CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022526Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 022526	Submission Date(s): 10/27/2009
Brand Name	ADDYI
Generic Name	Flibanserin
Primary Reviewer	Doanh Tran, Ph.D.
Secondary Reviewer	Shirley Seo, Ph.D.
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology
OND division	Division of Urology, Obstetrics, and Gynecology
Applicant	Sprout Pharmaceuticals, Inc.
Formulation; Strength(s)	Tablets; 100 mg
Indication	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to: • A co-existing medical or psychiatric condition, • Problems within the relationship, or • The effects of a medication or other drug substance.

The purpose of this review addendum is to resolve a discrepancy in language in the Clinical Pharmacology Question Based Review (DARRTS dated 8/26/2010) and the individual study review in the review appendix (DARRTS dated 8/26/2010) regarding whether the metabolite 1-(3-trifluoromethylphenyl) piperazine (also denoted as TFMPP or M30a) is considered active. TFMPP should be considered as a minor active metabolite.

In the individual study review for study 511.87 (page 54 of the Clinical Pharmacology review appendix) and on page 22 of the Clinical Pharmacology Question Based Review, it was stated that for the metabolite TFMPP, "AUCτ,ss and Cmax,ss geometric mean ratios were significantly increased to 500.4% and 382.0%, respectively (90% CIs: 394.51-634.72% and 309.15-471.93%), in EMs co-administrated with and without paroxetine" and "Through receptor screening, TFMPP possesses some affinity to serotonergic receptors with approximately 5% molar exposure in plasma compared to flibanserin. Therefore, exposure of TFMPP can be increased to a significant degree, but *there is little clinical concern regarding this accumulation as this metabolite is inactive* [emphasis added]." This last part of the latter sentence inadvertently stated that TFMPP is inactive and should be revised instead to state the following: "…there is little clinical concern regarding this increase in exposure of TFMPP because its contribution to the overall pharmacologic activity is low due to its low relative exposure of only 5% compared to the parent drug, flibanserin."

This reviewer arrived at the above conclusion based on the following:

1. It is documented elsewhere in the Clinical Pharmacology Question Based Review that in a broad receptor screening, TFMPP showed some affinity to serotonergic receptors and TFMPP also showed distribution into the brain in rats, similarly to the parent drug, flibanserin (page 11 of the review), suggesting that TFMPP could be active.
2. In the Pharmacology/Toxicology review dated 7/7/2010 (page 22), TFMPP is referred to as an "an active minor metabolite, which crossed the blood brain barrier to a large extent." The review also says "Based on pharmacological tests including a receptor screen, three metabolites were considered potentially active, M35, M38, and M30a (TFMPP). Considering the human plasma exposure at therapeutic doses and the brain penetration in rat in addition to the receptor binding data of flibanserin and its metabolites, sponsor concludes that flibanserin in the CNS active substance at therapeutic doses."
3. The sponsor's original NDA section 2.4 Nonclinical Overview (page 18) stated that "TFMPP showed binding in the receptor screen."

These findings are consistent with TFMPP having pharmacologic activity but under normal circumstances, where its exposure is low compared to the parent drug, flibanserin, it does not contribute significantly to the overall pharmacologic activity. Thus, TFMPP should be considered as a minor active metabolite.

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/s/

DOANH C TRAN
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OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA #	022526
Submission Type	Response to 2nd Complete Response
Submission Date	February 18, 2015 (Two previous NDA submission dates: October 27, 2009 and March 29, 2013)
Brand Name	ADDYI®
Generic Name	Flibanserin
Strength and Formulation; Regimen	100 mg tablet; orally once daily taken at bedtime
Sponsor	Sprout Pharmaceuticals
Proposed Indication	Treatment of Hypoactive Sexual Desire Disorder in Premenopausal Women (≥ 18 years of age)
Relevant IND	(b) (4)
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology-3
OND Division	Division of Bone, Reproductive and Urologic Products

1 Executive Summary

The Clinical Pharmacology review team recommended a Complete Response to NDA 022526 in the third cycle review for flibanserin (DARRTS July 17, 2015). The third cycle review included detailed review of two new phase 1 studies (SPR-14-06 and CYP08991 R1) submitted on February 18, 2015 and summarized relevant information from the two previous Clinical Pharmacology reviews of the original and second cycles (DARRTS August 26, 2010 and August 29, 2013). The purpose of this addendum is to correct incongruent information and clearly state the data regarding the effect of food flibanserin exposure and the effect of flibanserin on digoxin exposure.

Effect of Food on Flibanserin

$AUC_{0\text{-}inf}$ of flibanserin 50 mg increased by 17.7%, 43.4%, and 56.1% after administration of a light, medium, and high fat/caloric breakfast, compared to the fasted condition, respectively.

The following table summarizes the geometric mean ratios following various meal types, compared to fasted condition.

Parameter	Ratio (test/reference)	Adjusted Mean (%)	Two-sided 90% C. I. (%) Lower Limit	Upper Limit
$AUC_{0\text{-}\infty}$	light/fasted	117.7	106.9	129.7
	medium/fasted	143.4	130.2	157.9
	high/fasted	156.1	141.7	171.9

Cmax of flibanserin 50 mg decreased by 1.4%, increased by 12.3% and increased by 14.6%, after administration of a light, medium, and high fat/caloric breakfast, compared to the fasted condition, respectively.

Parameter	Ratio (test/reference)	Adjusted Mean (%)	Two-sided 90% C. I. (%) Lower Limit	Upper Limit
C_{max}	light/fasted	98.6	81.0	120.0
	medium/fasted	112.3	92.2	136.8
	high/fasted	114.6	94.1	139.5

As previously noted, the effect of food was evaluated with 50 mg (half the proposed therapeutic dose). The absolute exposure of flibanserin 100mg with concomitant intake of food was not characterized by the Applicant.

Effect of Flibanserin on Digoxin (in the third cycle review)
Under Section 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings on page 9, the summary states that digoxin $AUC_{0\text{-}inf}$ increased 96% and Cmax increased 46%. The following summarizes the effect of flibanserin on digoxin exposure as written in Section 1.3:

> *Effect of Flibanserin on Digoxin (P-glycoprotein, P-gp, substrate) PK*
> *The Applicant evaluated the effect of multiple doses of flibanserin on single dose PK of digoxin. Flibanserin 100 mg was given once daily over 7 days. On Day 5, a single 0.5 mg dose of digoxin (2 x 0.25 mg) was administered with 100 mg flibanserin. Digoxin exposure (AUC0-inf) increased by 96% and Cmax increased by 46% with multiple 100 mg doses of flibanserin co-administered with a single 0.5 mg dose of digoxin. Flibanserin is an inhibitor of P-gp.*

Under Section 2.7.1 Effect of Flibanserin on Digoxin PK on pages 30-31, the response to the question states that digoxin $AUC_{0\text{-}inf}$ increased 81% and Cmax increased 38%. The following summarizes the effect of flibanserin on digoxin exposure as written in Section 2.7.1:

> *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. This study was reviewed in the first NDA review cycle.*
>
> *This was a single center, open-label, randomized, two-way cross-over study in twenty-four healthy male (n=11) and female (n=13) subjects. Subjects were randomized to flibanserin and digoxin (following pre-treatment of flibanserin) or digoxin alone. Flibanserin 100 mg was given once daily over 7 days in 23 subjects (1 subject withdrew from study). On Day 5, a single 0.5 mg dose of digoxin (2 x 0.25 mg) was administered with 100 mg flibanserin.*
>
> *Digoxin exposure (AUC0-inf) increased 81% and Cmax increased 38% in the group that was coadministered flibanserin and digoxin compared to the group that received digoxin alone.*
>
> *Reviewer's Comments:*
> - *The Applicant 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 (CLR,0-24) (~8% decrease). However, based upon digoxin AUC0-inf, not AUC0-24, digoxin exposure increased 81% with flibanserin co-administration and digoxin Cmax increased 38%. The 8% reduction in digoxin renal clearance was based upon urine samples calculated from 0 to 24 hours. Based on the increased AUC0-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, Cmax 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.*

Correction: Digoxin exposure change was 96% for $AUC_{0\text{-}inf}$ and 47% for Cmax as stated in section 1.3. The exposure change ($AUC_{0\text{-}inf}$ increased 81% and Cmax increased 38%) as stated in section 2.7.1 is NOT correct. The effect of flibanserin on digoxin exposure is correctly stated in the review of the digoxin study report in the second review cycle.

