doses of flibanserin concomitantly. The analysis excluded subjects with renal or hepatic impairment.

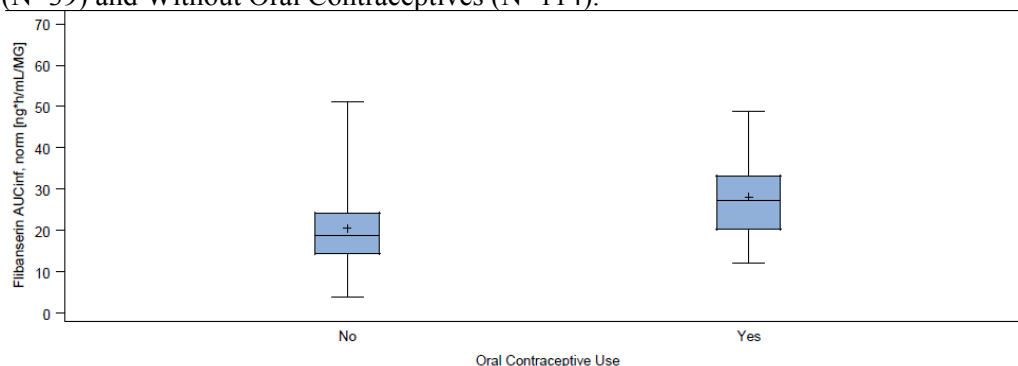
Subjects received a single dose of flibanserin (dose range from 25 to 100 mg from 7 studies). Based on adjusted geometric ratios that were dose-normalized, AUC_{0-inf} of flibanserin increased 42% and C_{max} increased 12% following a single dose of flibanserin and oral contraceptives compared to flibanserin alone.

Figure 2. Boxplot of C_{max} of flibanserin after oral administration of flibanserin in healthy female subjects and Patients with Hypoactive Sexual Desire Disorder With (N=39) and Without Oral Contraceptives (N=114).



Source: Applicant's FLIB_511.pk3-metaanalysis amended report, figure 3.

Figure 3. Boxplot of AUC_{0-inf} of flibanserin after oral administration of flibanserin in healthy female subjects and Patients with Hypoactive Sexual Desire Disorder With (N=39) and Without Oral Contraceptives (N=114).



Source: Applicant's FLIB 511.pk3-metaanalysis amended report, figure 2

Safety Findings:

- Phase 3 safety data showed that women taking both flibanserin and hormonal contraceptives tended to have a higher incidence of adverse events, compared to those taking hormonal contraceptives and placebo. See the Clinical Safety memorandum for additional details.

Division Comment:

- Flibanserin exposure was increased by 42% with concomitant use of flibanserin and oral contraceptives.

4) CYP2C9 and CYP2C19 Polymorphism

As discussed above, the 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.6-fold increase with ketoconazole, a strong CYP3A4 inhibitor. The exposure change with fluconazole was not anticipated based on the presumed metabolism pathway of flibanserin. Fluconazole is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor. The fluconazole study results suggested that CYP2C9 and/or CYP2C19 may be involved in the metabolism of flibanserin.

To understand the contribution of CYP2C9 and CYP2C19 to overall flibanserin clearance, the sponsor evaluated the pharmacokinetics of flibanserin in healthy premenopausal women with either CYP2C9 or CYP2C19 poor metabolizer (PM) genotype as compared to healthy premenopausal women with both CYP2C9 and CYP2C19 extensive metabolizer (EM) genotypes.

Subjects with a CYP2C9 PM or CYP2C19 PM genotype are deficient in CYP2C9 or CYP2C19 enzyme activity, respectively. Subjects with a CYP2C9 EM or CYP2C19 EM genotype have intact CYP2C9 or CYP2C19 enzyme activity, respectively. Comparing flibanserin exposure from a CYP2C9 PM to a CYP2C9 EM is analogous to comparing flibanserin exposure with and without a strong

CYP2C9 inhibitor. This study was done in lieu of a standard drug interaction study that includes CYP2C9 or CYP2C19 inhibitors.

The frequencies of CYP2C19 PM status are approximately 2–5% among Caucasians and Africans and approximately 2–15% in Asians, according to the Clinical Pharmacogenetics Implementation Consortium.

In subjects with a CYP2C9 PM genotype, flibanserin exposure (AUC_{0-inf}) decreased 19% and C_{max} decreased 18%, compared to those with a CYP2C9 EM genotype. Half-life ($t_{1/2}$) was essentially the same, at approximately 11 hours.

In subjects with a CYP2C19 PM genotype, flibanserin exposure (AUC_{0-inf}) increased 34% and C_{max} increased 49% compared to those with a CYP2C19 EM genotype. Half-life ($t_{1/2}$) was extended by 2.4 hours from 11.1 to 13.5 hours in subjects with the CYP2C19 PM genotype. There was one healthy female subject with a CYP2C19 PM genotype who experienced severe adverse events; she became hypotensive and unresponsive to stimuli, as described further below.

Table 5. Flibanserin Pharmacokinetic Parameters in Healthy Premenopausal Women With Different CYP2C9/2C19 Metabolizing Status Following a Single 100 mg Oral Dose of Flibanserin.

	Flibanserin		
PK parameter*	CYP2C9/CYP2C19 EM (N=8)	CYP2C9 PM (N=8)	CYP2C19 PM (N=9)
AUC_{0-inf} (ng*hr/mL)	2357 (49)	1903 (45)	3153 (56)
C_{max} (ng/mL)	379 (39)	310 (55)	557 (33)
T_{max} (hr) ¹	1.0 (0.5 – 2.0)	0.8 (0.5 – 3.0)	0.8 (0.75 – 1.5)
$t_{1/2}$ (hr)	11.1 (32)	10.7 (48)	13.5 (34)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Safety Findings:

- Subject #1014, a 47 year-old Asian woman with a CYP2C19 PM genotype (weight, 50.4 kg; BMI, 19.2 kg/m²) received a single 100 mg dose of flibanserin, after an overnight fast and suffered an adverse reaction that was classified as severe by the investigator. The subject reported the sudden onset of sleepiness 28 minutes after flibanserin dosing. Shortly thereafter, she exhibited pallor, experienced nausea, and retching for about 5 minutes, without emesis. While in a semi-recumbent position, her head suddenly fell to the side and she became unresponsive for about 1 minute. A blood pressure cuff was applied, and before the machine finished cycling, the subject had aroused with stimulation by a study nurse. She did not exhibit hypotension before or during the event. The subject was unable to stand for measurement of orthostatic vital signs at 1 hour post-dose even with the assistance of the site staff. She was placed in bed, had recovered by 20 minutes later, and was

able to stand for the orthostatic blood pressure measurement at 2 hours post-dose.

Division Comment:

- Compared to subjects with a CYP2C9 EM status, there was no increase in flibanserin exposure in the CYP2C9 PM subjects suggesting no involvement of the CYP2C9 enzyme in flibanserin metabolism.
- Compared to subjects with a CYP2C19 EM status, there was a mean increase in flibanserin exposure (AUC_{0-inf} increased 34% and C_{max} increased 49%) in the CYP2C19 PM subjects suggesting flibanserin is partially metabolized by CYP2C19.
- The greatest flibanserin exposure among the nine subjects with a CYP2C19 PM genotype occurred in a 29 year-old Asian subject who had flibanserin AUC_{0-inf} of 7526 ng*hr/mL and C_{max} of 698 ng/mL. In this subject, the AUC_{0-inf} was increased 3.2-fold and C_{max} increased 1.8-fold compared to the mean flibanserin exposure in CYP2C19 EM subjects.
- Antidepressants, anticonvulsants, and proton pump inhibitors are CYP2C19 inhibitors. Co-administration of these drugs with flibanserin, may increase flibanserin exposure.

b. Effect of Flibanserin on Other Drugs

1) CYP2B6 (bupropion)

The sponsor conducted an in vivo study, using bupropion as a CYP2B6 substrate, to assess whether flibanserin inhibits CYP2B6. The study was an open-label, randomized, two-period crossover study in healthy women. Subjects were given flibanserin 50 mg twice daily for 2 days followed by 100 mg once daily for 13 days. Bupropion 150 mg twice daily was given for 8 days beginning on Day 6 of flibanserin treatment.

