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APPLICATION NUMBER:

022526Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA #	NDA 022526
Applicant Name	Sprout Pharmaceuticals
Date of Submission	February 18, 2015
PDUFA Goal Date	August 18, 2015
Proprietary Name / Established (USAN) Name	Addyi (flibanserin)
Dosage Forms / Strength	100 mg tablets
Proposed Indication	Treatment of hypoactive sexual desire disorder in premenopausal women
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Catherine Sewell, M.D., M.P.H. (efficacy) and Olivia Easley, M.D. (safety)
Statistical Reviews	Kate Dwyer, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Alexander Jordan, Ph.D.
CMC Review	Zhengfang Ge, Ph.D. and Moo Jhong Rhee, Ph.D.
Clinical Pharmacology Review	LaiMing Lee, Ph.D., Myong-Jin Kim, Pharm.D. and E. Dennis Bashaw, Pharm.D.
Biopharmaceutics Review	Vidula Kolhatkar, Ph.D., Kelley Kitchens, Ph.D., and Tapash Ghosh, Ph.D.
CDTL Review	Christina Chang, M.D., M.P.H.
Deputy Director for Safety	Christine Nguyen, M.D.
Division of Neurology Products	Ronald Farkas, M.D., Ph.D. and William Dunn, M.D.
Controlled Substance Staff	Katherine Bonson, Ph.D. and Silvia Calderon, Ph.D., Michael Klein, Ph.D.
Clinical Outcomes Assessment Staff	Ashley Slagle, Ph.D., M.S. and Elektra Papadopoulos, M.D., M.P.H.
OSE/DMEPA	Walter Fava, R.Ph., M.S.Ed. and Danielle Harris, Pharm.D., B.C.P.S.
OSE/DRISK	Somya Dunn, M.D., Joan Blair, R.N., M.P.H., Kim Lehrfeld, Pharm.D., and Reema Mehta, Pharm.D., M.P.H.
OPDP	Lynn Panholzer, Pharm.D.
Office of Medical Policy, DMPP	Karen Dowdy, R.N., B.S.N., Marcia Williams, Ph.D., and LaShawn Griffiths, M.S.H.S.-P.H., B.S.N., R.N.
Office of Scientific Investigations	Chrissy Cochran, Ph.D.

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

OPDP=Office of Prescription Drug Promotion

DMPP= Division of Medical Policy Programs

Summary Review for Regulatory Action

1. Introduction

This is the third review cycle for flibanserin (tradename Addyi), a new molecular entity proposed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Flibanserin is a high affinity 5-hydroxytryptamine (HT)_{1A} receptor agonist and 5-HT_{2A} receptor antagonist, and a moderate antagonist at the 5-HT_{2B}, 5-HT_{2C}, and dopamine D₄ receptors. The mechanism by which flibanserin improves HSDD is unclear. Flibanserin is not approved in any country. The proposed dose is 100 mg taken orally at bedtime on a daily basis, (b) (4). Concerns precluding approval on the two prior review cycles are detailed in previously completed reviews. This memorandum focuses on developments since the second Complete Response letter, including the appeal to the Office of New Drugs, the current resubmission, and the June 4, 2015, public advisory committee meeting. There are three new clinical studies in the resubmission – a simulated driving study to assess whether bedtime flibanserin dosing impacts next-day driving performance and two clinical pharmacology studies that evaluate whether CYP2C9 and CYP2C19 contribute to the metabolism of flibanserin. This memorandum summarizes the key findings from these new studies, integrates efficacy and safety issues that inform the benefit-risk profile, and provides a recommendation on approvability of the application.

2. Background

Hypoactive Sexual Desire Disorder:

The following diagnostic criteria for HSDD are described in the text revision of 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 context of the person's life
- The disturbance causes marked distress or 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 further categorized as “life-long” (present since becoming sexually active) or “acquired” (present in a patient who previously had no problems with sexual desire), and as “generalized” (occurring regardless of the type of stimulation, situation or partner) or “situational.”

The flibanserin phase 3 trials enrolled women with acquired, generalized HSDD of at least six months duration.

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) that combines features of both HSDD and another condition from DSM-IV known as female sexual arousal disorder.

As with HSDD, patients with FSIAD must have associated distress and must not have an alternative explanation that better explains their symptoms. Patients must also have symptoms for approximately 6 months or longer, manifested by at least three of the following:

- Absent/reduced frequency or intensity of interest in sexual activity
- Absent/reduced frequency or intensity of sexual/erotic thoughts or fantasies
- Absent/reduced frequency of initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate
- Absent/reduced frequency or intensity of sexual excitement/pleasure on at least ~75% of sexual encounters
- Absent/reduced sexual interest/arousal in response to internal or external sexual/erotic cues
- Absent/reduced frequency or intensity of genital and/or nongenital sensations during sexual activity on at least ~75% of sexual encounters

There are no FDA approved medications for the treatment of HSDD or FSIAD. The FDA does not discount the importance of non-pharmacologic approaches for women who are diagnosed with these conditions, but recognizes there are women who could benefit from safe and effective pharmacologic treatment. The FDA has recognized the challenges involved in developing products to treat female sexual dysfunction. In 2012, we selected female sexual dysfunction as the focus of one of 20 high priority areas under the Patient Focused Drug Development initiative. We held this patient-focused meeting and a scientific workshop in 2014.¹ At the patient-focused meeting, we heard about the significant impact that symptoms of female sexual dysfunction can have on women's lives, and the challenges they face in finding safe, effective, and tolerable therapies to manage their conditions. Many of the individuals described the significant distress they experience daily, such as the measures they take to avoid intimacy and persistent anxiety, as well as the profound impact on their relationships, self-identity and emotional well-being.

Regulatory History:

This section summarizes the regulatory history of the flibanserin new drug application (NDA) since the last Complete Response letter, which was issued in 2013. This Complete Response letter listed the following concerns precluding approval of the NDA:

- Numerically small treatment differences compared to placebo, which did not clearly outweigh the risks

¹ <http://www.fda.gov/drugs/newsevents/ucm401167.htm>.

- Concerns with content validity of the female sexual function index (FSFI) sexual desire domain, used as the co-primary efficacy endpoint in the third 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 hypotension and syncope, including concerns that the study enrolled mostly men
- 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 appeared temporally associated with accidental injury
- Concerns for residual next-day impairment after bedtime dosing that could adversely affect activities requiring alertness, such as driving

The FDA recommended that the Applicant identify a population in whom a larger treatment effect size may be demonstrated. The FDA also requested 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.

Several months after we issued the second Complete Response letter, the Applicant appealed to John Jenkins, M.D., Director of the Office of New Drugs. The Applicant 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 the appeal, stating that FDA's benefit-risk assessment was sound and did not deviate from precedent for similar decisions. Dr. Jenkins recommended that the Applicant address the issues raised in the Second Complete Response letter to better inform the benefit/risk assessment before resubmitting the NDA.

After Dr. Jenkins denied the appeal, the Applicant conducted the requested driving and clinical pharmacology studies, then resubmitted the NDA.

Letters Written to FDA:

Since the 2013 Complete Response letter, the FDA has received more than two dozen letters about flibanserin from various groups and individuals, including advocacy organizations, clinicians, researchers, and members of Congress. Prior to the June 4, 2015, advisory committee meeting, most letters requested that FDA approve flibanserin or that FDA give flibanserin careful consideration in the context of limited treatment options for women with sexual dysfunction compared to the options available to men. Some of these letters also alleged that this inequality of treatment options reflects gender bias at the FDA, and that the FDA is holding drugs intended to treat female sexual dysfunction to more stringent standards of approval. The FDA has rejected these claims of gender bias and has stressed that our regulatory decision for each product is based on an assessment of whether the benefits

outweigh the risks. Other letters, particularly those received after the June 4, 2015, advisory committee meeting, have requested that FDA not approve flibanserin.

Those requesting approval of flibanserin state that HSDD is an unmet medical need because there are no approved pharmacologic therapies and the condition causes distress that can have a substantial impact on well-being. They also state that women should be able to decide for themselves in conjunction with their healthcare provider whether the benefits of flibanserin, even if modest, outweigh the risks. The letters comment only on adverse reactions of somnolence, fatigue, headache, dizziness and nausea and do not mention the more severe risks of hypotension and syncope.