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/s/

LAI M LEE
08/14/2015

MYONG JIN KIM
08/14/2015

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA #	022526
Submission Type	Response to 2nd Complete Response
Submission Dates	February 18, 2015; April 13, 2015; May 20, 2015; June 18, 2015 (Two previous NDA submission dates: October 27, 2009 and March 29, 2013)
Brand Name	Addyi® (accepted by the FDA)
Generic Name	Flibanserin
Strength and Formulation; Regimen	100 mg tablet; orally once daily taken at bedtime with or without food
Applicant	Sprout Pharmaceuticals
Proposed Indication	Treatment of Hypoactive Sexual Desire Disorder in Premenopausal Women (≥ 18 years of age)
Relevant IND	(b) (4)
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Clinical Pharmacology Team Leader	Myong-Jin Kim, PharmD
Division Director	E. Dennis Bashaw, PharmD
OCP Division	Division of Clinical Pharmacology-3
OND Division	Division of Bone, Reproductive, and Urologic Products

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1 EXECUTIVE SUMMARY

Sprout Pharmaceuticals is seeking approval of flibanserin oral tablets for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women (≥ 18 years of age). The proposed dosing regimen is one 100 mg tablet taken once daily at bedtime (qhs) with or without food. There is currently no FDA-approved pharmacologic therapy for HSDD.

Boehringer Ingelheim was the original owner of flibanserin and submitted the original NDA on October 27, 2009. Flibanserin efficacy and safety findings were discussed at the Reproductive Health Drugs Advisory Committee Meeting on June 18, 2010 with the committee members voting 11 to 0 against flibanserin on the overall benefit/risk profile. The Division of Bone, Reproductive, and Urologic Products (DBRUP) concluded there were limited efficacy benefit compared to placebo and major safety concerns (including dizziness, somnolence, nausea, and syncope); therefore, the Applicant received a Complete Response on August 27, 2010 due to an unfavorable benefit/risk assessment.

Following the Complete Response, Boehringer Ingelheim transferred ownership of the flibanserin NDA and associated IND to Sprout Pharmaceuticals. On March 29, 2013, Sprout resubmitted the NDA with Study 511.174, a new phase 3 trial (ongoing during the original review cycle) and 7 phase 1 studies (refer to Appendix 1) including drug-drug interaction (DDI) studies to address unresolved DDI concerns highlighted in the first Complete Response letter.

After a second cycle review and another unfavorable benefit/risk assessment, a Complete Response action was taken on September 27, 2013. The Applicant appealed the decision and requested a Formal Dispute Resolution meeting. During the meeting on January 10, 2014 with John Jenkins, Director of Office of New Drugs, the Applicant was advised to address the deficiencies outlined in the second Complete Response letter.

The Applicant submitted the NDA for a third cycle review on February 18, 2015. A Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee was held on June 4, 2015. http://www.fda.gov/AdvisoryCommittees/Calendar/ucm446094.htm. Of the twenty-four committee members, 6 members voted against approval and 18 members voted for approval with Risk Evaluation and Mitigation Strategies (REMS). Some of the members who voted to approve flibanserin stated they struggled and could have voted 'no'. Due to minimal efficacy and concerns over the safety profile, the majority of the 18 members who voted 'yes' recommended a strong REMS that would include prescriber and pharmacy certification (elements to assure safe use or ETASU). The committee members wanted a mechanism to ensure that prescribers select appropriate patients and counsel them about the risks and instructions for safe use.

In this third cycle submission, the Applicant included results from a driving study to assess the effect of residual sedation on driving (Study SPR-14-01), a pharmacokinetic study to assess the exposure of flibanserin in subjects with loss of CYP2C9 or CYP2C19 activity (Study SPR-14-06), and an in vitro metabolism study (CYP0899 R1). The Division of Neurology reviewed Study SPR-14-06 and concluded that they did not identify adverse events on next-day driving performance. However, the study was designed to identify driving impairment from somnolence, not other adverse events from flibanserin that might adversely affect driving performance (DARRTS July 1, 2015).

This Clinical Pharmacology review includes a detailed review of two new studies, SPR-14-06 (a CYP2C9/CYP2C19 poor metabolizer/extensive metabolizer, PM/EM study) and CYP0899 R1

(an in vitro metabolism study) submitted under this third cycle review, and summarizes relevant information from the two previous Clinical Pharmacology reviews of the original and second cycle NDA submissions (DARRTS dates: August 26, 2010 and August 29, 2013).

Analysis of Study SPR-14-06 showed subjects with a CYP2C19 PM status following a single dose of 100 mg flibanserin had an increase in flibanserin exposure ($AUC_{0\text{-}inf}$ increased 1.3-fold and Cmax increased 1.5-fold), compared to those with a CYP2C19 EM status. Half-life was extended by 2.4 hours. There was one healthy female subject with a CYP2C19 PM genotype who experienced severe adverse events; she became hypotensive and unresponsive to stimuli; her flibanserin exposure was greater than exposure in the CYP2C19 EM group. On the other hand, loss of CYP2C9 activity did not affect flibanserin exposure. Based upon this newly submitted CYP2C19 data, we conclude flibanserin clearance is mediated by CYP3A4 and, to a lesser extent, by CYP2C19.

DBRUP's analysis of efficacy during the first and second review cycles and feedback from the 2010 Advisor Committee concluded that flibanserin offers minimal benefit. Therefore, in the third review cycle, DBRUP requested the Applicant submit additional efficacy analysis of the three phase 3 trials, including responder and subgroup analyses (submitted on April 13, 2015).

The responder analysis was based on the Patient Global Improvement Index (PGI-I) anchored to responder rates for each endpoint using different cut points to define responders. Based on anchoring to the PGI-I, the difference between the percentage of responders on flibanserin and the percentage of responders on placebo was approximately 10%. Based on this responder analysis, approximately 90% of treated patients will not respond to flibanserin, but may be exposed to adverse events. Additionally, there was no clear demonstration that flibanserin improves desire - a key component of the HSDD.

The subgroup analyses showed no difference in treatment effect for flibanserin based upon the severity of baseline SSEs, FSFI desire score, and FSDS-R 13 distress score.

With the prevalent consumption of alcohol in the intended population and in the setting of flibanserin use, the potential for life-threatening adverse events with concomitant use of alcohol and flibanserin is a major safety concern. The results from an alcohol interaction study in 23 males and 2 females showed a significant decrease in blood pressure (decrease in systolic blood pressure of 30-60 mmHg and decrease in diastolic pressure of 10-50 mmHg). Syncope occurred in a healthy 26 year-old male subject after consuming low dose alcohol (equivalent to 2 drinks) with flibanserin. The safety profile of combination use of alcohol and flibanserin in premenopausal women is uncertain because the alcohol interaction study enrolled mostly men (92% of total subjects) and the phase 3 trials were not prospectively designed to assess the interaction between alcohol and flibanserin. Many members of the 2015 advisory committee expressed a serious concern that the results of the alcohol interaction study in males cannot be directly interpretable in women who may be more sensitive to alcohol.