For bupropion, the AUC_τ at steady state increased by 2.2% and C_{max} at steady state increased by 2.7% when co-administered with flibanserin 100 mg once daily, compared to bupropion alone.

Table 6. Bupropion Pharmacokinetic Parameters of in Healthy Female Subjects With and Without Pretreatment with Flibanserin.

	Bupropion	
Steady state (SS) PK parameter*	Bupropion 150 mg twice daily (N=23)	Bupropion 150 mg twice daily + Flibanserin 100 mg once daily (N=22)
AUC _{τ,ss} (ng.hr/ml)	549 (30)	561 (29)
C _{max,ss} (ng/ml)	74.6 (33)	76.6 (31)
T _{max,ss} (hr) ¹	3.0 (1.0 – 4.0)	3.0 (1.1 – 4.0)
t _{1/2,ss} (hr)	25.9 (28)	25.0 (24)

*arithmetic mean (%CV); ¹ median and range; FDA analysis

Safety Findings:

- Subject #4, a healthy 41 year-old subject experienced syncope 1 hour following her third dose of flibanserin (50 mg twice daily for 2 days, and then 100 mg once daily for 1 day). She was discontinued from the study due to this episode of syncope and therefore did not receive the full 13 days of flibanserin as planned.

Division Comment:

- There was no difference in bupropion exposure at steady-state when co-administered with flibanserin.
- It appears that flibanserin does not inhibit the metabolism of bupropion and will unlikely interfere with the metabolism of other 2B6 substrates.

2) P-glycoprotein (P-gp) Inhibition

Digoxin is a P-gp substrate and is commonly used as a probe in drug interaction studies to evaluate drug interactions with P-gp inhibitors. Flibanserin was evaluated as a potential inhibitor of P-gp using digoxin as a P-gp substrate. Flibanserin 100 mg was given once daily over 7 days in 23 subjects. On Day 5, a single 0.5 mg dose of digoxin (2 x 0.25 mg) was administered with 100 mg flibanserin. Digoxin exposure (AUC_{0-inf}) increased 81% and C_{max} increased 38% in the group that was co-administered flibanserin and digoxin compared to the group that received digoxin alone.

Table 7. Pharmacokinetic Parameters of Digoxin Following a Single Oral Dose of 0.5 mg Digoxin With and Without Multiple Doses of 100 mg Flibanserin (N=23).

PK parameter*	Digoxin	
	Without co-administration of flibanserin	With co-administration of flibanserin
AUC _{0-inf} (ng.hr/mL)	30 (48)	55 (46)
C _{max} (ng/mL)	2.1 (27)	2.9 (19)
T _{max} (hr) ¹	1.0 (0.5 – 2.0)	0.5 (0.5 – 2.0)
t _{1/2} (hr)	42.3 (73)	75 (59)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Division Comment:

- The sponsor concluded that flibanserin did not inhibit P-gp because the increase in digoxin exposure was moderate based upon digoxin AUC₀₋₂₄ (25% increase) and digoxin renal clearance (CLR₀₋₂₄) (~8% decrease). However, based upon digoxin AUC_{0-inf}, not AUC₀₋₂₄, digoxin exposure increased 81% with flibanserin co-administration and digoxin C_{max} increased 38%. The 8% reduction in digoxin renal clearance was based upon urine samples calculated from 0 to 24 hours. Based on the increased AUC_{0-inf}, reduction in digoxin renal clearance with flibanserin co-administration appears to be greater after 24 hours.

- In assessing the clinical drug interaction between flibanserin and digoxin, C_{max} and AUC ratios are more direct and sensitive compared to renal clearance ratio due to the nature of sample collection.
- The in vivo study with flibanserin + digoxin co-administration suggests that flibanserin inhibits digoxin (and other P-gp substrates) clearance possibly via P-gp inhibition.

Safety Findings:

- All 24 subjects who received once daily administration of flibanserin 100 mg (4 doses) experienced at least 1 drug-related AE. Fatigue, dizziness, somnolence, and headache were the most commonly reported AEs and were mild to moderate in severity. However, two healthy subjects experienced severe AEs.
 - Subject #5 was a 33 year-old women who suffered “circulatory collapse” and vomiting of severe intensity after the first dose of flibanserin 100 mg on Day 1. The circulatory collapse started with syncope, occurring 29 min after flibanserin administration and continuing for 2 hours. The subject required medical treatment consisting of 500 mL intravenous glucose with electrolytes. Severe vomiting was reported 54 minutes after flibanserin administration and occurred twice in a period of 15 minutes. The subject was treated with 10 mL intravenous dimenhydrinate for severe vomiting. The subject also suffered severe fatigue and mild asthenia. She was discontinued from the study.
 - Subject #6 was a 48 year-old women with somnolence of severe intensity and recovered without medical intervention.

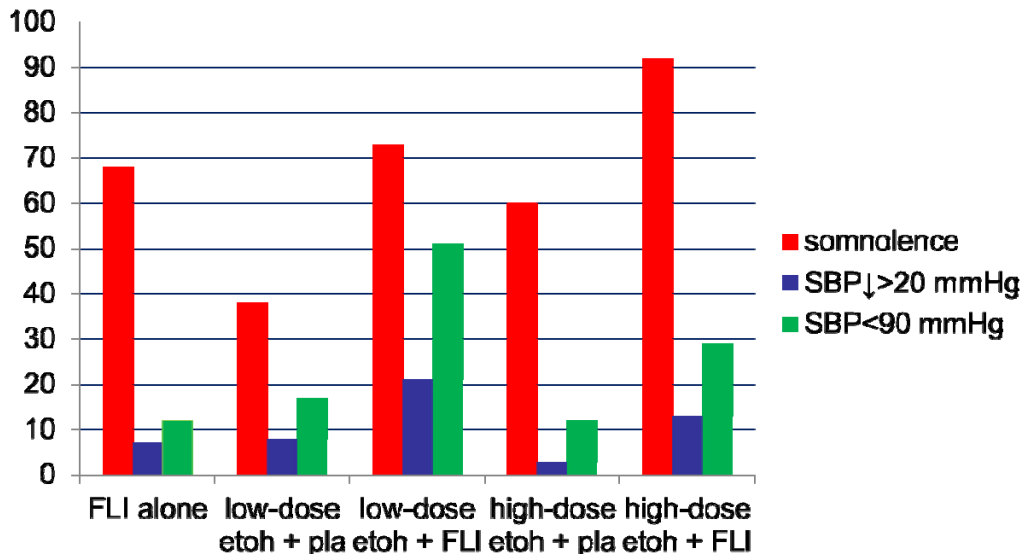
2. Pharmacodynamic-based DDI

a. Effect of Alcohol on Hemodynamics

The sponsor conducted a study to evaluate the effect of flibanserin 100 mg administered with two different concentrations of ethanol (equivalent to 2 and 4 drinks). The study was a single center, randomized, double-blind, single dose, 5-treatment crossover study in moderate alcohol drinkers. According to the sponsor’s definition, moderate alcohol consumption is defined as an average of approximately 5 to 21 drinks of alcohol per week. There were 23 healthy men and two healthy women. Ethanol (95%) was diluted in 240 mL total volume with orange juice. Subjects fasted for 10 hours prior to completing a light breakfast on the morning of Day 1 of each period. Following breakfast, subjects were instructed to swallow the study drug whole and drink the entire 240 mL ethanol and orange juice solution or orange juice alone. Subjects were given up to 10 minutes to complete intake of each treatment.

Flibanserin exposure as measured by partial AUC (AUC₀₋₄) decreased by 11% and 4% when flibanserin 100 mg was administered with 0.4 g/kg ethanol (equivalent to 2 drinks) and 0.8 g/kg ethanol (equivalent to 4 drinks), respectively, compared to flibanserin 100 mg alone.