Those letters against approval state that flibanserin has marginal benefits that are offset by the risks, particularly for a population of generally healthy women. They also state that there is inadequate information about the risks with alcohol use because the alcohol interaction study enrolled mostly men, and that it is infeasible to abstain from alcohol indefinitely while using flibanserin because alcohol is commonly used in the United States. Other concerns include the removal of HSDD from DSM-5, medicalization of differences in sexual desire, de-emphasis of the important role of non-pharmacologic approaches² for sexual complaints, and inappropriate pressure placed upon the drug approval process by the “Even the Score” campaign, which was partly funded by the Applicant.

Claims of Gender Bias:

Those alleging gender bias at the FDA have stated that there are more than 20 medications approved to treat male sexual dysfunction compared to no treatments for female sexual dysfunction. Through responses to press inquiries and proactively at the June 4, 2015, advisory committee meeting, the FDA has rejected the claims of gender bias and has clarified the actual number of approved medications for treating men and women with sexual dysfunction. I am not considering claims or public statements others have made about gender bias when coming to a decision on the approvability of flibanserin. My decision is based solely on the efficacy and safety data submitted in the NDA as well as the benefit/risk assessment of the product.

3. CMC

The Chemistry/Manufacturing/Controls (CMC) reviewers recommended approval of the NDA during the first and second review cycles, pending agreement on labeling.

In the current resubmission, the Applicant proposes:

- Changing the drug product manufacturer from Boehringer Ingelheim Roxane Inc. (b) (4)
- Changing the 30 count tablet containers (b) (4) to 30 cc HDPE bottles, with no change to the materials in contact with the drug product
- (b) (4)

² Frühauf S, Gerger H, Schmidt HM, et al. Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. *Arch Sex Behav*. 2013; 42 (6): 915-33.

The CMC reviewers again recommend approval of the NDA. They have found the Applicant's proposed changes to be acceptable and all chemistry-related portions of labeling have been satisfactorily resolved. In addition, the Office of Compliance has issued an overall acceptable recommendation for the inspections of the manufacturing facilities.

Based on the stability data, CMC supports an expiration dating period of 48 months for the drug product.

See the CMC review by Zhengfang Ge, Ph.D. and the Biopharmaceutics review by Vidula Kolhatkar, Ph.D., for further details.

4. Nonclinical Pharmacology/Toxicology

The current resubmission contains no new non-clinical pharmacology/toxicology data. The non-clinical pharmacology/toxicology reviewer recommended approval during the two prior review cycles, and again recommends approval for the current review cycle. See the reviews by Alexander Jordan, Ph.D., Lynnda Reid, Ph.D., and Abigail Jacobs, Ph.D., for details.

One item of note is that in the first review cycle, Dr. Jordan recommended that flibanserin be contraindicated in women with breast cancer or with a family history of breast cancer. There is a dose-related increase in malignant mammary tumors in mice at exposures about 3 and 10 times those achieved with the clinical dose, based on area under the time-concentration curve (AUC). The CDER Executive Carcinogenicity Assessment Committee concluded that these findings were drug-related. The mechanism by which flibanserin causes tumors in mice is unknown and human relevance is unknown (as discussed in the Safety Section of this memorandum, the clinical data are inconclusive with regard to the human risk of breast cancer). Since the second review cycle, Dr. Jordan is no longer recommending the contraindication, and instead recommends labeling of the mammary tumor findings under Section 13.1 of the package insert (Carcinogenesis, Mutagenesis, Impairment of Fertility). He states that the human risk of breast cancer related to flibanserin is likely to be small, if at all present, because the findings in mice only slightly exceeded the incidence among historical controls, findings were not seen in rats, and the weight of evidence indicates that flibanserin is not genotoxic (positive for mutagenesis in only one of five assays).

Dr. Reid, the Nonclinical Pharmacology/Toxicology supervisor, is recommending including the tumor findings under the Warnings and Precautions section of labeling as well as in Section 13.1. Dr. Reid states that the animal findings are particularly noteworthy given the intended target population of generally healthy premenopausal women and may be an important consideration for some healthcare providers and women when deciding whether or not to use flibanserin. Dr. Reid also notes that this information may be missed if it is included only in the Animal Toxicology section (Section 13.1) of the label.

The carcinogenicity studies also found statistically significant increases for combined hepatocellular adenomas/carcinomas in female mice (at exposures 10 times clinical exposure

based on AUC) and for hepatocellular carcinomas in male mice (at exposures eight times the clinical exposure based on AUC). This finding will be labeled in Section 13.1.

Flibanserin has no significant effects on fertility in male or female rats. There are also no concerning non-clinical signals for teratogenicity. In pregnant rats dosed during organogenesis, embryofetal toxicity was only seen in conjunction with maternal toxicity, with a no observed adverse effect level of 15 times the clinical exposure based on AUC. In pregnant rabbits dosed during organogenesis, there were no treatment-related teratogenic effects at any dose level.

5. Clinical Pharmacology/Biopharmaceutics

This resubmission contains two new clinical pharmacology studies, which are summarized in this section. Key Clinical Pharmacology findings from prior review cycles are also discussed here. See the reviews and addendum by LaiMing Lee, Ph.D. for details.

This section focuses only on the clinical pharmacology data. Pertinent safety data from these studies are included in the Safety section.

In premenopausal women, the 100 mg flibanserin dose has a median Tmax of 45 minutes (range 45 minutes to 4 hours) and mean half-life of about 11 hours. Cmax is dose proportional from 100 to 250 mg whereas overall exposure (AUC) appears to be greater than dose proportional across this dose range.

CYP3A4 Inhibitors: Table 1 summarizes the effects of moderate and strong CYP3A4 inhibitors on the pharmacokinetics of flibanserin.

Table 1. Effect of moderate and strong CYP3A4 inhibitors on flibanserin pharmacokinetics				
Co-administered product	Itraconazole 200 mg¹ for 8 days	Ketoconazole 400 mg for 5 days	Fluconazole² 400 mg loading then 200 mg for 3 days	Grapefruit Juice^{3,4} 240 mL Regular Strength
Flibanserin dose	50 mg once	50 mg once	100 mg once	100 mg once
Inhibition of CYP3A4	Strong	Strong	Moderate	Moderate
Flibanserin AUC _{0-inf} fold change	2.6	4.6	7.0	1.4
Flibanserin Cmax fold change	1.7	1.8	2.2	1.1
Change in flibanserin half-life	↑4.2 hours	↑7.4 hours	↑13 hours	↓0.7 hours
¹ CYP3A4 inhibition was not maximized because the itraconazole dose was only 200 mg, not 400 mg ² Fluconazole is a moderate CYP3A4 inhibitor, moderate CYP2C9 inhibitor, and strong CYP2C19 inhibitor ³ Extent of CYP3A4 inhibition depends on the source and strength of grapefruit juice ⁴ Single administration of grapefruit juice; does not adequately assess the effect of chronically administered grapefruit juice				

CYP2C9 and CYP2C19: As discussed by the Clinical Pharmacology reviewer, the 7-fold increase in flibanserin AUC_{0-inf} with fluconazole (a moderate CYP3A4 inhibitor) exceeds the 4.6-fold increase in flibanserin AUC_{0-inf} with ketoconazole (a strong CYP3A4 inhibitor). Fluconazole is also a moderate inhibitor of CYP2C9 and a strong inhibitor of CYP2C19, suggesting that either or both of these CYP enzymes are involved in the metabolism of flibanserin.

In lieu of a drug interaction study, the Applicant compared flibanserin exposures in CYP2C9 or CYP2C19 poor metabolizers to exposures in CYP2C9 and CYP2C19 extensive metabolizers. The poor metabolizers have deficient CYP2C9 or CYP2C19 enzyme activity, whereas the extensive metabolizers have intact enzyme activity. Flibanserin exposures were not increased in the CYP2C9 poor metabolizers, suggesting no involvement of CYP2C9 in the metabolism of flibanserin. In contrast, flibanserin systemic exposure (AUC_{0-inf}) increased 34% and C_{max} increased 49% in the CYP2C19 poor metabolizers compared to the extensive metabolizers, with one CYP2C19 poor metabolizer having a 3.2-fold increase in AUC_{0-inf} and 1.8-fold increase in C_{max} . Examples of CYP2C19 inhibitors include some antidepressants, anticonvulsants and proton pump inhibitors.

Effect of Oral Contraceptives (Weak CYP3A Inhibitor): Combined oral contraceptives are weak CYP3A4 inhibitors. Based on a meta-analysis of phase 1 pharmacokinetic data, women who concomitantly received oral contraceptives and various doses of flibanserin had modest increases in flibanserin exposures (AUC_{0-inf} increased 42% and C_{max} increased 12%).