With the newly available responder and subgroup analyses, additional information on flibanserin clearance and updated safety database, a benefit-risk assessment was conducted in this review cycle. In considering the benefit, the newly submitted responder analysis showed that clinical efficacy is limited to approximately 10% of flibanserin users and the subgroup analysis showed that patients with greater disease severity would derive no more benefit than those with minimal symptoms. Additionally, flibanserin therapy is chronic requiring once daily administration, there is limited efficacy after 4 weeks of therapy, and it may take up to 8-12 weeks of treatment before clinical benefit, if any, is achieved. In considering the risk, life-threatening adverse events

(including hypotension and syncope) have occurred in healthy premenopausal women with no concomitant medications or disease conditions. Hypotension and syncope occurred at approximately 1 hour following the first dose of flibanserin alone (at the proposed therapeutic dose and at half the therapeutic dose), flibanserin with alcohol, flibanserin with CYP3A4 inhibitors, and in subjects with loss of CYP2C19 activity taking flibanserin, based on phase 1 study results.

Some of the recent Advisory Committee members voted to approve flibanserin, but expressed deep concerns about the safety profile; therefore, their recommendation also included using REMS with ETASU to offset the low efficacy. REMS was authorized as part of the Food and Drug Administration Amendments Act of 2007 to provide safety measures needed beyond the product label to ensure that a drug's benefit outweigh its risks. The program was developed to mitigate safety risk for drugs that have been shown to be effective, but required additional measures to mitigate the risks. The key premise in using REMS is that the drug has been proven effective and that the safety risks are the main concern in the benefit-risk equation, which is not the case with flibanserin. Flibanserin efficacy has been deemed minimal over multiple review cycles. REMS with ETASU and labeling with contraindication of other concomitant drugs, sedating medications, and alcohol, cannot mitigate the safety risks with a minimally efficacious drug.

Based upon the existing efficacy data and the more recent responder and subgroup analyses submitted in this review cycle and the safety profile, particularly the lack of alcohol interaction information in premenopausal women, the Clinical Pharmacology review team finds the benefit-risk assessment of flibanserin unfavorable.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-3 (OCP/DCP-3) has reviewed NDA 022526 for flibanserin 100 mg oral tablets submitted to the Agency on October 27, 2009, March 29, 2013, and February 18, 2015. The Office of Clinical Pharmacology has identified cases of hypotension and syncope in healthy premenopausal women taking flibanserin alone or in combination with another drug. There are major safety concerns with use of flibanserin alone, flibanserin with moderate and strong CYP3A4 inhibitors, flibanserin with alcohol, and flibanserin alone in subjects with a loss of CYP2C19 activity. In addition to prescription drugs, there are non-prescription CYP3A4 inhibitors, CYP2C19 inhibitors and CNS depressants that will increase the risk of serious adverse events by increasing flibanserin exposure or by augmenting the sedative effects of flibanserin.

We are currently aware of the serious hypotensive effects from concomitant use of flibanserin and alcohol in mostly men; however, the proposed population is premenopausal women. An important safety element is currently missing from this NDA; an alcohol interaction study in premenopausal women is needed to assess the pharmacodynamic (PD) and pharmacokinetic (PK) effects of alcohol on flibanserin. The study should include the measurement of both alcohol and flibanserin exposure.

Based upon the phase 3 results showing potentially absent or minimal clinical efficacy and major adverse events identified in both phase 1 and 3 studies in healthy premenopausal women and lack of information alcohol interaction data in premenopausal women, OCP/DCP-3 recommends a Complete Response.

1.2 Post-Marketing Requirement

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Significant Clinical Pharmacology Findings

Blood samples for flibanserin concentration were not taken during the phase 3 studies; therefore, analysis of drug exposure and safety (obtained from phase 3 data) cannot be conducted. In our dose and safety response analysis, we conclude that for the same total daily dose the adverse events were more prevalent with bid dosing versus qhs dosing. For example, at the same total daily dose of 100 mg, giving flibanserin 100 mg qhs resulted in lower incidences of dizziness, nausea, fatigue, and somnolence, compared to 50 mg bid. This finding is not surprising considering the patients would be asleep after taking flibanserin and, therefore, not awake to report the adverse events. That was the rationale for the qhs dosing regimen proposed in this NDA.

Based upon dose and safety response analysis from a phase 1 dose-escalation study submitted under the second cycle review, we found that as the dose (and systemic exposure) increased from 100 to 250 mg, the incidences of adverse events increased as was previously observed in the phase 3 trials. For example, incidence rate of dizziness increased from 13% to 83% as the dose increased from 100 to 250 mg. The Applicant stopped the dose escalation study due to severe adverse events at the 250 mg dose.

The table summarizes the incidence rate for the most common adverse events as a function of dose (Study SPR-12-04).

	Flibanserin				
Number (%) of Subjects with AEs	Placebo (n=14)	100 mg (n=8)	150 mg (n=8)	200 mg (n=7)	250 mg (n=6)
Dizziness	1 (7%)	1 (13%)	3 (38%)	6 (86%)	5 (83%)
Somnolence	5 (36%)	6 (75%)	5 (63%)	6 (86%)	5 (83%)
Nausea	1 (7%)	1 (13%)	1 (13%)	4 (57%)	4 (67%)

Flibanserin is extensively metabolized by CY3A4 and to a lesser extent by CYP2C19. Data submitted to the original NDA showed that a strong inhibitor of CYP3A4, ketoconazole, significantly increased flibanserin $AUC_{0\text{-}inf}$ (4.5-fold). In this third cycle submission comparing flibanserin PK in CYP2C9 and CYP2C19 PMs to EMs, flibanserin exposure (Cmax and AUC) increased in CYP2C19 PMs were 1.3 to 3.1-fold higher, compared to CYP2C19 EMs. In a DDI with flibanserin and fluconazole, a moderate CYP3A4, moderate CYP2C9, and strong CYP2C19 inhibitor, flibanserin $AUC_{0\text{-}inf}$ increased 7-fold and Cmax increased 2.2-fold, compared to flibanserin alone, suggesting additional CYPs are involved with flibanserin clearance. Based upon PK data submitted over three review cycles from DDI studies and in subjects deficient in CYP2C19 activity, the clearance of flibanserin is mediated by CYP3A4 and CYP2C19. We observed major adverse events, including hypotension and syncope, in DDI studies with ketoconazole and fluconazole where the exposures were significantly increased. Based upon our dose and safety response analysis, we anticipated increased exposures from DDIs will likely increase the incidence of major adverse events.

Alcohol is used prevalently in the intended population and in the setting of flibanserin, and the potential for life-threatening adverse events with concomitant use of alcohol and flibanserin is a major concern. The Applicant completed an alcohol interaction study in 23 males and 2 premenopausal females. The results showed a significant decrease in blood pressure (decrease in systolic blood pressure of 30-60 mmHg and decrease in diastolic pressure of 10-50 mmHg). Syncope occurred in a healthy 26 year-old male subject after consuming low dose alcohol (2 drinks) with flibanserin. The safety profile of combination alcohol and flibanserin in premenopausal women is uncertain because the alcohol interaction study enrolled mostly men (92% of total subjects were males) and the phase 3 trials were not prospectively designed to assess the interaction between alcohol and flibanserin.