Figure 4. Percentage of Subjects who Experienced Somnolence or Change in Systolic Blood Pressure (SBP) Following Co-Administration of Ethanol and Flibanserin.



FLI=flibanserin; etoh=ethanol; pla=placebo

SBP=systolic blood pressure

FDA analysis

Safety Findings:

- The most commonly reported AEs were somnolence, headache, and dizziness. The incidence of somnolence, headache, and dizziness was highest in the group receiving the highest concentration of ethanol (0.8 g/kg) with flibanserin.
- Flibanserin alone resulted in approximately 67% of subjects (16 of 24 subjects) experiencing somnolence. Taking ethanol with flibanserin increased the incidence of somnolence to approximately 74% (17 of 23 subjects) with 0.4 g/kg ethanol and to 92% (22 of 24 subjects) with 0.8 g/kg ethanol. Alcohol, especially notable at high concentrations, increased the somnolence-inducing effect of flibanserin.
- Severe adverse events were reported in the following 6 subjects:
 - Subject #104 and Subject #111, male subjects, experienced severe somnolence following 0.8 g/kg ethanol and flibanserin 100 mg administration.
 - Subject #122, a male subject, experienced severe dizziness and asthenia following 0.8 g/kg ethanol and flibanserin 100 mg administration. His blood pressure declined from 141/71 mmHg supine to 88/51 mmHg standing.
 - Subject #123, a male subject, experienced severe somnolence and severe intermittent orthostatic hypotension (lowest blood pressure 72/44 mmHg) following 0.4 g/kg ethanol and flibanserin 100 mg administration. The orthostatic hypotension was treated by placing the subject in the trendelenburg position.
 - Subject #125, a female subject, experienced severe dizziness following 0.4 mg/kg ethanol and flibanserin administration. Her blood pressure declined from 100/69 mmHg sitting to 75/46 mmHg standing.

- Subject #110, a male subject, had 2 bouts of syncope approximately one hour apart following 0.4 mg/kg ethanol and flibanserin administration. Blood pressure at the time of the second syncopal event was 83/49 mmHg. He was placed in the supine position with legs elevated and received ammonia salts.

Division Comment:

- The alcohol doses (0.4 and 0.8 mg/kg) evaluated in this drug interaction study are consistent with alcohol doses evaluated in other alcohol interaction studies.
- Orthostatic hypotension, syncope, severe somnolence, and severe dizziness were observed when flibanserin was co-administered with ethanol at both concentrations. Flibanserin 100 mg alone was more sedating than low and high dose of ethanol with placebo.
- Flibanserin exposure as measured by partial AUC (AUC₀₋₄) decreased by 11% and 4% when flibanserin 100 mg was co-administered with 0.4 and 0.8 g/kg ethanol, respectively, compared to flibanserin alone. We have limited data to conclude how ethanol affects flibanserin exposure due to the incomplete flibanserin concentration-time profiles.

ORGAN IMPAIRMENT

A. Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of a single 50 mg dose of flibanserin was evaluated in an open-label, parallel group study. Twenty-eight subjects completed the study (14 patients with liver impairment and 14 healthy matched subjects). Of the 14 subjects enrolled in the liver impairment group, 10 patients (5 females and 5 males) had mild liver impairment (Child-Pugh classification A; Child-Pugh score of 6-8 points) and 4 patients (1 female and 3 males) had moderate liver impairment (Child-Pugh classification B; Child-Pugh score of at least 9 points). No subjects had severe liver impairment.

Systemic exposure to flibanserin was significantly affected by hepatic impairment. The AUC_{0-inf} of flibanserin was significantly higher (4.5-fold) in patients with mild hepatic impairment compared to normal subjects. The AUC_{0-inf} of flibanserin was higher (2.6-fold) in patients with moderate hepatic impairment compared to healthy subjects.

Compared to their matching control group, patients with mild hepatic impairment had a slightly reduced C_{max} (10%), but it was significantly lower (63% decrease) in patients with moderate hepatic impairment.

Table 8. Flibanserin Pharmacokinetic Parameters Following a Single Oral Dose of 50 mg Flibanserin in Mild and Moderate Hepatic Impairment Patients, and Matched Healthy Subjects.

PK parameter*	Mild hepatic impairment (N=10)	Mild healthy matched (N=10)	Moderate hepatic impairment (N=4)	Moderate healthy matched (N=4)
AUC _{0-inf} (ng*hr/mL)	3580 (43.0)	776 (35)	2780 (65)	1010 (43)
C _{max} (ng/mL)	214 (49)	227 (45)	100 (62)	276 (55)
T _{max} (hr) ¹	0.5 (0.25 – 4.0)	0.75 (0.5 – 1.5)	1.75 (0.5 – 3.0)	0.87 (0.75 – 1.00)
t _{1/2} (hr)	28.1 (48)	10.8 (22)	28.9 (50)	10.2 (27.4)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Division Comment:

- Due to the small number of patients with moderate hepatic impairment (N=4) enrolled in the study, there are limitations with using these data to make conclusions about the effect of moderate hepatic impairment on flibanserin exposure.
- The sponsor did not enroll patients with severe hepatic impairment.
- The dose evaluated in this hepatic impairment study was 50 mg, while the proposed dose for marketing is 100 mg.
- It is likely that patients with hepatic impairment will experience an increase in adverse events compared with subjects with normal hepatic function.

B. Renal Impairment

The effect of renal impairment on the pharmacokinetics of a single 50 mg dose of flibanserin was evaluated in an open-label, parallel group comparison study. The sponsor assessed the effect of mild-to-moderate renal impairment (CrCL 30-80 mL/min) in 11 patients and severe renal impairment (CrCL <30 mL/min) in 9 patients. There were 7 healthy subjects matched to the mild-to-moderate renal impairment group and 9 healthy subjects matched to the severe renal impairment group.

Mild-to-moderate renal impairment did not significantly impact the systemic exposure to flibanserin (AUC_{0-inf} increased by 12%), compared to subjects with normal renal function. C_{max} decreased by 4% in mild-to-moderate renal impairment patients, compared to subjects with normal renal function.

Severe renal impairment had a moderate impact on the systemic exposure to flibanserin (AUC_{0-inf} increased by 21%), compared to subjects with normal renal function. C_{max} increased 31% in severe renal impairment patients, compared to subjects with normal renal function.

Table 9. Flibanserin Pharmacokinetic Parameters Following a Single Oral Dose of 50 mg Flibanserin in Mild-to-Moderate and Severe Renal Impairment Patients, and Matched Healthy Subjects.

PK parameter*	Mild-moderate renal impairment (N=11)	Mild-moderate healthy matched (N=7)	Severe renal impairment (N=9)	Severe healthy matched (N=9)
AUC _{0-inf} (ng*hr/mL)	1150 (76)	934 (51)	1300 (40)	1080 (39)
C _{max} (ng/mL)	254 (43)	251 (30)	292 (35)	246 (69)
T _{max} (hr) ¹	0.75 (0.5 – 1.5)	0.75 (0.50 – 0.75)	0.75 (0.3 – 1.0)	0.75 (0.5 – 2.0)
t _{1/2} (hr)	10.3 (32)	11.1 (50)	11.5 (35)	11.3 (17.5)

*arithmetic mean (%CV)

¹ median and range

FDA analysis

Division Comment:

- The dose evaluated in this renal impairment study was 50 mg, while the proposed dose for marketing is 100 mg.
- Flibanserin exposure was not significantly impacted in subjects with renal impairment considering the level of variability (%CV) in the data.