CYP3A4 Inducers: Flibanserin AUC is lowered by 96% and C_{max} is lowered by 91% when flibanserin is co-administered with rifampin, a strong CYP3A4 inducer. Co-administration of flibanserin with the moderate CYP3A4 inducer, etravirine, had modest effects on flibanserin pharmacokinetics (AUC decreased 21% and C_{max} decreased 3%).

Alcohol: The Applicant conducted a randomized, double-blind, cross-over alcohol interaction study involving 25 healthy subjects, 23 of whom were men. The subjects received the following treatments in random order:

- Flibanserin 100 mg alone
- 0.4 g/kg 95% ethanol alone (equivalent to about 2 drinks³ in a 70 kg person)
- 0.8 g/kg 95% ethanol alone (equivalent to about 4 drinks in a 70 kg person)
- Flibanserin 100 mg plus 0.4 g/kg 95% ethanol
- Flibanserin 100 mg plus 0.8 g/kg 95% ethanol

Subjects had a light breakfast after a 10-hour fast then took flibanserin and/or ethanol. Subjects had up to 10 minutes to drink the ethanol.

³ In the United States, one drink of alcohol contains 14 grams of ethanol and is equivalent to a 12 ounce can of beer containing 5% alcohol content, 5 ounces of wine containing 12% alcohol content, or a 1.5 ounce shot of 80-proof spirits (see <http://www.cdc.gov/alcohol/faqs.htm> and http://pubs.niaaa.nih.gov/publications/Practitioner/PocketGuide/pocket_guide2.htm).

The data from this study suggest that alcohol modestly reduces flibanserin exposures. Partial AUC (AUC_{0-4 hr}) was reduced by about 10% with 0.4 g/kg ethanol and by about 4% with 0.8 g/kg ethanol. Because of the limited data and incomplete concentration-time profiles, the effect of ethanol on flibanserin exposure is not conclusive.

Digoxin: Digoxin is a P-glycoprotein (P-gp) substrate. Flibanserin increases digoxin AUC_{0-inf} by 96% and Cmax by 47%. Based on these *in vivo* results, Clinical Pharmacology concludes that flibanserin is an inhibitor of P-gp.

Food Effect: The Applicant conducted a food-effect study using a single 50 mg dose of flibanserin similar to the 50 mg tablet formulation tested in some phase 3 trials. Compared to the fasted state, flibanserin AUC_{0-inf} increased 17% with a low-fat breakfast, 43% with a medium fat breakfast, and 56% with a high fat/high calorie breakfast. Flibanserin Cmax decreased 1% with the low-fat breakfast and increased 12% with the medium fat breakfast and 15% with the high fat/high calorie breakfast. Tmax was 0.8 hours under fasted conditions and 2 hours after the high fat/high caloric meal. The phase 3 trials did not include instructions about timing of flibanserin in relation to meals. The Applicant proposes that flibanserin be taken at bedtime (b) (4).

Hepatic Impairment: The Applicant studied the pharmacokinetics of flibanserin following a single 50 mg dose in 14 patients with hepatic impairment (10 with mild impairment and 4 with moderate impairment) and 14 healthy matched controls. In patients with mild hepatic impairment, flibanserin systemic exposure (AUC_{0-inf}) was increased 4.5-fold and Cmax was reduced 10% compared to healthy controls. In patients with moderate hepatic impairment, flibanserin AUC_{0-inf} was increased 2.6-fold and Cmax was reduced 63% compared to healthy controls. The fold-increase in flibanserin systemic exposure in patients with mild hepatic impairment is comparable to what is seen with co-administration of flibanserin and the strong CYP3A4 inhibitor ketoconazole. The available data are inconclusive as to whether flibanserin exposures would be lower in patients with more advanced hepatic impairment because there are insufficient pharmacokinetic data in patients with moderate hepatic impairment (n=4) and no pharmacokinetic data in patients with severe hepatic impairment.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The three randomized, double-blind, placebo-controlled phase 3 trials (Study 511.71, 511.75 and 511.147) submitted to support the efficacy of flibanserin for the treatment of HSDD in premenopausal women have been extensively reviewed during the prior review cycles. In this section, I summarize the key efficacy findings and design features that will be taken into account in the benefit-risk assessment. See the clinical efficacy review by Catherine Sewell,

M.D., M.P.H., the statistical review by Kate Dwyer, Ph.D. and the Cross-Discipline Team Leader (CDTL) memorandum by Christina Chang, M.D., M.P.H. for further details.

These trials had two co-primary efficacy endpoints, one that assessed the number of satisfying sexual events (standardized over a 28-day period) and the other that measured sexual desire.

The 28-day sexual desire score was used as the sexual desire co-primary endpoint for the first two trials. For these trials, the change from baseline to the final visit in the 28-day sexual desire score was calculated based on patient responses to the question: “Indicate your most intense level of sexual desire.” Patients rated their level from 0 (no desire) to 3 (strong desire) daily in an electronic diary. These responses were summed over a 28-day period to yield the 28-day sexual desire score, which ranged from 0 to 84.

The desire domain of the Female Sexual Function Index (FSFI) was used as a secondary endpoint in the first two trials and as the sexual desire co-primary endpoint in the third trial. The desire domain of the FSFI has two questions. The first question asks patients “Over the past 4 weeks, how often did you feel sexual desire or interest?” Response options range from 1 (almost never to never) to 5 (almost always or always). The second question asks patients “Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?” Response options range from 1 (very low or none at all) to 5 (very high). The FSFI desire score was calculated by adding the patient’s responses to these two questions, then multiplying the sum by 0.6, with a range from 1.2 to 6.0.

The three trials each had a secondary efficacy endpoint that measured distress related to sexual desire using Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R). This question asks “How often did you feel: Bothered by low sexual desire?” Patients assessed their sexual distress over a 7-day recall period and responded on a scale of 0 (never) to 4 (always).

Table 2 summarizes the main efficacy results. All three trials showed a statistically significant improvement with flibanserin compared to placebo in the number of satisfying sexual events. The first two trials failed on their co-primary sexual desire endpoint (the daily sexual desire score), but showed improvement with flibanserin over placebo on the secondary endpoints of desire assessed with the FSFI and distress related to low desire. The associated p-values for these two secondary analyses were less than 0.05, but are considered nominal p-values because the trials failed on their co-primaries. The third trial used the FSFI desire domain as the pre-specified co-primary endpoint for sexual desire and showed statistically significant improvement with flibanserin over placebo for both the FSFI desire co-primary and the secondary distress endpoint.

For all three trials, sensitivity analyses for handling of missing data yielded results consistent with the primary efficacy analyses.

**Table 2. Main Efficacy Results from the Phase 3 Trials for Flibanserin 100 mg Dosed at Bedtime
Full Analysis Set**

(Adapted from Tables 5-8 in the Clinical Review, with Corrections by the Statistical Reviewer)

Full Analysis Set	Study 511.71		Study 511.75 ^a		Study 511.147	
	Flibanserin n=280	Placebo n=290	Flibanserin n=365	Placebo n=372	Flibanserin n=532	Placebo n=536
Satisfying Sexual Events (Per 28 Days)						
Baseline (mean)	3.0	2.7	2.6	2.7	2.5	2.7
Change from Baseline (mean)	1.6	0.8	1.8	1.1	2.5	1.5
Change from Baseline (median) ^b	1.0	0.0	1.0	0.5	1.0	0.5
Treatment Difference (median) ^b	1.0		0.5		0.5	
p-value	<0.01		<0.01		<0.0001	
Sexual Desire (Daily Electronic Diary) – Range 0-84						
Baseline (mean)	13	12	12	10	Not done	Not done
Change from Baseline (LS mean)	9	7	8	7		
Treatment Difference	2 (-0.1, 5)		2 (-0.5, 4)			
p-value	Not significant		Not significant			
Sexual Desire (FSFI) – Range 1.2-6.0						
Baseline (mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from Baseline (LS mean)	0.9	0.5	0.9	0.5	1.0	0.7
Treatment Difference ^c	0.4 (0.2, 0.5)		0.3 (0.2, 0.5)		0.3 (0.2, 0.4)	
p-value	<0.05 ^d		<0.05 ^d		<0.0001	
Distress Related to Desire – Range 0-4						
Baseline (mean)	3.2	3.2	3.2	3.2	3.4	3.4
Change from Baseline (LS mean)	-0.8	-0.5	-0.8	-0.5	-1.0	-0.7
Treatment Difference ^c	-0.4 (-0.5, -0.2)		-0.3 (-0.4, -0.1)		-0.3 (-0.4, -0.1)	
p-value	<0.05 ^d		<0.05 ^d		0.0001	
Full analysis set = all randomized patients who took at least one dose of study medication and had at least one on-treatment efficacy assessment. Missing data were imputed using last-observation-carried-forward.						
FSFI = female sexual function index; CI = confidence interval						
^a Excludes two sites because of data integrity issues (see Section 11 of this memorandum for details)						
^b Medians also shown because the data were not normally distributed						
^c LS mean (95% confidence interval)						
^d Nominal p-value because the study failed on the co-primary desire endpoint						

Results for satisfying sexual events, the FSFI desire score, and the distress score are consistent across all three trials but there are sizeable placebo effects and the treatment differences are numerically small, as summarized below.