Systemic flibanserin exposure increased 4.5-fold in patients with mild hepatic impairment, compared to subjects with normal hepatic function. Due to the small number of patients (n=4) with moderate hepatic impairment enrolled in the study, there are limitations with using these data to make conclusions about the effect of moderate hepatic impairment on flibanserin exposure. Additionally, Cmax was lower in the moderate hepatic impairment group, compared to the matched healthy subjects and the other groups, suggesting a lower degree of drug absorption. Based upon the dose and safety response analysis, the safety profile in women with hepatic impairment taking flibanserin at the therapeutic dose of 100 mg will likely experience significant adverse events as the absolute exposure will be higher than those observed in the hepatic impairment study with 50 mg.

PK characteristics

Following administration of a single 100 mg dose of flibanserin tablet in healthy premenopausal women (N=8), mean (SD) Cmax was 419 (206) ng/mL and mean (SD) $AUC_{0\text{-}inf}$ was 1543 (511) ng.hr/mL. Median (range) Tmax was 0.75 (0.75 – 4.0) hrs and mean (SD) $t_{1/2}$ was 11.7 (1.9) hrs. Cmax of flibanserin appears to be dose proportional from 100 to 250 mg. For flibanserin $AUC_{0\text{-}inf}$, exposure appears to be greater than dose proportional from 100 to 250 mg.

Compared to the fasted condition, the exposure ($AUC_{0\text{-}inf}$) of flibanserin 50 mg was 17%, 41%, and 53% higher after administration of a light, medium, and high fat/caloric breakfast, respectively. The total flibanserin exposure increased with increasing fat/calorie content. Cmax was essentially the same between the light breakfast and fasted groups, with slight decrease of 3.9% in the light breakfast group. Cmax increased by 12 and 14% in the medium and high fat/caloric breakfast groups, respectively, compared to the fasted group. Tmax was prolonged slightly from 0.8 hr under fasted condition up to 2 hrs under high fat/caloric meal.

Efficacy Endpoints

The two co-primary endpoints used to demonstrate clinical efficacy for flibanserin in women with HSDD were change from baseline in number of satisfying sexual events (SSEs) and change from baseline in desire as assessed by an electronic diary or Female Sexual Function Index (FSFI) desire domain. A key secondary endpoint was change from baseline in distress assessed by Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R). Endpoints for demonstration of efficacy have been the same throughout the development program.

Blood samples for flibanserin concentration were not taken during the phase 3 studies; therefore, analysis of drug exposure and efficacy cannot be conducted.

Dose-Response Relationship

The Applicant submitted three pivotal Phase 3 trials (511.71, 511.75 and 511.147) to support efficacy with two co-primary efficacy endpoints – SSE and desire (summary of data in the tables

below). Studies 511.71 and 511.75 were submitted to the original NDA and evaluated 50 mg qhs, 100 mg qhs, 25 mg twice daily (bid), 50 mg bid (up-titrated from 50 mg qhs), and 100 mg qhs (up-titrated from 50 mg qhs). Efficacy results with the 25 mg bid or 50 mg qhs doses were less positive than those for the 100 mg qhs dose. The proposed 100 mg is the highest dose studied and showed a higher response than lower doses studied.

Dose and Efficacy Response

In the first two phase 3 trials(Studies 511.71 and 511.75) flibanserin 100 mg qhs showed statistically significant improvement in SSE but did not show a statistically significant improvement over placebo in the co-primary endpoint for sexual desire, as assessed with a daily electronic diary. The Applicant did show a statistically significant improvement over placebo for a secondary endpoint that used FSFI to assess sexual desire. The Applicant stated that sexual desire was better assessed with FSFI, but the advisory committee members did not agree with altering the pre-specified primary endpoint for sexual desire.

The third pivotal phase 3 trial (Study 511.147) was ongoing during the original NDA review and included one dosing regimen (100 mg qhs). The co-primary efficacy endpoints were SSE and sexual desire using FSFI. 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. See Clinical efficacy review by Catherine Sewell.

Clinical Meaningfulness: The clinical meaningfulness of the small numerical changes in SSE, FSFI Desire, and Distress were assessed by responder analysis, which showed that the absolute difference in the percentage of responders with flibanserin and the percentage of responders with placebo is approximately 10% (range: 9-15%). In DBRUP's assessment of clinical meaningfulness, the change in baseline should range from 1.3 to 2.9 SSEs/month, 0.6 to 1.2 for FSFI Desire/28-day recall, and 0 to -1 for Distress. Though statistically significant, the small numerical changes in SSE, FSFI, and FSDS do not appear to be clinically meaningful.

Responder Analysis: The responder analysis, conducted in the third review cycle, showed that clinical efficacy is limited to approximately 10% of flibanserin users and the subgroup analysis showed that patients with greater disease severity would derive no more benefit than those with minimal symptoms.

Subgroup Analysis: A post-hoc efficacy analyses was conducted in this third cycle review 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. The Clinical review team concluded there were no notable differences in efficacy among any subgroups evaluated.

Onset of Efficacy: Flibanserin therapy is chronic requiring once daily administration. The Clinical review team concluded that there may be minimal efficacy 4 weeks after initiating therapy and it may take up to 8-12 weeks of therapy before clinical benefit, if any, is achieved.

Intrinsic and Extrinsic Factors

Effect of Strong CYP3A4 Inhibitors, Itraconazole and Ketoconazole

Itraconazole 200 mg daily given 8 days then co-administered with flibanserin 50 mg increased flibanserin $AUC_{0\text{-}inf}$ by 2.6-fold and Cmax 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.

Ketoconazole 400 mg daily for 5 days inhibited flibanserin 50 mg metabolism leading to a 4.5-fold increase in flibanserin $AUC_{0\text{-}inf}$. Cmax increased 1.8-fold. $t_{1/2}$ was significantly prolonged by 7.5 hrs from 8.5 to 16 hrs. Ketoconazole inhibition of CYP3A4 was more significant compared with itraconazole.

Based on the observed relationship between dose and AEs, it is likely that patients using a CYP3A4 inhibitor will experience more AEs compared with patients not taking a CYP3A4 inhibitor (see original Clinical Pharmacology review dated August 26, 2010 in DARRTS).

Effect of Moderate CYP3A4 Inhibitor, Fluconazole and Grapefruit Juice

Fluconazole resulted in a 2.2-fold increase in Cmax and 7.0-fold in $AUC_{0\text{-}inf}$ of flibanserin. Mean terminal half-life of flibanserin increased from 10 to 23 hrs. Mean clearance (CL/F) of flibanserin decreased significantly from 76 to 9.8 L/hr with fluconazole administration. 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. Fluconazole is an inhibitor of CYP3A4, CYP2C9 and CYP2C19. The data suggest that fluconazole may inhibit other metabolism pathways of flibanserin in addition to CYP3A and that flibanserin may be metabolized by additional CYP enzymes. Results from Study SPR-14-06 (CYP2C9/2C19 EM/PM study) submitted in this review cycle showed that CYP2C19, but not CYP2C9, also is involved in the flibanserin clearance (to a lesser extent than CYP3A).

Grapefruit juice (regular strength) co-administered with flibanserin increased flibanserin Cmax by 1.1-fold and $AUC_{0\text{-}inf}$ by 1.4-fold.

Co-administration of a single dose flibanserin and multiple doses of fluconazole resulted in more frequent and profound AEs, compared to flibanserin alone or flibanserin + grapefruit juice. All 15 subjects who received flibanserin + fluconazole experienced at least 1 AE. Hypotension occurred in the flibanserin + fluconazole group only. One of 15 subjects who received flibanserin and fluconazole experienced a severe hypotensive event and required medical intervention. The study stopped early due to severe adverse events.