**IV. Memorandum on Study Endpoints
– Study Endpoint and Labeling
Development Team, Office of New
Drugs**

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs, Study Endpoints**

Date: May 7, 2015

To: Members of the Joint Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

From: Study Endpoints
Office of New Drugs

Subject: Outcome Assessments in the Flibanserin Development Program

Product: Flibanserin (NDA 22526)

A. BACKGROUND INFORMATION

The Applicant has used several patient-reported outcome (PRO) assessments as primary and secondary endpoints to evaluate treatment benefit of flibanserin in three phase 3 clinical trials (511.71, 511.75, 511.147) of premenopausal women with hypoactive sexual desire disorder (HSDD). The endpoints and assessments include:

- Change from baseline in the number of satisfying sexual events (SSEs) assessed with an SSE electronic diary (eDiary): Co-primary endpoint in three pivotal trials (Studies 511.71, 511.75, 511.147)
- Change from baseline in sexual desire assessed with the Female Sexual Function Index – Sexual Desire domain (FSFI-SD): Co-primary endpoint in one pivotal trial (Study 511.147) and secondary endpoint in two trials (Studies 511.71, 511.75)
- Change from baseline in sexual desire assessed with an eDiary daily measure of desire: Co-primary endpoint in two pivotal trials (Studies 511.71, 511.75)
- Change from baseline in sexual distress due to desire assessed with the Female Sexual Distress Scale-Revised (FSDS-R) item 13 (distress related to desire item): Secondary endpoint in three pivotal trials (Studies 511.71, 511.75, 511.147)
- Additional exploratory endpoints to aid in interpretation including: Patient global impression of improvement (PGI-I) and patient benefit evaluation (PBE)

The Division has accepted the assessments of SSE using an eDiary and the assessment of desire using the FSDS-R item 13. The focus of this review is therefore primarily on the FSFI-SD. This review also comments on the eDiary daily measure of desire, which was the co-primary endpoint in the two earlier phase 3 trials.

B. EFFICACY OUTCOME MEASURES

1. Description of Efficacy Measures

a. Female Sexual Function Index – Sexual Desire (FSFI-SD)

The FSFI (Rosen et al., 2000) is a multidimensional 19 item self-report questionnaire developed to assess female sexual function in women with HSDD. A representation of the FSFI reproduced from the Applicant's Study Protocol for 511.147 is shown in Section 1 of the document entitled "Key Outcomes Assessment Instruments Used in the Flibanserin Development Program." As shown in Table 1, the instrument consists of 6 domains: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. The version employed in Study 511.147 uses a 4-week recall period, meaning that patients are asked to reflect back over the past 28 days when responding to the questions in the instrument. While this PRO assessment also produces a total score, only the

sexual desire domain score (using items 1 and 2) was used as a co-primary endpoint in Study 511.147 and as a secondary endpoint in Studies 511.71 and 511.75.

The assessment of desire in the FSFI includes introductory instructions that define desire as being “a feeling that includes wanting to have a sexual experience, feeling receptive to a partner’s sexual initiation, and thinking or fantasizing about having sex.” Item 1 asks “How often did you feel sexual desire or interest?” with response options ranging from 5 (Almost always or always) to 1 (Almost never or never). Item 2 asks “How would you rate your level (degree) of sexual desire or interest?” with response options ranging from 5 (Very high) to 1 (Very low or none at all). The two item scores are summed, and raw scores are multiplied by a factor of 0.6, providing a sexual desire domain score that ranges from 1.2 to 6.0.

Table 1. FSFI Conceptual Framework

Item	Domains	Concept
1. How often feel sexual desire/interest	Sexual Desire	Sexual Function
2. Rate level of sexual desire		
3. How often feel sexually aroused	Arousal	
4. Rate level of sexual arousal		
5. How confident about becoming sexually aroused		
6. How often been satisfied with arousal		
7. How often become lubricated	Lubrication	
8. How difficult to become lubricated		
9. How often maintain lubrication		
10. How difficult to maintain lubrication		
11. How often reach orgasm	Orgasm	
12. How difficult to reach orgasm		
13. How satisfied with ability to reach orgasm		
14. How satisfied with amount of emotional closeness	Satisfaction	
15. How satisfied with sexual relationship with partner		
16. How satisfied with overall sexual life		
17. How often experience discomfort/pain during	Pain	
18. How often experience discomfort/pain following		
19. Rate level of discomfort/pain following		

Source: Rosen et al. (2000)

b. Daily eDiary Measure of Desire

Studies 511.71 and 511.75 used an electronic daily diary assessment of sexual desire as a co-primary endpoint. 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 (calculated by adding the daily scores) from 0 to 84 if data were entered on all 28 days. 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 and considered missing.

c. eDiary of SSEs

Using an electronic diary, 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. The eDiary questions are shown in Section 2 of the document entitled “Key Outcomes Assessment Instruments Used in the Flibanserin Development Program.”

Patients were instructed to complete the eDiary for SSEs every morning, with up to a 7-day window allowed for recalling and reporting previous events in Study 511.147 (and up to a 3-day window in Studies 511.71 and 511.75).

SSEs were standardized to a 28-day period using the following formula:

Total monthly SSEs = $28 \times (\text{sum of the number of events}) / (\text{sum of the number of days entered})$.

For example, if a woman entered 6 events over a 24 day period, the standardized SSE score would be $28 \times 6/24 = 7$.

d. FSDS-R item 13

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

The FSDS-R (Derogatis et al., 2008) 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 7 days. Specifically, item 13 asks, “How often did you feel bothered by low sexual desire?”, with response options (0-4) that range from “never,” “rarely,” “occasionally,” “frequently,” to “always.” A representation of the FSDS-R reproduced from the applicant’s NDA submission is shown in Section 3 of the document entitled “Key Outcomes Assessment Instruments Used in the Flibanserin Development Program.”

e. Additional supportive PRO measures

Additional endpoints were included as secondary or exploratory endpoints to provide supportive information and that can be informative to help interpret meaningful change. Total scores of the FSFI and FSDS-R were included as endpoints, as well as a patient global impression of improvement (PGI-I) and patient benefit evaluation (PBE).

i. PGI-I

The patient’s global impression of improvement is a single item instrument, asking patients to rate their condition today compared to when they started study medication.

Response options include:

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

7=Very much worse

ii. PBE

The patient benefit evaluation (PBE) is a single item that asks, “Overall, do you believe that you have experienced a meaningful benefit from the study medication?” with response options of Yes or No.

2. Evaluation of Efficacy Measures

a. FSFI-SD

The FSFI is a commonly proposed and used assessment in women with HSDD. While commonly used, there are continued challenges associated with its use and questions about its adequacy as an efficacy measure to support drug approval.

i. Development of the FSFI and Content Validity

To support claims of treatment benefit, it is important that outcome assessments first have adequate evidence of content validity. Content validity is supported by evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use (i.e., evidence that the instrument measures what it is intended to measure in that clinical context). Testing other measurement properties will not replace or rectify problems with content validity. It is important to ensure adequate content validity so that score changes identified within a trial can be interpreted as clear evidence of treatment benefit and so the treatment benefit can be accurately described in product labeling.

The Applicant provided Study SPR-FSFI-01 that summarizes the evaluation and validation of the FSFI, including the 2-item sexual desire domain. Initial development work of the FSFI was completed using input from experts and patients with female sexual arousal disorder (FSAD), not HSDD. FSAD was a diagnosis based on DSM-IV criteria, and included women with “the persistent or recurrent inability to attain or to maintain sufficient sexual excitement, which causes personal distress. It may be expressed as lack of subjective excitement or lack of genital (lubrication/swelling) or other somatic responses.” Women with FSAD in the initial development work may or may not have had desire-related concerns as well. Additional evaluation work in patients with HSDD has been subsequently completed or otherwise provided by the Applicant.

In the Complete Response letter issued in 2010, the Division indicated that “the instrument that is used to measure sexual desire should have adequate content validity, including recall validity, and acceptable measurement properties when used to evaluate premenopausal women with HSDD, consistent with the concepts set forth in the [FDA PRO Guidance].” The Applicant provided two additional validation studies (Study 511.144 and 511.151) in an effort to address the FDA’s concerns related to content validity and recall period, which are summarized in a publication by Revicki et al. (2011).

The first study included 15 premenopausal women aged 18-50 years with a diagnosis of HSDD. Participants were required to have been in stable relationships, defined as a duration ≥ 6 months.