- From a median baseline of about 2-3 satisfying sexual events/month, flibanserin resulted in

a median increase over placebo of about 0.5-1.0 satisfying sexual events/month.

- From a mean baseline of 10-12 on the daily sexual desire score (performed in the first two trials only), flibanserin resulted in a non-significant mean increase over placebo of 2 (the daily sexual desire score range is 0-84)
- From a mean baseline of about 1.8-1.9 on the FSFI desire score, flibanserin resulted in a mean increase over placebo 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 mean improvement over placebo of 0.3-0.4 (on a scale of 0-4).

Based on descriptive analyses (the trials were not prospectively designed to formally assess timing of onset of effect), most of the treatment effect is apparent by eight weeks after starting treatment.

During this review cycle, we conducted *post hoc* subgroup analyses to explore whether the magnitude of the treatment effect depends on baseline severity of symptoms (e.g., baseline number of satisfying sexual events, baseline FSFI desire score, and baseline FSFS-R Question 13 distress score). We did not identify notable patterns or differences in treatment effect among any of the subgroups evaluated.

Both the Applicant and FDA conducted supportive responder analyses to help interpret the clinical meaningfulness of the observed changes in the efficacy parameters. Here I discuss the FDA approach. The Applicant's approach yielded similar results. We used the receiver operating characteristic (ROC) method to relate changes in the efficacy endpoints to the results of the patient global impression-improvement (PGI-I) scale. The PGI-I asks "How is your condition – meaning decreased sexual desire and feeling bothered by it – today compared to when you started study medication?" Responses are rated from 1 (very much improved) to 7 (very much worse).

The analysis I focus on here categorizes a patient as "satisfied" if they responded "very much improved" or "much improved" at the final visit. Everyone else was classified as "unsatisfied". Using this dichotomy, we used the ROC analysis to estimate the cutpoint (by maximizing sensitivity and specificity) for the change from baseline in satisfying sexual events that represents the smallest allowed change to be considered a responder. Similar ROC analyses were used for the FSFI sexual desire endpoint and desire distress endpoint.

As shown in Table 3, when anchoring to "very much improved" or "much improved" on the PGI, the absolute difference between the percentage of responders with flibanserin and the percentage of responders with placebo is 8-9% for satisfying sexual events, 10-13% for FSFI sexual desire, and 7-13% for distress. Again, there is a sizeable placebo effect. The primary clinical review states that it is not "reasonable for the approximately 90% of treated patients who will not respond to the product to be exposed to the numerous serious risks posed by flibanserin therapy." To clarify, the percentage of responders (anchored to much improved or very much improved) among flibanserin-treated patients ranges from 21% to 48%, depending

on the endpoint and trial (Table 3).

Table 3. Percentage of Responders in the Phase 3 Trials by Anchoring Efficacy to the Patient Global Impression of Improvement (Much Improved or Very Much Improved) (Adapted from Table 17 in the Clinical Review)						
	Study 511.71		Study 511.75 ^a		Study 511.147	
	Flibanserin	Placebo	Flibanserin	Placebo	Flibanserin	Placebo
Satisfying Sexual Events (Per 28 Days)						
Responder Rate (%)	29%	21%	39%	31%	31%	22%
Treatment Difference	8%		9%		9%	
Sexual Desire (FSFI)						
Responder Rate (%)	43%	31%	46%	33%	48%	38%
Treatment Difference	12%		13%		10%	
Distress Related to Desire						
Responder Rate (%)	28%	14%	21%	15%	34%	25%
Treatment Difference	13%		7%		9%	
FSFI = female sexual function index						
^a Excludes two sites because of data integrity issues						

The Clinical Outcomes Assessment Staff (previously known as the Study Endpoints Labeling and Development Team) have extensively reviewed the validity of the FSFI sexual desire domain. See the reviews by Ashley Slagle, Ph.D., for details. Based on two validation studies completed by the Applicant, most of the participants described the definition of sexual desire in the FSFI instructions as relevant and important. Most of the women also reported that the two desire items were clear, easy to understand, and relevant. Most preferred a recall period of 1-2 weeks or four weeks, although in one study, nearly one-half of the participants stated they would answer differently if recalling the past 24 hours or seven days compared to the past four weeks with comments such as “because each week is different.” About one in five participants favored a 24-hour recall. Clearly, there is residual uncertainty about the optimal recall period for this instrument in terms of patient preference, but importantly also in terms of what produces the more valid and reliable measurement of desire. One possibility is that the longer recall period could increase noise in the assessment, which would attenuate observed treatment effects and bias towards the null. However, with a longer recall period, it is also possible that patient recollection could be more heavily influenced by other feelings or experiences or by more recent desire experiences. The Applicant’s view is that desire is a “state,” which is best assessed over a monthly recall period and not by frequent assessments, such as daily. This view seems somewhat at odds with the preferences reported in the validation studies described above.

Other concerns identified by the Clinical Outcomes Assessment Staff include the multi-barreled FSFI instructions (which preclude the ability to assess which aspect of sexual desire is driving changes in the score), whether the response options are an appropriate reflection of benefit (e.g., reporting sexual desire “almost always or always”), and uncertainty about what

change in score constitutes meaningful improvement.

Based on the residual concerns described above, the Clinical Outcomes Assessment Staff have concluded that the FSFI sexual desire items may not be an optimal instrument, but may provide interpretable findings of efficacy if there is a meaningful and reasonably sized magnitude of effect.

The two methods used to assess sexual desire (daily desire with an electronic diary in the first two trials and the FSFI desire domain) each have their strengths and limitations. The concerns with the FSFI desire domain are summarized above. Concerns raised with the daily desire assessment include diary fatigue due to entering information every day for six months and too frequent an assessment of desire, which is better assessed over longer periods as a “state”. Neither instrument is perfect. However, it is noteworthy that the results with the FSFI desire domain consistently mirrored the improvement seen in the number of satisfying sexual events and the reduction in distress related to low sexual desire.

Based on the totality of the data and the consistency of the treatment differences (e.g., point estimates, 95% confidence intervals, and responder analyses) across the trials, I conclude that efficacy has been established for the treatment of HSDD. While, on average, treatment effects appear small, there is consistent evidence across the three trials that some patients considered the improvement with flibanserin to be clinically meaningful when compared to placebo.

8. Safety

This section focuses on the most significant safety concerns with flibanserin. See the Clinical Safety review by Olivia Easley, M.D., and the CDTL memorandum by Christina Chang, M.D., M.P.H. for further details.

Hypotension and Syncope: Flibanserin alone causes hypotension and syncope in some patients. This risk is increased when flibanserin is co-administered with alcohol or with moderate or strong CYP3A4 inhibitors. This section summarizes the data supporting these conclusions.

Flibanserin alone: In phase 1 studies there were 6 reports of syncope in subjects who received flibanserin alone, dosed during the daytime. Five events occurred in women (two with a 50 mg dose and three with the 100 mg dose), and one occurred in a man (who received a 200 mg dose). Syncope in one of the subjects who received the 50 mg dose occurred four days after the flibanserin dose, which virtually excludes a drug-related event. The remaining events occurred 20 minutes to 1 hour after dosing, which is close to T_{max}. One of the three subjects who had syncope after the 100 mg dose was in the CYP2C19 pharmacogenomic study and was a CYP2C19 poor metabolizer. This subject had flibanserin C_{max} 2.1-fold higher than the mean C_{max} among the extensive metabolizers. Blood pressure at the time of the event was normal in two of these subjects and not recorded in the other four subjects. One of the five subjects who had syncope within one hour of dosing required intravenous fluids, another was placed supine, and the remaining three reportedly required no medical intervention.