Oral Contraceptives, a weak CYP3A4 Inhibitor

The meta-analysis is entitled "Amended Statistical comparison of dose normalized PK parameters $AUC0\text{-}\infty$,norm, Cmax,norm, $AUC\tau$,ss,norm, Cmax,ss,norm of flibanserin with and without oral contraceptives across Phase I trials – exclusion of subjects with renal or hepatic impairment" was submitted in the second review cycle. Subjects were on flibanserin doses ranging from 25 to 100 mg from 7 studies. The adjusted geometric mean ratios for AUC0-inf and Cmax of flibanserin (dose-normalized) were 1.42 and 1.12, respectively, following a single dose flibanserin and oral contraceptives. Flibanserin exposure was affected by oral contraceptives. Safety analysis from patients enrolled in the phase 3 trials showed that there was a greater incidence of adverse events in women taking flibanserin and oral contraceptives, compared with those on flibanserin alone.

Loss of CYP2C19 Activity

In subjects with a CYP2C19 PM genotype, flibanserin exposure (AUC0-inf) increased 34% and Cmax increased 49% compared to those with a CYP2C19 EM genotype. Half-life (t1/2) 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. This subject had a Cmax 2.1-fold and $AUC_{0\text{-}inf}$ 1.2-fold greater than the exposure in the CYP2C19 EM group.

Effect of Strong CYP3A4 Inducer, Rifampin
Rifampin reduced flibanserin $AUC_{0\text{-}inf}$ by 96% and Cmax by 91%. Flibanserin metabolism is clearly influenced by the strong CYP3A4 inducer rifampin.

Effect of Moderate CYP3A4 Inducer, Etravirine
Etravirine decreased flibanserin Cmax by 3.2% and $AUC_{0\text{-}inf}$ by 21%.

Effect of Alcohol (Ethanol)
The Applicant conducted a study to evaluate the effect of flibanserin 100 mg administered with two different concentrations of alcohol (equivalent to 2 and 4 drinks in a 70 kg person). The study was a single center, randomized, double-blind, single dose, 5-treatment crossover study in twenty-three healthy adult male and two female subjects. Flibanserin exposure as measured by partial AUC ($AUC_{0\text{-}4}$) decreased by 10.5% and 3.9% when flibanserin 100 mg was administered with 0.4 and 0.8 g/kg ethanol, respectively, compared to flibanserin alone.

Flibanserin alone resulted in approximately 67% of subjects experiencing somnolence. The addition of ethanol to flibanserin intake increased the frequency of somnolence to approximately 74% with 0.4 and 92% with 0.8 g/kg ethanol, respectively. Alcohol, especially notable at high concentrations, increased the somnolence-inducing effect of flibanserin.

Orthostatic hypotension, characterized by an increase of >20 beats per minute (bpm) in sitting to standing pulse rate (3 to 4 time points), was observed when flibanserin was co-administered with ethanol at both concentrations. The results in 23 males and 2 premenopausal females showed a significant decrease in blood pressure (decrease in systolic blood pressure of 30-60 mmHg and decrease in diastolic pressure of 10-50 mmHg). Syncope occurred in a healthy 26 year-old male subject after consuming low dose alcohol (equivalent to 2 drinks) with flibanserin. The safety profile of concomitant use of alcohol and flibanserin in premenopausal women is uncertain because the alcohol interaction study enrolled mostly men and the phase 3 trials were not prospectively designed to assess the interaction between alcohol and flibanserin.

Flibanserin is proposed for use in women; however, the alcohol study included mostly men. An important safety element is currently missing from this NDA - complete characterization of flibanserin and alcohol interaction in premenopausal women. Therefore, the Applicant needs to assess the PD and PK effects of alcohol on flibanserin, and should include the measurement of both alcohol and flibanserin exposure.

Effect of Flibanserin on Digoxin (P-glycoprotein, P-gp, substrate) PK
The Applicant evaluated the effect of multiple doses of flibanserin on single dose PK of digoxin. Flibanserin 100 mg was given once daily over 7 days. On Day 5, a single 0.5 mg dose of digoxin (2 x 0.25 mg) was administered with 100 mg flibanserin. Digoxin exposure ($AUC_{0\text{-}inf}$) increased by 96% and Cmax increased by 46% with multiple 100 mg doses of flibanserin co-administered with a single 0.5 mg dose of digoxin. Flibanserin is an inhibitor of P-gp.

2 QUESTION-BASED REVIEW

2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Sprout Pharmaceutical is seeking approval of flibanserin for the treatment of HSDD in premenopausal women (≥ 18 years of age). There is currently no FDA-approved pharmacologic therapy for HSDD. The proposed dose and dosing regimen is one 100 mg oral tablet to be given daily at bedtime with or without food. Boehringer Ingelheim, the original NDA holder, transferred ownership to the NDA and relevant IND to Sprout Pharmaceuticals after an Advisory Committee Meeting voted against approval and receiving a Complete Response letter August 2010. The deficiencies identified in the first Complete Response Letter included a lack of demonstrating statistically significant efficacy in the phase 3 trials for one of the pre-specified co-primary efficacy endpoints, abuse potential of flibanserin, potential exacerbation of depression with concomitant use of selective serotonin or norepinephrine reuptake inhibitors, and DDIs.

In March 2013, Sprout Pharmaceuticals submitted the application that included a new phase 3 study (511.147) and additional phase 1 studies (new DDI studies and a driving study to assess central nervous system depression). The second cycle ended with another Complete Response September 27, 2013. The issues identified in the second review cycle outlined concerns of potentially other CYPs (CYP2C9 and/or CYP2C19) mediating the metabolism of flibanserin.

The Applicant appealed the decision and requested a Formal Dispute Resolution meeting. During the meeting with Dr. John Jenkins on January 10, 2014, the applicant was advised to address the deficiencies (driving impairment, CYP2C9/2C19) outlined in the second Complete Response letter.

The Applicant submitted the NDA for a third cycle review on February 18, 2015. A Joint Members of the BRUDAC and DSaRM Advisory Committee was held on June 4, 2015.

2.2 GENERAL ATTRIBUTES OF THE DRUG

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Flibanserin is a benzimidazolone derivative with the chemical name 2H-benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(tri-fluoromethyl)phenyl]-1-piperazinyl]ethyl]. The molecular formula is $C_{20}H_{21}F_3N_4O$ and the molecular weight is 390.41 g/mol. The free base is used to make the drug product. The drug substance does not contain any chiral centers and does not exhibit any optical isomerism. The drug substance exists (b) (4)

Flibanserin is a white to off-white powder, non-hygroscopic, and is poorly insoluble in neutral pH. In acidic solution (phosphate buffer at pH 8.0, 0.002 mg/ml; 0.01 N HCl), aqueous solubility is 3.3 mg/ml. In water, aqueous solubility is 0.008 mg/ml. (b) (4)

See original Clinical Pharmacology review dated August 26, 2010 in DARRTS.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Flibanserin is a serotonin 5-HT1A agonist and a 5-HT2A antagonist with high affinity binding to 5-HT1A and 5-HT2A receptors. Flibanserin also has moderate affinity for dopamine D4, 5-HT2B and 5-HT2C receptors. The exact mechanism of action for treatment of HSDD is

unknown. The Applicant believes the therapeutic benefit is derived from its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system.

2.2.3 What are the proposed dosages and routes of administration?

The proposed dose is 100 mg given orally at bedtime with or without food.

2.2.4 What drugs indicated for the same indication are approved in the US?

There are no pharmacologic products approved by FDA for the treatment of HSDD or other subtypes of Female Sexual Dysfunction.

2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and clinical studies used to support dosing or claims?