Participants also needed a Female Sexual Distress Scale (Appendix C) total score ≥ 15 to qualify for inclusion. The second study used similar criteria, although it allowed recruitment of postmenopausal (N=31) and premenopausal (N=30) women, and excluded women who might have any other form of FSD.

Both interview studies began with open questions about the woman's experiences with sexual desire (concept elicitation) and were described as cognitive debriefings on the entire FSFI, augmented with general questions regarding the comprehensiveness of the instrument, and a few questions on the redundancy or completeness of the sexual desire items (items 1 and 2). The results of those queries among premenopausal women suggested that 68% (N=10) in one study and 53% (N=16) in the other felt the two desire items (items 1 and 2) of the FSFI captured their feelings about reduced sexual desire.

Patients were asked during these studies if the questions are relevant and comprehensive. Upon review of the transcripts provided by the Applicant, it is clear that most patients agree that multiple components make up the concept of sexual desire. While some patients describe other elements of desire that are important, most indicate that the multiple components described in the definition of sexual desire in the FSFI instructions are relevant and important. These include wanting to initiate sexual activity, being receptive to sexual activity, and thinking or fantasizing about it. In addition, evidence provided suggests that the assessment (i.e., specific words and phrases) are understood by patients. Most women (93-100%) reported that the two desire items were clear, easy to understand, and were relevant to them.

Study participants were also queried about their preference for a recall period that fits the most appropriate timeframe over which to assess frequency and intensity of sexual desire. The findings were not wholly conclusive, as the authors report "[a]mong those who had preference, most women in both studies thought that a recall period of 4 weeks or 1-2 weeks was the most appropriate time frame over which to assess the frequency of sexual desire (question 1) or level of sexual desire (question 2). Overall, there was no clear preference for 1-2 week recall, or a 4-week recall period." A minority of participants ($\leq 17\%$ across the two studies) favored a 24-hour recall. According to the 511.144 study report, "When participants were asked how often their answer to item 1 (*"How often did you feel sexual desire or interest?"*) would change if asked about recalling the past 24 hours or 7 days, rather than the past 4 weeks, six (40%) said they would answer differently (*"Because each week is different."*).

Remaining Concerns about Content Validity

While important elements of desire are covered by the FSFI desire domain items and instructions, concerns persist with the structure of the desire domain that could impact interpretation of efficacy findings based on the FSFI-SD. Specifically, this domain includes multi-barreled instructions making it unclear what is driving any change identified on the assessment (e.g., receptivity, sexual fantasies, and/or initiating sex). For example, if only one component (e.g., sexual fantasies) is actually increased in the women, but other components (e.g., wanting, initiating or feeling receptive to sex) have not improved, a score change suggesting improvement could be shown; however, it is unclear whether this represents a meaningful benefit to patients. In addition, with a drug known to cause sedating effects, like flibanserin, it is difficult to determine the extent to which sedation itself contributes to

receptivity to sexual advances and the observed changes in the FSFI desire domain score. These limitations should be considered when interpreting the efficacy findings.

Patients in the qualitative research provide support that they are able to interpret and respond to the questions in the FSFI desire domain using the provided response options. However, evidence has not been provided that women experiencing desire “all the time” would identify this as a benefit, or whether this could represent a different concern to women.

During the recent public meeting on female sexual dysfunction, hosted by the FDA on October 27-28, 2014, many of the panelists during the scientific workshop expressed support for the use of the FSFI desire domain in clinical trials to support regulatory approval, though there were some concerns raised about the appropriateness of response options.

Questions about Recall Period

A 28-day recall period is used in the FSFI-SD. The impact of this recall period on the ability to accurately reflect upon desire is unclear. For example, the longer recall period may increase noise in the assessment, thus attenuating treatment effects. With a longer recall period, it is also possible that patient recollection could be more heavily influenced by other experiences or by the more recent desire experiences. In addition, it is unclear how to resolve the discrepancy between the statistically significant improvement with the FSFI-SD and the lack of statistically significant improvement with the daily measure of desire in Studies 511.71 and 511.75.

ii. Other measurement properties of the FSFI-SD

Some of the other measurement properties of the FSFI are briefly described here. The instrument, including the desire domain, is generally able to discriminate between women with HSDD and those without HSDD. Meston (2003) reports that the FSFI desire domain has moderate internal consistency (Cronbach’s alpha = 0.58) among patients with HSDD. Rosen (2000) provides evidence of adequate test-retest reliability, with a Pearson product-moment correlation coefficient of 0.80.

iii. Interpreting meaningful change on the FSFI-SD

Anchoring approaches using data from the flibanserin trial show a range of what might be considered a meaningful improvement, from 0.9 to 1.7 change in score on the FSFI desire domain:

- Based on an anchor analysis using the PGI group of “minimally improved”, there was an average increase of 0.9 in FSFI domain score from baseline
- Based on an anchor analysis using the PGI group of “much improved”, there was an average increase of 1.7 in FSFI domain score from baseline
- Based on an anchor analysis among patients reporting a benefit on the PBE, there was an average increase of 1.6 in FSFI domain score from baseline

Given residual concerns regarding content validity (i.e., we don’t know exactly what has changed for the women to produce the identified score change), these numbers may be of limited value.

b. eDiary for SSEs

The FDA has consistently agreed with the approach of assessing SSEs with an electronic diary.

It is not yet clear what constitutes meaningful change in 28-day SSE scores. The Applicant provided findings from a survey (subsequently published in Kingsberg, 2014) of a convenience sample of 450 women with self-described low sexual desire and related distress, wherein 95% indicated that a change of 1-2 SSEs per month is meaningful. Other anchoring approaches using data from the flibanserin trial show a range of what might be considered a meaningful improvement, from >1 to 4.4 SSEs per month:

- Based on an anchor analysis using the PGI group of “minimally improved”, there was an average increase of 1.7 SSEs/month from baseline
- Based on an anchor analysis using the PGI group of “much improved”, there was an average increase of 4.4 SSEs/month from baseline
- Based on an anchor analysis among patients reporting a benefit on the PBE, there was an average increase of 3.8 SSEs/month from baseline

c. FSDS-R item 13

The FDA has consistently agreed to the use of the FSDS-R, item 13 as a measure of distress related to desire. During the recent public meeting on female sexual dysfunction, hosted by the FDA on October 27-28, 2014, the panelists during the scientific workshop expressed support for the use of the FSDS distress item as a key endpoint in clinical trials for HSDD.

C. REFERENCES

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**V. Memorandum – Division of Risk
Management, Office of Medication
Error Prevention and Risk
Management,
Office of Surveillance and
Epidemiology**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: May 8, 2015

To: Members of the Joint Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DsARM) Advisory Committee

From: Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology (OSE)

Subject: Risk Management Options for Flibanserin-Associated Hypotension and Syncope

Product: Flibanserin (NDA 022526)

1 INTRODUCTION

This memorandum summarizes the Division of Risk Management (DRISK) analysis of the strengths and limitations of possible risk management options for the serious risks of hypotension and syncope that occur with flibanserin alone, and that are exacerbated when flibanserin is used concomitantly with alcohol. These options include labeling alone or labeling with one or more risk evaluation and mitigation strategy (REMS) elements. This memorandum does not cover all the known risks of flibanserin. See the Clinical Safety section of the FDA background materials for further information.

2 BACKGROUND

2.1 PRODUCT INFORMATION

Flibanserin, a new molecular entity, is a 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist with the proposed indication for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The symptoms associated with HSDD are absent or reduced sexual desire associated with personal distress. The precise mechanism of action with regard to the treatment of HSDD is unknown. To date, flibanserin has not been approved for any indication in any country. The recommended dose for flibanserin for premenopausal HSDD is 100 mg taken orally, once daily at bedtime, administered chronically.

2.2 RISK EVALUATION AND MITIGATION STRATEGIES¹

The Food and Drug Administration Amendments Act (FDAAA) created a new section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), which authorizes the FDA to require a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. In determining if a REMS should be required, the FDA must consider the following factors:

- (A) The estimated size of the population likely to use the drug involved.
- (B) The seriousness of the disease or condition that is to be treated with the drug.
- (C) The expected benefit of the drug with respect to such disease or condition.
- (D) The expected or actual duration of treatment with the drug.
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- (F) Whether the drug is a new molecular entity.