In the five phase 3, placebo-controlled HSDD trials in premenopausal women, syncope⁴ was reported in 6/1543 (0.4%) patients treated with flibanserin 100 mg at bedtime and 4/1905 (0.2%) patients treated with placebo. One of the cases with flibanserin was coded as serious because the syncope led to a concussion requiring hospitalization. It is unclear what role flibanserin played in this event because the patient had a history of hypotension and orthostatic dysregulation. The findings from phase 3 support a numerical imbalance in events of syncope not favoring flibanserin. The incidence of syncope is low and differences between groups are small, but these findings are noteworthy and cannot be dismissed given the concerning cases of syncope seen with flibanserin in other settings, such as with daytime use in the phase 1 studies and when coadministered with alcohol or with moderate or strong CYP3A4 inhibitors.

Alcohol: As discussed previously, the Applicant conducted a dedicated alcohol interaction study in 25 healthy subjects, 23 of whom were men. Four subjects (all men) co-administered 100 mg of flibanserin and 0.4 g/kg 95% ethanol (equivalent of about 2 standard alcohol drinks in a 70 kg person) had concerning events of hypotension or syncope. The events occurred 1.5 to 4 hours after dosing. One of the subjects was placed in Trendelenburg position, and the remaining three subjects were placed supine. One subject also received ammonia inhalant. Among these four subjects, the magnitude of the systolic blood pressure reductions ranged from 28 to 54 mmHg, and the magnitude of the diastolic blood pressure reductions ranged from 24 to 46 mmHg.

In addition, six subjects who received flibanserin with 0.8 g/kg 95% ethanol experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions in these six subjects ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. One of these subjects also required therapeutic intervention (ammonia salts and placement supine with the foot of the bed elevated).

The phase 3 HSDD trials in premenopausal women had no restrictions on alcohol consumption. However, these trials were not prospectively designed to assess the interaction between alcohol and flibanserin, and did not capture data on alcohol use during the randomized treatment period. Therefore, the frequency and quantity of alcohol use among flibanserin-treated patients in these trials is unknown.

Moderate or Strong CYP3A4 Inhibitors: As discussed previously, fluconazole (a moderate CYP3A4 inhibitor, moderate CYP2C9 inhibitor, and strong CYP2C19 inhibitor) increases flibanserin AUC_{0-inf} 7-fold. One of the subjects co-administered flibanserin and fluconazole became unresponsive 1 hour after dosing, and had a reduction in blood pressure from 92/65 mmHg to 64/41 mmHg with a heart rate of 50 beats/minute and oxygen saturation of 88%. The subject was given oxygen and intravenous fluids and transferred to the emergency room where she was initially unable to speak, responding only to painful stimuli. She fully recovered within a few hours. Two other subjects dosed with the combination developed symptomatic hypotension about 1 hour after dosing, with a blood pressure of 80/49 mmHg in one of the

⁴ MedDRA preferred terms of syncope, circulatory collapse, syncope vasovagal and loss of consciousness.

subjects and a blood pressure of 73/41 mmHg in the other subject. Due to these events, the Applicant terminated this portion of the study early before all subjects could be dosed.

Ketoconazole (a strong CYP3A4 inhibitor) increases flibanserin AUC_{0-inf} 4.6-fold. One subject who received flibanserin 50 mg with ketoconazole developed orthostatic hypotension and syncope about 1 hour after dosing. Blood pressure at the time of the event was not recorded, and a medical intervention was reportedly not needed.

Central Nervous System Depression: Flibanserin can cause central nervous system depression. For example, in the pooled placebo-controlled phase 3 database in premenopausal women with HSDD, the incidence of somnolence was 17% with flibanserin 50 mg twice daily, 11% with flibanserin 100 mg at bedtime and 3% with placebo.

The risk of central nervous system depression is increased if flibanserin is taken during waking hours, with alcohol, or in settings that increase flibanserin concentrations. For example, in the alcohol interaction study, the incidence of somnolence was numerically higher with morning dosing of flibanserin (16/24 or 67%) compared to 0.4 g/kg 95% ethanol (9/24 or 38%) or 0.8 g/kg 95% ethanol (15/25 or 60%). In addition, the incidence of somnolence was numerically higher when flibanserin and alcohol were co-administered compared to flibanserin alone or alcohol alone.

Although flibanserin is dosed at bedtime, the half-life is about 11 hours, raising the potential for residual next day impairment. There were 42 patients treated with flibanserin 100 mg at bedtime (2.7%) and 47 patients treated with placebo (2.5%) who reported accidental injury in the pooled, placebo-controlled, phase 3 database in premenopausal women with HSDD. The Clinical Reviewer searched for adverse events reported within 24 hours prior to these accidental injuries that may be related to central nervous system depression.⁵ Accidental injury with corresponding central nervous system depression was reported by 9 flibanserin-treated patients (21% of those reporting accidental injury) compared to 3 placebo-treated patients (6% of those reporting accidental injury).

The FDA requested that the Applicant conduct a driving study to further evaluate whether flibanserin could potentially impair next-day activities requiring mental alertness, such as driving. This simulated driving study enrolled 83 healthy premenopausal women (33 of whom were taking hormonal contraceptives) and assessed driving performance nine hours after bedtime dosing of flibanserin, placebo or zopiclone (positive control). Subjects were assessed after a single 100 mg dose of flibanserin, after a single 200 mg supratherapeutic dose of flibanserin, and at steady-state after taking flibanserin 100 mg for seven nights. There were no adverse effects of flibanserin on the ability to maintain lane position (the prespecified primary endpoint) or on other measures of driving performance. See the review by Ronald Farkas, M.D., Ph.D., for further details.

⁵ Using MedDRA preferred terms of somnolence, fatigue and sedation.

Other Notable Safety Findings:

- **Death:** The only death reported in a flibanserin-treated patient occurred in a 54 year-old postmenopausal woman with asthma, hypertension and hyperlipidemia who died 14 days after starting flibanserin 100 mg at bedtime. She was found unresponsive lying face down on her bed. The autopsy reported the cause of death as acute alcohol intoxication, and also noted coronary artery disease, with a 65 to 70% stenosis of her left anterior descending coronary artery. The patient weighed 150 lbs. and reported a history of having 1-3 alcoholic drinks per day. On autopsy, her alcohol concentration was 0.289 g/100 mL in the blood and 0.327 g/100 mL in the vitreous humor. Various factors can impact the postmortem blood alcohol concentration, including how quickly the alcohol was consumed, the time between alcohol consumption and death, and whether there has been fermentation due to bacteria as the body undergoes decomposition.⁶ Therefore, it is not possible to definitively determine the number of alcoholic drinks consumed by this patient. However, it appears that she had considerable alcohol intake leading up to her death, because the blood alcohol concentration was about 3.5 times the legal limit of 0.08 g/100 mL adopted by all states for an adult operating a motor vehicle (this legal limit corresponds to about 3 alcoholic drinks consumed over 1 hour by a 150 lb. woman⁷). As discussed previously, flibanserin can interact with alcohol to cause severe hypotension and central nervous system depression. Therefore, it is not possible to exclude a role of flibanserin in this patient's death.
- **Breast Cancer:** As discussed previously, flibanserin causes malignant mammary tumors in female mice at exposures 3 and 10 times those achieved with the clinical dose. Data from the entire phase 3 placebo-controlled clinical trial database are inconclusive because these trials did not exceed six months in duration and event rates were low. Therefore, the clinical significance of the findings in mice is unknown.
- **Concomitant Use of Oral Contraceptives:** As discussed previously, oral contraceptives are weak CYP3A4 inhibitors and modestly increase flibanserin exposures. Subgroup analyses in the premenopausal HSDD phase 3 database suggest that these modest effects on flibanserin exposures may slightly increase the incidence of some adverse events, particularly dizziness and fatigue, as shown below:

Dizziness

- 9.9% for flibanserin alone vs. 13.4% for flibanserin + hormonal contraceptive
- 2.1% for placebo alone vs. 2.4% for placebo + hormonal contraceptive

Fatigue

- 7.5% for flibanserin alone vs. 11.4% for flibanserin + hormonal contraceptive
- 4.9% for placebo alone vs. 5.1% for placebo + hormonal contraceptive

⁶ Kugelberg FC and Jones AW. Interpreting results of ethanol analysis in postmortem specimens: A review of the literature. *Forensic Science International*. 2007; 165: 10-29.