The Applicant conducted two proof-of-concept clinical trials in women with HSDD in North America using dosages studied in prior depression trials. In these 12-week trials, women were treated with flibanserin or placebo with the initial dosage of 50 mg bid. Up-titration to 100 mg bid was permitted at Week 8 if efficacy was unsatisfactory. The Applicant states that through proof-of-concept studies, flibanserin appeared to benefit premenopausal women with HSDD based on positive findings on several endpoints, including statistically significant differences on some endpoints. But they found more dropouts, due to AEs, from Week 8 to Week 12 associated with 100 mg flibanserin bid than with 50 mg flibanserin bid. Therefore, the Applicant chose 50 mg flibanserin bid and 100 mg flibanserin qd as the maximum dosages for further clinical evaluation. Based on prior results in depression studies, the Applicant expected the daily total dosage of 100 mg qd to produce improved tolerability compared to 50 mg bid, and with lower incidences of sedative effects compared to placebo.

To offset the sedative effect, flibanserin was administered at bedtime in the three HSDD pivotal phase 3 studies. In pivotal phase 3 trial 511.71, the dosages were 50 mg qhs and 100 mg qhs. In the pivotal phase 3 trial 511.75, the dosages were 25 mg bid; 50 mg qhs for 14 days, then up-titrated to 50 mg bid; and 50 mg qhs, then up-titrated to 100 qhs. In the third trial 511.147, the dose was 100 mg qhs.

Clinical pharmacology studies were conducted with 50 mg or 100 mg flibanserin as capsules or tablets administered in the morning at the research clinic.

2.3.2 What is the basis for selecting the response endpoints (i.e. clinical endpoints or biomarkers) and how are they measured in clinical pharmacology and clinical studies?

The co-primary efficacy endpoints for the 24-week pivotal phase 3 studies are change from baseline in SSEs and desire, measured by subject responses in an electronic diary or by FSFI. In the Phase 2 studies proof-of-concept studies, ASEX was the primary endpoint due to its use in prior depression trials. In clinical pharmacology studies, the endpoints for the majority of studies were PK parameters of flibanserin. In some cases such as drug-drug interactions, the endpoints in clinical pharmacology studies were PK parameters of the interacting drug.

2.3.3 Are the active moieties in the plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. See Clinical Pharmacology review (DARRTS August 26, 2010)

2. 4 EXPOSURE-RESPONSE

2.4.1 Does the dose-response relationship support evidence of effectiveness?

The basis for drug approval is through demonstrating that a drug can ameliorate symptoms or improvement outcome as assessed by the patients in clinical trials. Demonstration of statistical significance between the treatment and placebo groups is one component in the approval process. In the flibanserin NDA, the Applicant showed statistically significant difference in SSEs, desire assessed by FSFI (not by daily electronic diary), and distress. However, in this NDA, the Applicant did not show that flibanserin improves desire outcomes in a clinically meaningful manner.

The Applicant submitted three pivotal Phase 3 trials (511.71, 511.75 and 511.147) to support efficacy with two co-primary efficacy endpoints – SSE and desire (summary of data in the tables below). Studies 511.71 and 511.75 were submitted to the original NDA and evaluated 50 mg qhs, 100 mg qhs, 25 mg twice daily (bid), 50 mg bid (up-titrated from 50 mg qhs), and 100 mg qhs (up-titrated from 50 mg qhs). Efficacy results with the 25 mg bid or 50 mg qhs doses were less positive than those for the 100 mg qhs dose. The proposed 100 mg is the highest dose studied and showed a higher response than lower doses studied.

Studies 511.71 and 511.75 showed statistically significant improvement in SSE but did not show a statistically significant improvement over placebo in the co-primary endpoint for sexual desire, as assessed with a daily electronic diary. The Applicant did show a statistically significant improvement over placebo for a secondary endpoint that used FSFI to assess sexual desire. The Applicant stated that sexual desire was better assessed with FSFI, but the advisory committee members did not agree with altering the pre-specified primary endpoint for sexual desire.

The third pivotal phase 3 trial (Study 511.147) was ongoing during the original NDA review and included one dosing regimen (100 mg qhs). The co-primary efficacy endpoints were SSE and sexual desire using FSFI. 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.

SSEs: The mean baseline monthly count for SSEs was 2.6. The increase in SSEs with flibanserin 100 mg qhs treatment was a mean of 3.67 SSEs for the last month of treatment, while the placebo group had an average increase 2.86 SSEs. The mean treatment difference between flibanserin and placebo was 0.81 SSEs during the last 28 days of recorded data.

Table 8. Summary Results for SSEs (FAS)#

	Study 71		Study 75*		Study 147	
	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- value[1]	< 0.05		< 0.05		< 0.05	

Desire: The mean (SD) baseline data for the FSFI desire score was 1.9 (0.7). Compared with placebo, there were statistically significant improvements in the FSFI desire score with flibanserin 100 mg qhs. The mean difference between flibanserin treatment and placebo in the improvement of the FSFI desire score was 0.30.

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

	Study 71		Study 75*		Study 147	
	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- value[2]	< 0.05		< 0.05		< 0.05	

FSFI Desire score range: 1.2 to 6.0

Distress: The mean baseline scores for distress showed a relatively high level of distress (~3.3 on a scale of 0-4). The mean difference between flibanserin treatment and placebo in the improvement of the FSDS-R Q13 Distress score was approximately -0.30.

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

	Study 71		Study 75*		Study 147	
	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- value[2]	< 0.05		< 0.05		< 0.05	

FSDS-R Q13 score range: 0 to 4

Clinical Meaningfulness: The clinical meaningfulness of the small numerical changes in SSE, FSFI Desire, and Distress were assessed by responder analysis, which showed that the absolute difference in the percentage of responders with flibanserin and the percentage of responders with placebo is about 9-15%. The placebo response rates were high and ranged from 29 to 49%.

In DBRUP's assessment of clinical meaningfulness, the change in baseline should range from 1.3 to 2.9 SSEs/month, 0.6 to 1.2 for FSFI Desire/28-day recall, and 0 to -1 for Distress. Though statistically significant, the small numerical changes in SSE, FSFI, and FSDS do not appear to be clinically meaningful.

The following table is a summary of the percent responders in the pivotal phase 3 studies by anchoring the efficacy endpoints to the Patient Global Impression of Improvement (PGI) (see Clinical review).

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

	Study 71			Study 75*			Study 147		
Endpoints	**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%

Subgroup Analysis: A post hoc efficacy analyses was conducted 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. The Clinical review team concluded there were no notable differences in efficacy among any subgroups evaluated.

Onset of Efficacy: The onset of efficacy of flibanserin for each endpoint for the three pivotal phase 3 studies (511.71, 511.75, and 511.147) showed that there may be limited efficacy by Week 4 of treatment and that it may take up to 8-12 weeks until the treatment effect plateaus. The onset of efficacy is important in the assessment of benefit/risk, where the AEs particularly hypotension and syncope occurred after the first dose of flibanserin.

2.4.2 What are the characteristics of the dose-response relationships for safety?

The safety database included five phase 3 trials– three pivotal for efficacy and two exploratory. Phase 3 studies 511.71 and 511.75 were submitted in the original NDA and included multiple doses and dosing regimen. The 3rd pivotal phase 3 trial 511.147 evaluated the safety and efficacy of 100 mg qhs versus placebo and was ongoing during the original NDA review; it was submitted in the second review cycle. Studies 511.70 and 511.77 were exploratory studies and were not considered pivotal for efficacy. Safety data from the five phase 3 trials were included in the safety analysis. Dizziness, nausea, fatigue, and somnolence were again the most frequent AEs.