The elements of a REMS can include: a Medication Guide (MG) or patient package insert, a communication plan to healthcare providers, elements to assure safe use (ETASU), and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under NDA and BLA have a timetable for submission of assessments of the REMS. These assessments are prepared by the Sponsor and reviewed by FDA.²

ETASU can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.

¹ FDA Draft Guidance for Industry – *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*, dated September 2009. Available at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>.

² A list of all FDA-approved products that include a REMS, including details of what elements are including in the REMS, can be found on the FDA REMS website at: <http://www.fda.gov/Drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm>

- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

3 BENEFIT AND RISK CONSIDERATIONS FOR FLIBANSERIN

3.1 EFFICACY RESULTS

The proposed indication for flibanserin is the treatment of HSDD in premenopausal women. The Applicant has conducted three randomized, double-blind, placebo-controlled clinical trials to support flibanserin's efficacy in HSDD in premenopausal women. These 24-week trials have demonstrated statistically significant improvement over placebo in the number of satisfying sexual events, sexual desire scores, and distress. See the clinical review for details of the efficacy findings.

3.2 SERIOUS RISK OF HYPOTENSION AND SYNCOPE ASSOCIATED WITH FLIBANSERIN

3.2.1 Drug interactions with cytochrome P450 3A4 (CYP3A4) inhibitors

Clinically significant drug interactions with CYP3A4 inhibitors resulting in hypotension and syncope were seen in the dedicated drug-drug interaction (DDI) studies for flibanserin. As a result, if flibanserin is approved, moderate to severe CYP3A4 inhibitors will be contraindicated in the flibanserin product label and this DDI may also be included as a boxed warning.

Because the number of moderate to severe CYP3A4 inhibitors is extensive and continues to grow, and patients receive prescriptions from multiple prescribers, the healthcare system relies on DDI screening technology to identify and prevent serious DDIs. The healthcare system's existing DDI screening technology includes screening performed by electronic medical records before prescribing, by insurance companies during prescription claim adjudication and by pharmacy management systems that perform a drug utilization review prior to dispensing every prescription. Further assurance is provided by 42 CFR 456.705 which requires states to establish detailed information for how pharmacies document the prospective drug utilization review performed by pharmacists.

However, the aforementioned technological tools have limitations. For example, the following situations may not be addressed by the current healthcare system's existing DDI screening technology:

- DDI with over-the-counter medications or nutritional supplements may not be identified.
- DDI screening technology may not be conducted for uninsured patients if a cash payment is not adjudicated through an insurance company and the patient uses more than one pharmacy and/or has multiple prescribers.

The DDI screening technology offers assurances that DDIs with CYP3A4 inhibitors will be detected and mitigated in most patients obviating the need for additional risk management measures beyond approved labeling. Based on the currently available DDI

screening technology available in the healthcare system, the Agency has not determined that this risk warrants further consideration for a REMS to ensure the benefits outweigh the risks at this time. Therefore, the REMS options provided in this memo do not address this risk associated with flibanserin.

3.2.2 Syncope with Flibanserin Alone

Clinically significant syncope was reported with the use of flibanserin alone at the proposed clinical dose of 100 mg. In phase 1 studies of healthy premenopausal women, there were three reports of clinically significant syncope considered to be drug-related. These events occurred within one hour of flibanserin administration, with two subjects experiencing syncope after a single dose of flibanserin. Medical interventions included supine placement and intravenous fluids. In the phase 3 controlled trials in premenopausal women with HSDD, the incidence of syncope was 0.4% in the flibanserin 100 mg administered nightly treatment group compared to 0.2% in the placebo group. The syncopal events in the phase 3 trials occurred between 11 and 34 days after initiating flibanserin treatment.

No risk factors or predictors for syncope could be identified based on the clinical trial data. In addition, the timing of events was not predictable, with events observed after a single dose of flibanserin or with more prolonged use.

3.2.3 Hypotension and Syncope with Flibanserin Used Concomitantly with Alcohol

A dedicated interaction study of flibanserin 100 mg with alcohol was conducted in 25 healthy, moderate drinkers, 23 of whom were men. Four of these 25 participants (16%) experienced clinically significant adverse events of severe hypotension and syncope within 1.5 to 4 hours after the co-administration of alcohol and flibanserin. These significant events required medical interventions, such as placement in the supine or Trendelenburg position, leg elevation, and medical monitoring.

It is notable that the alcohol interaction study enrolled only two women, and only moderate alcohol drinkers. Therefore, the risks of hypotension and syncope with the concomitant use of flibanserin and alcohol in women and in less frequent drinkers were not adequately characterized in this study. However, based on gender differences in body size, blood volume, and potential pharmacological responses to drugs^{3,4}, one could anticipate that these risks in women would be at least as concerning as seen in men.

4 FACTORS TO CONSIDER IN DETERMINING THE RISK MANAGEMENT APPROACH FOR FLIBANSERIN-ASSOCIATED HYPOTENSION AND SYNCOPES

When considering the extent and scope of risk management for a drug with serious adverse events the FDA considers a variety of factors in addition to the factors that the FDA is required to consider when contemplating the need for a REMS. The factors

³ Anderson, GD Gender differences in pharmacological response. (2008) *Int Rev Neurobiol* 83:1-10

⁴ Soldin, OP [Sex Differences in Pharmacokinetics and Pharmacodynamics](#). (2009) *Clin Pharmacokinet*. 48(3): 143-157

include but are not limited to available treatment options and any serious risks associated with those treatment options, the specific risks to be mitigated and the presence of any modifiable factors (e.g. the prevalence of alcohol use in the expected patient population and the practicality of modifying this behavior), as well as the clinical context of patient care.

HSDD is a chronic condition characterized by “a deficiency or absence of sexual fantasies and desire for sexual activity” causing “marked distress or interpersonal difficulty.” Estimates of HSDD in U.S. women vary widely, depending on the instruments used for assessment of the condition, as well as menopausal status of the women studied. Two survey studies have estimated the prevalence of HSDD in U.S. premenopausal women to be 7.7% to 14%,^{5,6} potentially affecting 5.5 to 8.6 million U.S. women ages 20 to 49. Currently, there are no approved pharmacotherapies for treating female HSDD.

Hypotension and syncope associated with flibanserin alone or when used concomitantly with alcohol is clinically significant and can result in serious, irreversible, or life-threatening injuries. For patients on flibanserin alone (e.g., those not concomitantly using alcohol), no risk factors or predictors for hypotension and syncope have been identified, with events occurring after a single dose or with more prolonged use. Therefore, a woman receiving flibanserin may be at risk for hypotension/syncope at any time during the course of her treatment, which is expected to be chronic and potentially lifelong. The risk of hypotension and syncope appears to increase with concomitant use of alcohol, and the use of alcohol in the intended population is expected to be prevalent.

The clinical specialties and experience in treating HSDD of potential prescribers of flibanserin are expected to be wide ranging. Prescribers may include sexual medicine specialists, gynecologists, psychiatrists, internists, family medicine practitioners, nurse practitioners and physician assistants. Therefore, any risk mitigation strategy beyond labeling will potentially impact a large number and a wide variety of prescribers.

5 RISK MANAGEMENT OPTIONS FOR FLIBANSERIN-ASSOCIATED HYPOTENSION AND SYNCOPES

In considering risk management options, it is important to clarify certain key aspects about the risks of hypotension and syncope. No predisposing factors have been identified for those events occurring with flibanserin alone; therefore, no known strategies can prevent their occurrence in an individual treated with flibanserin. In addition, the risk window for syncope and hypotension is unpredictable; based upon what was observed in the clinical trials and the alcohol interaction study, these events may occur after the first dose or with more prolonged use. The risks of hypotension and syncope increase when flibanserin is taken with alcohol. Although avoidance of alcohol could mitigate this risk, this approach may not be feasible. According to 2013 national survey data,

⁵ West SL, D'Aloisio AA, Agans RP, Kalsbeek WD, Borisov NN, et al. Prevalence of low sexual desire and hypoactive sexual desire disorder in a nationally representative sample of U.S. women. *Arch Intern Med* 2008;168:1441-9.