⁷ See http://my.clevelandclinic.org/health/tools-quizzes/Blood_Alcohol_Calculator, which is referenced by the National Institute of Alcohol Abuse and Alcoholism (<http://www.rethinkingdrinking.niaaa.nih.gov/tools/calculators/Default.aspx>)

- Appendicitis: The incidence of appendicitis in phase 3 trials, including data from the post-menopausal HSDD trials is 0.13% (6/4979) for flibanserin and 0.0% (0/2924) for placebo. It is unclear whether this minor imbalance (one would have expected about 3 events with placebo given the 1.7:1 overall randomization ratio) reflects a chance finding or a drug-related effect. There is potential biological plausibility based on data from eplivanserin, a serotonin 2A receptor antagonist.
- Abuse Potential: During the last review cycle, the Controlled Substances Staff (CSS) reviewed the human abuse potential study and concluded that the study was invalid because of methodological and outcome issues, including the lack of statistical differentiation between the positive control and placebo. In the current resubmission, CSS reviewed the adverse events from all clinical studies, including the newly completed studies, and concluded that there is no signal for euphoria and no signal indicative of abuse potential. Therefore, CSS recommends that flibanserin not be scheduled under the Controlled Substances Act (b) (4). See the review by Katherine Bonson, Ph.D., for details.

9. Advisory Committee Meeting

The FDA convened two public advisory committee meetings to discuss flibanserin, one during the first review cycle in 2010 and another during the current review cycle on June 4, 2015.

The 2010 advisory committee voted 10 to 1 that the Applicant had not provided sufficient evidence of efficacy. The two phase 3 trials completed at that time had failed to show a statistically significant improvement compared to placebo on the pre-specified co-primary efficacy endpoint that assessed daily sexual desire using an electronic diary. Although these trials showed improvement compared to placebo for the secondary endpoint that used FSFI desire, most of the advisory committee members did not agree with deviating from 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 and alcohol interactions with flibanserin.

We convened another advisory committee meeting on June 4, 2015, to revisit the benefit/risk profile of flibanserin, taking into account data generated in response to FDA's two Complete Response letters issued after the 2010 advisory committee. To ensure sufficient expertise, we held a joint meeting with the Drug Safety and Risk Management advisory committee and supplemented the panel with temporary voting members with expertise in sexual medicine, patient reported outcome assessments, alcohol use, cardiology, emergency medicine, pharmacoepidemiology, and internal medicine.

Nearly 40 individuals signed up to speak at the open public hearing. To ensure that all viewpoints were heard, we extended the open public hearing from the standard one hour duration to 1 hour and 45 minutes. These speakers covered the spectrum of opinions as to whether flibanserin should be approved, and raised the main controversies surrounding flibanserin and treatments for female sexual dysfunction. Panel members heard perspectives from women suffering with low sexual desire, heard concerns about flibanserin's benefit/risk assessment, heard about the Applicant's ties to the "Even the Score" advocacy group, and heard opposing viewpoints as to whether there is gender bias at the FDA with regard to treatments for female sexual dysfunction.

There were 24 voting members on the advisory committee panel. Six of these members voted against approval, citing marginal efficacy and significant safety concerns that outweighed the potential benefits. The remaining 18 members voted that the overall benefit/risk profile of flibanserin is acceptable to support approval but only if risk management options beyond labeling are implemented. Some of the members who voted for approval stated that the vote was difficult. In general, members who voted for approval acknowledged the marginal efficacy and significant safety concerns but took into account the unmet medical need and the fact that some patients seemed to have clinically meaningful benefit. There was strong support among the panel members for a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU), with prescriber and pharmacy certification to ensure that healthcare providers and patients are well-informed about the risks. Some committee members also recommended incorporating informed consent to document that patients understand the risks of treatment. A few members expressed concerns that a restricted program could unduly limit access to the drug and at least one member noted that there are limited data in the public domain about the effectiveness of currently approved REMS programs.

Other noteworthy comments from committee members included the following:

- Recognition that syncope and somnolence are not necessarily benign adverse reactions as there could be significant consequences, including accidental injuries and motor vehicle accidents.
- General agreement that there is insufficient information to assess the alcohol interaction in women because alcohol use was not prospectively assessed in the phase 3 trials and the alcohol interaction study enrolled mostly men and did not assess typical alcohol or flibanserin use (the study required participants to drink all the alcohol within 10 minutes following a morning dose of flibanserin). Some committee members recommended that alcohol use should be contraindicated in patients using flibanserin, although the feasibility of indefinitely abstaining from alcohol was also raised. Others felt that there were insufficient data to conclude whether or not alcohol use should be contraindicated.
- Questions about whether flibanserin could adversely affect fertility or pregnancy outcomes, given that unintended pregnancies are expected to occur based on the indication and target population.
- Mammary tumors in female mice at low clinical exposures and the unknown long-term risk of breast cancer in the indicated population.
- Questions about generalizability of existing clinical data to patients who will likely use the product in the real world setting, such as those with comorbidities, those using concomitant

medications that could interact with flibanserin (e.g., sedatives), those prescribed flibanserin off-label (e.g., postmenopausal women or those with low sexual desire who do not meet the criteria for HSDD), and those who may experience potential interactions with non-prescription CYP3A4 inhibitors (e.g., grapefruit juice, over-the-counter medications, and dietary supplements).

10. Pediatrics

This NDA triggered the Pediatric Research Equity Act (PREA) because of the new active ingredient. The Division and the Pediatric Review Committee (PeRC) concurred with the Applicant's request for a full waiver of the pediatric requirements. Such studies would be impossible because the condition does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

Tradename Review: During this review cycle, the Division of Medication Error Prevention and Analysis re-reviewed the tradename "Addyi" and found it to be acceptable. See the review by Loretta Holmes, B.S.N., Pharm.D., and Danielle Harris, Pharm.D., B.C.P.S., for details.

Site Inspections: No new site inspections were conducted during this review cycle. As discussed in the Clinical Review, the Applicant previously closed two investigator sites for cause because of significant data integrity concerns. These two sites enrolled patients in Study 511.75 (the second pivotal phase 3 trial) and in Study 511.84 (the long-term extension trial). The Office of Scientific Investigations inspected these two sites and issued a Warning Letter to one in 2012, and an Untitled letter to the other in February 2015. Because the identified violations raise concerns about data integrity, we excluded these two sites for the efficacy analyses for Study 511.75 shown in our reviews, the advisory committee briefing materials, and the product label. These data are still included in the safety analyses because the number of affected subjects (69) was small relative to the total size of the safety database.

12. Labeling

Key aspects of labeling are summarized below.

- There will be a Boxed Warning regarding the increased risk of severe hypotension and syncope when flibanserin is used with alcohol, when flibanserin is used with moderate or strong CYP3A4 inhibitors, and when flibanserin is used in patients with hepatic impairment. The Boxed Warning, Contraindications, and Warning and Precautions Sections state that the use of flibanserin is contraindicated in these settings. This labeling is supported by the cases of severe hypotension and syncope that have been observed when flibanserin is used with alcohol or moderate or strong CYP3A4 inhibitors. There are no such cases in patients with hepatic impairment; however, sample sizes were small, only a

50 mg dose of flibanserin was tested in these patients, and the increase in flibanserin exposures was similar to that seen with strong CYP3A4 inhibitors. Therefore, it is appropriate to align the labeling for hepatic impairment with the labeling for strong CYP3A4 inhibitors.

- The Boxed Warning will state that healthcare providers are expected to assess whether patients can reliably abstain from alcohol use prior to prescribing flibanserin, and to counsel patients taking flibanserin about the importance of abstaining from alcohol intake.
- The Dosage and Administration section will state that flibanserin should be taken at bedtime to reduce the risk of central nervous system depression, hypotension and syncope, and to skip missed doses and resume routine dosing at bedtime on the next day. This section will also state that flibanserin should be discontinued after eight weeks if there is no improvement in symptoms.
- There will be a Warning about central nervous system depression, stating that this risk can occur with flibanserin alone and is exacerbated when flibanserin is used with alcohol and other central nervous system depressants, when flibanserin is taken during waking hours, and when flibanserin is used in settings that increase exposures (e.g., with moderate or strong CYP3A4 inhibitors). The Warning will communicate that patients should not participate in activities requiring full alertness (e.g., driving) until at least six hours after the bedtime flibanserin dose and until they know how flibanserin affects them. The Adverse Reactions section will summarize the accidental injury data from the phase 3 trials.
- There will be a Precaution under the Warnings and Precautions section about the malignant mammary tumors that occurred in female mice. Labeling will state that the clinical significance of this finding is unknown. This information is prominently located under the Warnings and Precautions section because the animal findings may be an important consideration for some healthcare providers and women when deciding whether or not to use flibanserin.
- The Adverse Reactions section will summarize the death attributed to acute alcohol intoxication and will state that the role of flibanserin in this death is unknown. This information is pertinent because of the pharmacodynamic interaction between flibanserin and alcohol that can increase the risk for hypotension and central nervous system depression. The Adverse Reactions section will also summarize the appendicitis imbalance in the phase 3 database.
- The Indication will state that the drug is approved in premenopausal women who have acquired, generalized HSDD (because this is the form of HSDD that was studied in the phase 3 trials). There will be a Limitation of Use stating that the efficacy and safety of flibanserin have not been established in postmenopausal women, in men, (b) (4)
[REDACTED], and that flibanserin has not been shown to enhance sexual performance.
- Labeling will not include an established pharmacologic class because the mechanism by which flibanserin improves symptoms of HSDD is unknown.