Dose-Response and Safety

The most common treatment-emergent adverse events for subjects treated with flibanserin are dizziness, nausea, fatigue, and somnolence from five phase 3 trials that included lower doses and twice daily (bid) dose regimens submitted in the first review cycle. We concluded that for the

same total daily dose the adverse events were more prevalent with bid dosing versus qhs dosing. For example, at the same total daily dose of 100 mg, giving flibanserin 100 mg qhs resulted in lower incidences of dizziness, nausea, fatigue, and somnolence, compared to 50 mg bid. This finding is not surprising considering the patients would be asleep after taking flibanserin and, therefore, not awake to experience or to report the AEs. That is the rationale for the qhs dosing regimen proposed in this NDA.

At the same dosing interval, the incidence of adverse events increased with dose. For example, at the qhs dosing regimen, the incidence of dizziness was approximately 2-fold higher (6.3% vs. 12.0%) when the dose increased from 50 mg qhs to 100 qhs. At the bid dosing regimen, the incidence of dizziness was approximately 3-fold higher (4.3% vs. 15.3%) when the dose increased from 25 mg bid to 50 bid.

The following table summarizes the AEs occurring in >1% in the randomized treatment groups in five Phase 3 placebo-controlled HSDD Trials (3 pivotal)*

	Placebo	**25 mg bid**	**50 mg qhs**	**50 mg bid**	**100 mg qhs**
	N = 1905 n (%)	**N = 733 n (%)**	**N = 969 n (%)**	**N = 728 n (%)**	**N = 1543 n (%)**
Dizziness	41 (2.2)	31 (4.2)	61 (6.3)	111 (15.3)	171 (11.4)
Somnolence	59 (3.1)	51 (7.0)	55 (5.7)	122 (16.8)	173 (11.2)
Nausea	71 (3.7)	41 (5.6)	68 (7.0)	90 (12.4)	161 (10.4)
Fatigue	95 (5.0)	35 (4.8)	59 (6.1)	101 (13.9)	142 (9.2)
Insomnia	46 (2.4)	14 (1.9)	19 (2.0)	20 (2.8)	75 (4.9)
Dry mouth	17 (0.9)	6 (0.8)	12 (1.2)	10 (1.4)	37 (2.4)
Anxiety	17 (0.9)	5 (0.7)	19 (2.0)	10 (1.4)	28 (1.8)
Constipation	9 (0.5)	4 (0.6)	4 (0.4)	9 (1.2)	24 (1.6)
Abdominal pain	15 (0.8)	5 (0.7)	17 (1.8)	8 (1.1)	23 (1.5)
Sedation	3 (0.2)	1 (0.1)	6 (0.6)	10 (1.4)	20 (1.3)
Somnolence or sedation or fatigue (i.e. CNS depression)	152 (7.9)	87 (11.9)	120 (12.4)	224 (30.8)	319 (20.6)

* Include trials 511.70, 511.71, 511.75, 511.77 and 511.147
Source: Table 2.1.2.1.1, p 93, Integrated Summary of Safety

Exposure-Response and Safety

Blood samples for flibanserin concentration were not taken during the phase 3 trials; therefore, analysis of drug exposure and safety (obtained from phase 3 data) cannot be conducted.
This reviewer assessed drug exposure and safety using a phase 1 dose-escalation study (SPR-12-04) submitted under the second cycle review. As the dose increased, the incidences of adverse events increased as demonstrated in the phase 3 trials.

The Applicant evaluated the orthostatic effects of flibanserin at doses greater than the proposed therapeutic dose. It was a single-center, 2-stage, 3-treatment, double-blind, placebo-controlled, single dose study in healthy premenopausal women. The mean (range) age was 31 (18 – 45) years, mean (SD) weight was 75 (12) kg, and mean (SD) BMI was 28.2 (3.8) kg/m^2.

Flibanserin exposure (Cmax and $AUC_{0\text{-inf}}$) and AEs increased as dose increased from 100 to 250 mg (Study SPR-12-04). The following tables summarize flibanserin PK and incidences of AEs.

Flibanserin PK in Healthy Premenopausal Women Following a Single Oral Dose of Flibanserin.

	Flibanserin			
PK parameter*	100 mg (n=8)	150 mg (n=8)	200 mg (n=7)	250 mg (n=6)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1543	2674	2982	5390
Cmax (ng/mL)	419	529	675	822
Tmax (hr)[1]	0.75 (0.75 – 4.0)	1.0 (0.5 – 4.0)	1.0 (0.5 – 1.1)	0.875 (0.75 – 6.0)
$t_{1/2}$ (hr)	11.7	11.2	11.5	15.3

*arithmetic mean (%CV)
[1] median and range

Treatment-emergent adverse events in healthy premenopausal women following a single oral dose of flibanserin (SPR-12-04).

	Flibanserin				
Number (%) of Subjects with AEs	Placebo (n=14)	100 mg (n=8)	150 mg (n=8)	200 mg (n=7)	250 mg (n=6)
Dizziness	1 (7%)	1 (13%)	3 (38%)	6 (86%)	5 (83%)
Somnolence	5 (36%)	6 (75%)	5 (63%)	6 (86%)	5 (83%)
Nausea	1 (7%)	1 (13%)	1 (13%)	4 (57%)	4 (67%)

Summary of Syncope Cases Observed in Phase 1 Studies
Hypotension requiring medical intervention and syncope was observed in healthy subjects with no history of hypotension and concomitant medications. Syncope was reported in phase 1 studies in healthy subjects who received flibanserin alone, flibanserin with a moderate or strong CYP3A4 inhibitor, flibanserin with alcohol, or flibanserin alone with a CYP2C19 deficiency. These events occurred approximately 1 hr following flibanserin administration and coincide with Tmax.

For reference, SD 100 mg flibanserin Cmax was 419 (206) ng/mL and mean (SD) $AUC_{0\text{-}inf}$ was 1543 (511) ng.hr/mL.

The following table summarizes cases of syncope observed in healthy subjects enrolled in phase 1 studies.

Study#/ Subject #	**Flibanserin Dose/ Concomitant Medication**	**Demographics (age, race, weight, BMI)**	**Pharmacokinetic Parameters**			
			Cmax (ng/mL)	**Fold Change***	**$AUC_{0\text{-}inf}$ (ng*hr/mL)**	**Fold Change***
511.111 (ketoconazole) Subject #11	SD flibanserin 50 mg alone	40 yo white female; 52 kg; 23 kg/m^2	356	1.4	1330	1.2
511.158 (digoxin/P-gp) Subject #5	SD flibanserin 100 mg alone	33 yo white female; 53 kg; 19 kg/m^2	No post-dose PK samples were taken			

SPR-14-06 (CYP2C19) Subject #1014	SD flibanserin 100 mg alone - CYP2C19 PM genotype	47 yo Asian female; 50 kg; 19 kg/m^2	797	2.1	2868	1.2
511.88 (bupropion) Subject #4	MD flibanserin 100 mg alone (after dosing on 3rd day)	41 yo white female; 61 kg; 25 kg/m^2	No PK data as the subject did not complete study			
511.111 (ketoconazole) Subject #13	SD flibanserin 50 mg + MD ketoconazole 400 mg	19 yo white female; 70 kg; 24 kg/m^2	673	2.6	8350	7.3
SPR-12-01 (fluconazole) Subject #1001	SD flibanserin 100 mg + MD fluconazole 200 mg	41 yo white female; 75 kg; 28 kg/m^2	1370	3.3	12944	7.4
SPR-12-03 (alcohol) Subject #110	SD flibanserin 100 mg + 0.4 mg/kg ethanol	26 yo black male; 65 kg; 22 kg/m^2	463	n/a	1058 (AUC_{0-4})	n/a

SD = single dose
MD = multiple doses
*fold change over mean value for reference treatment group in the respective study

2.4.3 Is the dose and dosing regimen selected by the applicant consistent with the known dose-response relationship?

Yes.