⁶ Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: U.S. results from the Women's International Study of Health and Sexuality (WISHeS). *Menopause* 2006;13:46-56.

approximately 50% of premenopausal women report drinking alcohol on a regular basis (at least one drink in the past 30 days), and approximately 25% reported binge drinking (5 or more drinks on the same occasion).⁷ There is no known strategy that effectively ensures that patients taking flibanserin would consistently abstain from consuming alcohol.

Regulatory options under consideration to mitigate the risks of hypotension and syncope, if flibanserin is approved, include labeling alone or labeling with one or more REMS elements. These options are discussed below.

5.1 LABELING

Labeling tools for flibanserin would include the U.S. Prescribing Information (PI) for the prescribers, pharmacists and other healthcare professionals and a MG for the patient. With labeling alone, the PI and MG will be used as the primary tool to communicate to prescribers and patients about the risks of hypotension and syncope, with flibanserin alone and with concomitant alcohol use. The PI provides information for healthcare providers about the safe and effective use of drugs to assist them in deciding whether to prescribe flibanserin as well as to inform them of the importance of avoiding alcohol. The flibanserin MG provides information for patients in patient-friendly language about the risks associated with flibanserin and the importance of avoiding alcohol.

5.1.1 Communication Plan

A REMS with a communication plan (CP) that targets prescribers and pharmacists could be used to inform them of the most serious risks of a drug. A CP can also be developed to support implementation of an element of the REMS, and can inform key audiences (i.e. professional organizations and other healthcare providers involved in the care of patients taking the drug) about risks of a drug.⁸

Recently approved CP REMS have included, but are not limited to, the following tools:

- REMS Letters for healthcare providers and Professional Societies that includes targeted ‘concise’ risk messaging.
- Factsheet: Summary targeted for healthcare providers and addresses the specific risk(s) of concern that the REMS is addressing.
- Journal Information Piece: Content would be similar to a factsheet

A CP for flibanserin could inform prescribers about the serious risks associated with flibanserin (e.g., serious risk of hypotension/syncope and increased risk with alcohol use).

⁷ SAMHSA 2013 National Survey on Drug Use and Health (NSDUH) 2012-2013 (Page 37)
<http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf>

⁸ FDA Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications Draft Guidance September 2009
<http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>

Benefits of a CP REMS

- Targeted risk messaging distributed to healthcare providers to reinforce certain serious risks and safe use conditions described in prescribing information
- PI can be distributed with the CP materials

Limitations of a CP REMS

- Passive communication and will not ensure that every flibanserin prescriber receives and/or reviews the information.
- Not directed at patients, therefore will not ensure that patients will receive the risk messages

5.1.2 Communication Plan and Pharmacy Certification

This option would include the CP REMS mentioned above, and a requirement for pharmacy certification. Pharmacy certification could include the following requirements:

- Pharmacists understand the need to, and agree to, provide counseling each time the drug is dispensed to patients about the risk of hypotension/syncope which can be exacerbated when flibanserin is used concomitantly with alcohol
- Pharmacists understand the need to, and agree to, distribute REMS-related educational information to patients that informs patients of the serious risks associated with flibanserin use.

Benefits of adding Pharmacy Certification

- Provides additional assurance that pharmacists are informed of the risks
- Provides the requirement that the pharmacist is trained about the risks and greater assurance that, prior to receiving flibanserin, patients will be counseled about the serious risk of hypotension/syncope and the need to avoid alcohol while taking flibanserin.

Limitations of adding Pharmacy Certification

- As with all options described, this does not ensure patients will avoid concomitant alcohol use with flibanserin
- Patient access may be impacted if pharmacy certification is required and patients are challenged to find a participating certified pharmacy.

5.1.3 Prescriber and Pharmacy Certification

This option would require prescriber and pharmacy certification.

Prescriber certification could include the following requirements:

- Prescribers acknowledge that they have reviewed REMS materials.
- Prescribers understand the need to, and agree to, provide counseling to patients about the risk of hypotension/syncope alone and the exacerbation of hypotension/syncope with alcohol
- Prescribers understand the importance of proper patient selection (e.g. diagnosis of HSDD, premenopausal women with no contraindicated

medications or other medical conditions, ability to refrain from alcohol use and no history of alcohol abuse).

Pharmacy certification could include all the required elements as outlined above in Section 5.1.2.

Benefits of Adding Prescriber Certification

- Provides additional assurance that, prior to prescribing flibanserin, prescribers have reviewed the REMS materials and are aware of the need to counsel patients about the risks of hypotension and syncope and the increased risk with concomitant alcohol use
- Prescribers may be more informed about proper patient selection and thereby more likely to identify patients who may not be appropriate candidates for flibanserin treatment. Screening out patients who may not be appropriate candidates for therapy may minimize drug exposure at a population level.

Limitations of adding Prescriber Certification

- Screening of patients for alcohol use/abuse may not be effective, because patients historically fail to self-report or underreport alcohol use^{9,10}
- Does not ensure patients will not use alcohol concomitantly
- Because of difficulty accurately screening patients for alcohol use, it may impose additional burden that may have limited benefit.
- Patient access may be impacted if patients seeking treatment are challenged to find a prescriber or pharmacy certified in the REMS program.

6 DISCUSSION

In considering risk management strategies for flibanserin, the benefit of treatment must be weighed carefully against the seriousness of the risks associated with use, including the risks of hypotension/syncope associated with flibanserin alone and exacerbated when used concomitantly with alcohol. If approved, flibanserin has the potential to be used in millions of women in the U.S. and prescribed by a variety of prescriber specialties with diverse clinical expertise in treating female sexual dysfunction.

As detailed above, there are several risk management options that provide progressive levels of assurances that prescribers, pharmacists, and patients have been educated and understand the safe use conditions when taking flibanserin. However, each option has limitations.

None of the risk management strategies described above will prevent or attenuate the risks of hypotension/syncope in an individual woman treated with flibanserin, because no risk factors or predictors for these adverse events have been identified. The temporal

⁹ de Beaupaire R, et al. Comparison of self-reports and biological measures for alcohol, tobacco, and illicit drugs consumption in psychiatric inpatients. *Journal of European Psychiatry*. November (2007) 22 (8):540-548.

¹⁰ Spiegel, DR, I'm Sober Doctor, Really: Best Biomarkers for underreported alcohol use. *Current Psychiatry*, November (2008) 7(9):15-27.

relationship between hypotension/syncope and administration of flibanserin is unpredictable, with events occurring after the first dose, within the first 28 days, and after 28 days of initiating treatment.

Hypotension and syncope exacerbated by concomitant use of flibanserin and alcohol could be mitigated if patients refrain from consuming alcohol. This may not be feasible; because of prevalent alcohol use among the indicated patient population. Patient counseling about the risks associated with drinking alcohol may not necessarily translate into patient understanding or safe patient behavior. Published literature has historically cited the challenges presented by patient non-compliance with medication regimens. One study evaluated the effects of dual-modality (written and spoken) literacy-appropriate education strategies on patient knowledge of, and safe use of, opioid analgesics which included educational directives to avoid alcohol use while taking opioids. Despite both written and verbal directives, patient knowledge tested poorly (overall 18% patient recall of ‘don’t drink alcohol’ directive) around the safe use of alcohol while taking an opioid and patients also reported similar patterns of “actual use” of alcohol while on the opioid.¹¹

Given the above discussion, even the most restrictive REMS may be limited in effectively mitigating the risks of hypotension and syncope alone and when used concomitantly with alcohol in the postmarketing setting, should flibanserin be approved.

7 SUMMARY

This memorandum summarizes several options for risk management of the serious risks of hypotension and syncope with flibanserin. Each option provides progressive levels of assurance that prescribers, pharmacists, and patients have been educated and understand the safe use conditions when taking this drug. However, no risk management strategy will eliminate the risks of hypotension/syncope associated with flibanserin use alone or the exacerbated risks of hypotension/syncope when combined with alcohol.