- The Clinical Studies section will summarize the patient-reported outcome measures used for the key efficacy endpoints. This section will mention that the co-primary endpoint for sexual desire failed in the first two trials and will include those results. For the first two trials, p-values will not be reported for the secondary endpoints of FSFI and distress because of the failed co-primary endpoint. This section will also include summary statements about clinical meaningfulness based on the anchoring analyses, and will include findings from the driving study.
- There will be a Medication Guide that aligns with the messaging in the package insert.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval of flibanserin for the treatment of premenopausal women with acquired, generalized HSDD.

- Risk Benefit Assessment

In reaching my recommendation, I have considered the efficacy and safety data submitted by the Applicant and the reviews completed by the FDA staff. I have also considered the advisory committee vote, recommendations, and comments. In addition, I have considered the statements made during the open public hearing at the advisory committee meeting and the views expressed in the numerous letters that have been written to FDA, requesting approval or rejection of flibanserin. I am also aware of the controversies surrounding flibanserin and treatments for female sexual dysfunction, including the Applicant's ties to the "Even the Score" advocacy group.

Below, I first put forth the conclusions of the reviewers not recommending approval of flibanserin then I provide my rationale for why I believe flibanserin can be approved.

Clinical Pharmacology Recommendations: During the first two review cycles, the Clinical Pharmacology reviewers concluded that the NDA is acceptable, pending agreement on labeling. In this review cycle, the Clinical Pharmacology primary reviewer and team leader are recommending a Complete Response action. They conclude that the benefit/risk assessment is unfavorable because of minimal efficacy, significant safety concerns (particularly hypotension and syncope occurring with flibanserin alone, with alcohol and with moderate or strong CYP3A4 inhibitors), and the lack of an alcohol interaction study in premenopausal women.

In the decisional memorandum for Clinical Pharmacology, CAPT Edward D. Bashaw, Pharm.D., Director, Division of Clinical Pharmacology-3, acknowledges the concerns raised by the Clinical Pharmacology reviewers but concludes that flibanserin can be adequately labeled based on existing clinical pharmacology data while an alcohol interaction study is ongoing in women. Dr. Bashaw recommends a Boxed Warning for sedation, alcohol and drug

interactions, and that the warnings on alcohol intake be broadened to include other central nervous system depressants. Dr. Bashaw also supports the development of a REMS with ETASU.

Clinical Recommendations: The Clinical Reviewers and CDTL recommend a Complete Response. They conclude that the marginal clinical benefits do not outweigh the serious risks. With regard to efficacy, their concerns include the numerically small treatment differences, the suboptimal FSFI desire domain instrument, the change in the co-primary desire endpoint from the failed daily electronic diary (in the first two trials) to the FSFI desire domain (in the third trial), and inability to establish efficacy using secondary endpoints from the first two trials because the co-primary desire endpoint failed in those trials. They state that there is insufficient evidence to demonstrate the effectiveness of an ETASU REMS in clinical practice and that a REMS cannot overcome the limitations of marginal efficacy. The CDTL also states that an alcohol interaction study should be conducted pre-approval in women.

My Recommendation: As stated in FDA's draft implementation plan for a Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, the FDA's assessments of the benefits and risks of a product under review are "informed by science, medicine, policy, and judgment, in accordance with applicable legal and regulatory standards. The intersection of these components constitutes the framework in which FDA makes its regulatory decisions." This document goes on further to state that "Variations in clinical and scientific judgments among FDA experts can lead to differing individual opinions and conclusions regarding the benefit-risk assessment. For example, while two experts may agree on a set of facts regarding the benefits and risks of a drug, the experts may not agree on accepting the risk given the demonstrated benefits of the drug." This is the situation facing the flibanserin application – there is internal agreement on the facts, but not on whether the demonstrated benefits outweigh the known risks.

First, it is important to note that there are no medications that are FDA-approved for treating sexual desire disorders and associated distress. It is true that, on average, there are small treatment effects seen with flibanserin compared to placebo. However, based on FDA's supportive analyses, about 10% more flibanserin-treated patients reported clinically meaningful improvement compared to placebo-treated patients. The treatment differences (point estimates, 95% confidence intervals) and the proportions of responders reporting meaningful improvement are consistent across all three trials. These consistent results essentially rule out a chance finding. I agree with the review team that the FSFI desire domain is not an optimized instrument. However, for reasons previously discussed, daily desire reported via electronic diary is not perfect, either. It is noteworthy that the results with the FSFI desire domain consistently mirrored the improvement seen in the number of satisfying sexual events and the reduction in distress related to low sexual desire. Based on the totality of the data and the consistency of the treatment differences across the trials, I conclude that efficacy has been sufficiently established for the treatment of acquired, generalized HSDD in the premenopausal population.

The question comes down to whether we withhold flibanserin treatment from everyone in the United States – including those who would have meaningful benefit – or whether there is a

reasonable approach to allow flibanserin to be marketed, so that it will be available to patients who need it. This depends on whether the risks can be reasonably managed so that the benefits outweigh the risks.

The major risks with flibanserin that were identified during drug development are as follows:

- Central nervous system depression that could lead to accidental injury
- Increased risk of severe hypotension and syncope due to drug interactions (particularly with moderate or strong CYP3A4 inhibitors)
- Increased risk of severe hypotension and syncope due to an interaction with alcohol

Central Nervous System Depression: There are many FDA-approved drugs besides flibanserin that cause central nervous system depression. This risk is typically labeled as a Warning and Precaution, with a recommendation that patients know how the medication affects them before participating in activities requiring alertness, such as driving. It is reasonable to apply a similar approach to flibanserin, and to also include this important information in the Medication Guide, which the patient will receive with each prescription. Other important messages in the package insert and Medication Guide to help mitigate the risk and consequences of central nervous system depression include taking flibanserin only at bedtime, not taking extra doses to make up for missed doses, and not participating in activities requiring alertness until at least 6 hours after the dose.

Severe Hypotension and Syncope due to Drug Interactions: Many FDA-approved drugs besides flibanserin have important clinical interactions with other prescription or over-the-counter drug products. The list of moderate or strong CYP3A4 inhibitors is large and will continue to grow as new drug products are approved. It is not reasonable to expect a healthcare provider to know off-hand all the medications on this list. Instead, the healthcare system relies on drug-drug interaction screening technology to identify and prevent serious interactions. This technology includes screening performed by electronic medical records at the time the prescription is written, screening by insurance companies during prescription claim adjudication, and screening by pharmacy management systems prior to dispensing every prescription. However, this technology is not perfect. For example, it cannot detect interactions with non-prescription drugs or herbal supplements. It also cannot detect interactions if a cash payment is not adjudicated through an insurance company and the patient uses more than one pharmacy or different prescribers. Therefore, this technology will mitigate the risk of important drug interactions in many patients, but it cannot prevent all drug interactions. The risk of drug interactions is also mitigated by labeling – the package insert informs healthcare providers about the important drug interactions and the Medication Guide (which the patient will receive with each prescription) informs patients not to take or start taking any prescription medication, non-prescription medication or herbal supplement while taking flibanserin until discussing the new medication with the healthcare provider. I believe these risk mitigation strategies are sufficient to mitigate the risk of serious drug-drug interactions with flibanserin, just as these strategies are sufficient for other drugs that have serious drug-drug interactions.

Severe Hypotension and Syncope due to an Interaction with Alcohol: In the alcohol interaction study, co-administration of flibanserin and alcohol, both dosed in the morning, caused concerning cases of hypotension and syncope. These cases occurred with the equivalent of

about two standard alcoholic drinks for a 70 kg person consumed over 10 minutes. The results from this study do not adequately inform risk in the target population because the study mostly enrolled men, the study tested only rapid consumption of alcohol, and flibanserin was dosed in the morning. Although the phase 3 trials did not exclude patients who reported drinking alcohol at baseline, these trials cannot definitively inform risk because the amount and frequency of alcohol use during the treatment periods is unknown. However, it is likely that some of the flibanserin-treated patients used some alcohol during the trials based on the epidemiology of alcohol use in the United States.

Nonetheless, the results from the alcohol interaction study are important to consider because flibanserin requires daily administration on a chronic basis and alcohol use is prevalent in the female population in the United States expected to use flibanserin. According to the Centers for Disease Control and Prevention (CDC), among non-pregnant women 18-44 years of age in the United States (2006-2010), approximately 50% reported drinking alcohol within 30 days of taking the self-reported survey and approximately 15% reported binge drinking (four or more drinks on one occasion) at least one time during that same timeframe.⁸

Because the extent of the alcohol interaction in the target population is currently uncertain, alcohol use will need to be contraindicated in women taking flibanserin until there are data that more clearly define the risk and reconcile the findings from the alcohol interaction study with the existing phase 3 data. Because alcohol use is common in the United States, labeling alone will not be sufficient to ensure that women abstain from alcohol chronically while taking flibanserin daily. In addition to contraindicating alcohol use, a broader strategy is needed to maximize provider, pharmacy and patient understanding about the importance of abstaining from alcohol use while taking flibanserin. After consultation with the Office of Surveillance and Epidemiology, I have concluded that a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU) would be necessary to ensure that the benefits of flibanserin outweigh the increased risks of severe hypotension and syncope due to the interaction between flibanserin and alcohol. See the REMS memorandum by Christine Nguyen, M.D., and the Division of Risk Management review by Somya Dunn, M.D., for further details.

The REMS that has been developed for flibanserin, and with which I agree, will require that prescribers be certified by enrolling and completing training to ensure they understand that alcohol use is contraindicated with flibanserin, and that they agree to counsel patients about the increased risks of severe hypotension and syncope with flibanserin due to the alcohol interaction, and the need to abstain from alcohol use during treatment with flibanserin. The certified provider must use the Patient-Provider Agreement Form (developed specifically for flibanserin and agreed to by FDA) when counseling patients about the alcohol contraindication for the first time. This form states that patients must not drink alcohol while taking flibanserin because doing so increases the risk of severe hypotension and syncope. After the prescriber and patient sign the form, the top portion is placed in the patient's chart, and the patient takes home the bottom portion which contains the key messages in patient-friendly language.

⁸ <http://www.cdc.gov/ncbddd/fasd/kf-alcohol-use2006-2010.html>

In addition, pharmacies that dispense flibanserin must be certified by enrolling and completing training. Certified pharmacies must only dispense flibanserin to patients with a prescription from a certified prescriber. Before dispensing each prescription for flibanserin (including refills), pharmacists must counsel patients not to drink alcohol during treatment with flibanserin.

The package insert (which will include a Boxed Warning about the alcohol interaction) will also advise healthcare providers to assess the likelihood of the patient abstaining from alcohol before prescribing flibanserin, taking into account the patient's current and past drinking behavior and other pertinent social and medical history.

The major goal of this REMS is to ensure that healthcare providers and patients are fully informed of the risk of severe hypotension and syncope due to the interaction between flibanserin and alcohol. Once fully informed, the patient together with her healthcare provider can determine whether to start or continue treatment with flibanserin, weighing the benefits while on flibanserin (or potential for benefit prior to starting flibanserin) against the risks and downsides, such as the need to abstain from alcohol. HSDD is a symptomatic condition so the patient will be able to decide whether any improvement she is experiencing is worth the risks and downsides. Some women will decide those risks and downsides are not worth taking, whereas others will decide that the risks and downsides are acceptable given the benefit they are experiencing. The decision to initiate flibanserin therapy will be an individualized decision between provider and patient. It is critical, though, that the healthcare provider and patient make a fully informed decision. This REMS helps ensure that.

One may ask why not issue a Complete Response and ask the Applicant to evaluate the alcohol interaction in premenopausal women before considering approval. This approach is not unreasonable but, in my view, is not required because flibanserin is being approved assuming that the alcohol interaction in women is at least as severe as the alcohol interaction in men. We will continue to assess the risk mitigation approaches as more data become available, including the REMS assessments, data from the required postmarketing alcohol interaction trials in women, and data from other sources (e.g., analyses from enhanced pharmacovigilance). We will modify the REMS or take other regulatory actions, as needed, if the REMS is not adequately achieving its stated goals.

My approach described above is consistent with the independent, expert advice from the joint Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Committee, which recommended approval with risk mitigation strategies beyond labeling, with strong support for a REMS that includes ETASU.

Approval of flibanserin should not supplant the existing non-pharmacologic approaches to treating problems with sexual desire. Rather, it adds a pharmacologic option to the treatment armamentarium for premenopausal women with acquired, generalized HSDD.

Lastly, with regard to the change in the DSM from HSDD to FSIAD, it is noteworthy that someone can be diagnosed with FSIAD if they have a low sexual desire disorder, an arousal disorder, or a combination of both. Therefore, the new condition does not invalidate disorders

of low sexual desire with associated distress, rather it allows for diagnosis of women whose symptoms overlap between desire and arousal disorders.

In summary, I conclude that flibanserin has a positive benefit/risk assessment. I have taken into account that there are no approved medications for HSDD, that the condition can cause substantial distress and have profound effects on relationships and well-being, that some women have a clinically meaningful response to treatment, that the major risks due to central nervous system depression are adequately mitigated with labeling, that the major risks of drug-drug interactions are adequately mitigated with labeling and existing drug-drug screening technology, and that a REMS with ETASU will ensure the benefits of flibanserin outweigh the risks of severe hypotension and syncope due to an interaction with alcohol.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

I recommend approval of flibanserin with a REMS containing elements to assure safe use ETASU and an Implementation System to ensure that the benefits of flibanserin outweigh the risks of severe hypotension and syncope due to an interaction with alcohol.

- Recommendation for other Postmarketing Requirements and Commitments

I recommend a total of seven postmarketing required studies and clinical trials. I agree with the study descriptions and timelines as described in the Approval letter. The postmarketing requirements include:

- An enhanced pharmacovigilance study to assess and analyze the risks of hypotension, syncope, accidents, injuries, and fatal outcomes reported with flibanserin. The enhanced pharmacovigilance plan includes the use of specialized case intake forms to capture pertinent information around the time of the event, such as use of alcohol, timing of dosing and use of concomitant medications.
- A prospective observational study to evaluate the risk of appendicitis in women 18-44 years of age using flibanserin. There is a numerical imbalance of appendicitis in the flibanserin safety database. There is biological plausibility for a drug-effect based on data from eplivanserin, a serotonin 2A receptor antagonist. At present, it is unclear whether the appendicitis imbalance is a chance finding or a drug-effect. This epidemiological study will help inform the risk of appendicitis with flibanserin.
- A pregnancy registry and a separate maternal-fetal outcome study to evaluate adverse pregnancy outcomes and birth defects in pregnancies exposed to flibanserin. There are no concerning safety signals based on the animal data. However, flibanserin is indicated in premenopausal women and the treatment effect is expected to lead to more sexual intercourse, which, if unprotected, could lead to pregnancy. These studies will obtain useful information on pregnancy, maternal and fetal/neonatal outcomes.
- Three alcohol interaction trials in women 18-44 years of age will characterize the risk of severe hypotension and syncope in the following settings:

- a. “Worst case scenario” testing flibanserin with varying quantities of alcohol
- b. Timing of flibanserin administration relative to alcohol intake
- c. Typical real world use with alcohol at dinner and flibanserin dosed at bedtime

The doses for the timing and real world use trials will be selected based on results from the worst case scenario trial.

Finally, the review team and I have considered whether nonclinical studies, an epidemiological study or a clinical trial should be required to address the unknown clinical relevance of the mouse mammary tumor findings. The non-clinical pharmacology/toxicology reviewers have not identified additional animal or *in vitro* studies that could better assess the human relevance or risk. The Division of Epidemiology in the Office of Surveillance and Epidemiology has identified major feasibility and methodological issues as well as uncertainties with regard to utilization of flibanserin (e.g., as a result of the restricted program), and, therefore, is not recommending an epidemiology study at this time. Lastly, a clinical trial is not feasible because such a trial would need to have a long treatment period (during which, symptomatic patients would need to remain on placebo) and be very large (given the low background event rates of breast cancer in premenopausal women). Therefore, at present, I recommend only that the unknown clinical significance of the mouse mammary tumors be prominently placed in the label under the Warnings and Precautions section and also in the Animal Toxicology section.

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/s/

HYLTON V JOFFE
08/18/2015