¹¹ McCarthy, DM et. al. Improving Patient Knowledge and Safe Use of Opioids: A Randomized Controlled Trial. *Academic Emergency Medicine* (2015) 22:331-339.

VI. Outcomes Assessment Instruments Used in the Flibanserin Development Program

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Date: May 7, 2015

To: Members of the Joint Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee

From: Division of Bone, Reproductive and Urologic Products
Study Endpoint and Labeling Development Team

Subject: Key Outcomes Assessment Instruments Used in the Flibanserin Development Program

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4. Patient Global Impression of Improvement (PGI-I)	9

1. FSFI Instrument (sexual desire domain includes questions 1-2)

[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2010]

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential.

In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

- 5 ☐ = Almost always or always
- 4 ☐ = Most times (more than half the time)
- 3 ☐ = Sometimes (about half the time)
- 2 ☐ = A few times (less than half the time)
- 1 ☐ = Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

- 5 ☐ = Very high
- 4 ☐ = High
- 3 ☐ = Moderate
- 2 ☐ = Low
- 1 ☐ = Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most times (more than half the time)
3 ☐ = Sometimes (about half the time)
2 ☐ = A few times (less than half the time)
1 ☐ = Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

0 ☐ = No sexual activity
5 ☐ = Very high
4 ☐ = High
3 ☐ = Moderate
2 ☐ = Low
1 ☐ = Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

0 ☐ = No sexual activity
5 ☐ = Very high confidence
4 ☐ = High confidence
3 ☐ = Moderate confidence
2 ☐ = Low confidence
1 ☐ = Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most times (more than half the time)
3 ☐ = Sometimes (about half the time)
2 ☐ = A few times (less than half the time)
1 ☐ = Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most times (more than half the time)
3 ☐ = Sometimes (about half the time)
2 ☐ = A few times (less than half the time)
1 ☐ = Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

0 ☐ = No sexual activity
1 ☐ = Extremely difficult or impossible
2 ☐ = Very difficult
3 ☐ = Difficult
4 ☐ = Slightly difficult
5 ☐ = Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

0 ☐ = No sexual activity
5 ☐ = Almost always or always
4 ☐ = Most times (more than half the time)
3 ☐ = Sometimes (about half the time)
2 ☐ = A few times (less than half the time)
1 ☐ = Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

0 ☐ = No sexual activity
1 ☐ = Extremely difficult or impossible
2 ☐ = Very difficult
3 ☐ = Difficult
4 ☐ = Slightly difficult
5 ☐ = Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- 0 ☐ = No sexual activity
- 5 ☐ = Almost always or always
- 4 ☐ = Most times (more than half the time)
- 3 ☐ = Sometimes (about half the time)
- 2 ☐ = A few times (less than half the time)
- 1 ☐ = Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- 0 ☐ = No sexual activity
- 1 ☐ = Extremely difficult or impossible
- 2 ☐ = Very difficult
- 3 ☐ = Difficult
- 4 ☐ = Slightly difficult
- 5 ☐ = Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- 0 ☐ = No sexual activity
- 5 ☐ = Very satisfied
- 4 ☐ = Moderately satisfied
- 3 ☐ = About equally satisfied and dissatisfied
- 2 ☐ = Moderately dissatisfied
- 1 ☐ = Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- 0 ☐ = No sexual activity
- 5 ☐ = Very satisfied
- 4 ☐ = Moderately satisfied
- 3 ☐ = About equally satisfied and dissatisfied
- 2 ☐ = Moderately dissatisfied
- 1 ☐ = Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- 5 ☐ = Very satisfied
- 4 ☐ = Moderately satisfied
- 3 ☐ = About equally satisfied and dissatisfied
- 2 ☐ = Moderately dissatisfied
- 1 ☐ = Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- 5 ☐ = Very satisfied
- 4 ☐ = Moderately satisfied
- 3 ☐ = About equally satisfied and dissatisfied
- 2 ☐ = Moderately dissatisfied
- 1 ☐ = Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- 0 ☐ = Did not attempt intercourse
- 1 ☐ = Almost always or always
- 2 ☐ = Most times (more than half the time)
- 3 ☐ = Sometimes (about half the time)
- 4 ☐ = A few times (less than half the time)
- 5 ☐ = Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- 0 ☐ = Did not attempt intercourse
- 1 ☐ = Almost always or always
- 2 ☐ = Most times (more than half the time)
- 3 ☐ = Sometimes (about half the time)
- 4 ☐ = A few times (less than half the time)
- 5 ☐ = Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- 0 ☐ = Did not attempt intercourse
- 1 ☐ = Very high
- 2 ☐ = High
- 3 ☐ = Moderate
- 4 ☐ = Low
- 5 ☐ = Very low or none at all

Thank you for completing this questionnaire

2. e-Diary for Satisfying Sexual Events (SSEs)

[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2010]

10.11 ELECTRONIC DIARY (E-DIARY FOR HSDD TRIALS)

The eDiary will be interactive. The precise question(s) which appear (and the wording of those questions) depend upon the responses entered by the patient and the time of the last eDiary entry (e.g., if a patient enters a response indicating that she has not had sexual activity since the last entry, questions asking for descriptions of sexual activity since the last entry will not appear). The first eDiary entry will ask about the previous 24 hour period only. Minor details regarding how questions appear may be different.

1. Did you have sex. . .

["in the last 24 hours" for first assessment] OR
["since you last entry" if last entry is < 7 days ago] OR
["in the last 7 days" if last entry is > 7 days 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 patient answers "yes" to the previous question.

2. How many times did you have sex . . .

["in the last 24 hours" for first assessment] OR
["since you last entry" if last entry is < 7 days ago] OR
["in the last 7 days" if last entry is > 7 days ago]

<Number spinner to increase by increments of 1>

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

3. Select the day of your sexual activity.

3a. Was the sex satisfying for you? ¹

☐ NO

☐ YES

3b. Did you have an orgasm?

☐ NO

☐ YES

¹ satisfying for you = gratifying, fulfilling, satisfactory, and/or successful *for you*. Your partner's satisfaction is not the subject of this question.

3. Female Sexual Distress Scale-Revised (FSDS-R)

[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2010]

(FSDS-R)©
FEMALE SEXUAL DISTRESS SCALE
(Revised-2005)

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST _____7 DAYS_____ INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems.**

<u>NEVER</u>	<u>RARELY</u>	<u>OCCASIONALLY</u>	<u>FREQUENTLY</u>	<u>ALWAYS</u>
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1. Distressed about your sex life	0	1	2	3	4
2. Unhappy about your sexual relationship	0	1	2	3	4
3. Guilty about sexual difficulties	0	1	2	3	4
4. Frustrated by your sexual problems	0	1	2	3	4
5. Stressed about sex	0	1	2	3	4
6. Inferior because of sexual problems	0	1	2	3	4
7. Worried about sex	0	1	2	3	4
8. Sexually inadequate	0	1	2	3	4
9. Regrets about your sexuality	0	1	2	3	4
10. Embarrassed about sexual problems	0	1	2	3	4
11. Dissatisfied with your sex life	0	1	2	3	4
12. Angry about your sex life	0	1	2	3	4
13. Bothered by low sexual desire	0	1	2	3	4

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4. Patient Global Impression of Improvement (PGI-I)

[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2010]

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

Patient Global Impression of Improvement

1 ☐ Very much improved

2 ☐ Much improved

3 ☐ Minimally improved

4 ☐ No change

5 ☐ Minimally worse

6 ☐ Much worse

7 ☐ Very much worse

**VII. Complete Response Letter,
August 27, 2010**

6 PAGES HAVE BEEN WITHHELD IN FULL

VIII. Complete Response Letter, September 27, 2013

9 PAGES HAVE BEEN WITHHELD IN FULL

IX. Dispute Appeal Denied Letter, February 7, 2014

8 PAGES HAVE BEEN WITHHELD IN FULL