2.5 WHAT ARE THE PK CHARACTERISTICS OF THE DRUG?

2.5.1 What are the single dose PK parameters of flibanserin in healthy premenopausal women?

Following administration of a single 100 mg dose of flibanserin tablet in healthy premenopausal women (N=8), mean (SD) Cmax was 419 (206) ng/mL and mean (SD) AUC_{0-inf} was 1543 (511) ng.hr/mL. Median (range) Tmax was 0.75 (0.75 – 4.0) hrs and mean (SD) $t_{1/2}$ was 11.7 (1.9) hrs. Cmax of flibanserin appears to be dose proportional from 100 to 250 mg. For flibanserin AUC_{0-t} and AUC_{0-inf}, exposure appears to be greater than dose proportional from 100 to 250 mg.

2.6 INTRINSIC FACTORS

2.6.1 What intrinsic factors (hepatic impairment, renal impairment, and CYP2C9/2C19 activity) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Hepatic Impairment
The effect of hepatic impairment on the PK 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 score of 6 points) and 4 patients (1 female and 3 males) had moderate liver impairment (two

patients with Child-Pugh score of 8; two patients with Child-Pugh score of 9). The gender distribution was the same in the healthy matched groups, as compared to the impairment groups – 5 females and 5 males in the healthy group matched to the mild impairment group; and 1 female and 3 males in the healthy group matched to the moderate impairment group.

Systemic exposure to flibanserin was significantly affected by hepatic impairment. The $AUC_{0\text{-}inf}$ of flibanserin was significantly higher (4.5-fold) in patients with mild hepatic impairment compared to subjects with normal hepatic function. The $AUC_{0\text{-}inf}$ of flibanserin was higher (2.6-fold) in patients with moderate hepatic impairment compared to subjects with normal hepatic function. Compared to their matched control group, patients with mild hepatic impairment had a slightly reduced Cmax (10%), but it was significantly lower (63% decrease) in patients with moderate hepatic impairment.

The following table summarizes flibanserin pharmacokinetic 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)	Healthy matched (N=10)	Moderate hepatic impairment (N=4)	Healthy matched (N=4)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	3580 (43.0)	776 (35)	2780 (65)	1010 (43)
Cmax (ng/mL)	214 (49)	227 (45)	100 (62)	276 (55)
Tmax (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

Reviewer's Comments:

- 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.
- Cmax was lower in the moderate hepatic impairment group, compared to the matched healthy subjects and the other groups, suggesting a lower degree of absorption.
- The exposure in the two healthy matched groups was different – the moderate healthy matched subjects had higher exposure than the mild healthy matched subjects. Compared to the mild healthy matched subjects, the change in flibanserin exposure ($AUC_{0\text{-}inf}$) is 3.6-fold in the moderate hepatic impairment patients.
- Patients with hepatic impairment will likely experience an increase in adverse events compared with subjects with normal hepatic function.
- 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. Based upon the dose and safety response analysis, the safety profile in women with hepatic impairment taking flibanserin at the therapeutic dose of 100 mg will likely experience significant adverse events as the absolute exposure will be higher than those observed in the hepatic impairment study with 50 mg.

Renal Impairment
The effect of mild-to-moderate renal impairment (7 patients) and severe renal impairment (9 patients) on the PK of flibanserin administered as a single oral dose of 50 mg in an open-label, single dose, parallel group comparison study was evaluated by the Applicant. Mild-to-moderate renal impairment did not significantly impact the systemic exposure to flibanserin ($AUC_{0\text{-}inf}$ increased by 12%), compared to subjects with normal renal function. Severe renal impairment had a moderate impact on the systemic exposure to flibanserin ($AUC_{0\text{-}inf}$ increased by 21%), compared to subjects with normal renal function.

Cmax decreased by 4.2% in mild-to-moderate renal impairment patients, compared to subjects with normal renal function. This is not significant given the level of variability in the data. Cmax increased 31% in severe renal impairment patients, compared to subjects with normal renal function.

The following table summarizes flibanserin PK 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- healthy matched (N=7)	Severe renal impairment (N=9)	Severe healthy matched (N=9)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1150 (76)	934 (51)	1300 (40)	1080 (39)
Cmax (ng/mL)	254 (43)	251 (30)	292 (35)	246 (69)
Tmax (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

Reviewer's Comments:

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

CYP2C9 or CYP2C19 Activity Loss
To assess the contribution of CYP2C9 and CYP2C19 to overall flibanserin clearance, the Applicant evaluated the PK of flibanserin in healthy premenopausal women with either CYP2C9 or CYP2C19 PM genotype as compared to healthy premenopausal women with both CYP2C9 and CYP2C19 EM genotypes. This study is new to the 3rd cycle review; details on the study design can be found in the individual study review.

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 (AUC0-inf) decreased 19% and Cmax decreased 18%, compared to those with a CYP2C9 EM genotype. Half-life (t1/2) was essentially the same, at approximately 11 hours.

In subjects with a CYP2C19 PM genotype, flibanserin exposure (AUC0-inf) increased 34% and Cmax increased 49% compared to those with a CYP2C19 EM genotype. Half-life (t1/2) 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. This subject had a Cmax of 797 ng/mL (2.1-fold over CYP2C19 EM group) and $AUC_{0\text{-}inf}$ of 2868 ng.hr/mL (1.2-fold over CYP2C19 EM group).

The following table summarizes flibanserin pharmacokinetics 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)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	2357 (49)	1903 (45)	3153 (56)
Cmax (ng/mL)	379 (39)	310 (55)	557 (33)
Tmax (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

Safety Findings:

- Subject #1014, a 47 year-old Asian woman with a CYP2C19 PM genotype (weight, 50.4 kg; BMI, 19.2 kg/m^2) 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.

Reviewer's Comments:

- 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 ($AUC_{0\text{-}inf}$ increased 34% and Cmax 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 $AUC_{0\text{-}inf}$ of 7526 ng.hr/mL and Cmax of 698 ng/mL. In this subject, $AUC_{0\text{-}inf}$ increased by 3.2-fold and Cmax increase by 1.8-fold compared to the mean flibanserin exposure in CYP2C19 EM subjects.
- Some antidepressants, anticonvulsants, and proton pump inhibitors (prescription and non-prescription) are CYP2C19 inhibitors. Co-administration of these drugs with flibanserin may increase flibanserin exposure.

2.7 EXTRINSIC FACTORS

2.7.1 What extrinsic factors (CYP inhibitors, CYP inducers, and ethanol) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Effect of a Strong CYP3A4 Inhibitor, Itraconazole

The Applicant evaluated the influence of multiple doses itraconazole at steady state on the PK of a single dose flibanserin (Study 511.37). This was a randomized, open label, two-way crossover study in male and female subjects to investigate the influence of CYP3A4 inhibitor itraconazole (oral 200 mg qd for 8 days) on the PK of a single tablet administration of 50 mg flibanserin with water.

Itraconazole co-administered with flibanserin increased flibanserin $AUC_{0\text{-}inf}$ by 2.6-fold and Cmax by 1.7-fold. Half-life was extended by 4.2 hrs from 7.4 to 11.6 hrs in the presence of itraconazole.

The following table summarizes flibanserin PK 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.

	Flibanserin	
PK parameter*	Without co-administration of itraconazole	With co-administration of itraconazole
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1090 (58)	2810 (76)
Cmax (ng/mL)	201 (50)	341 (33)
Tmax (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

Reviewer's Comments:

- 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 sub-optimally designed study using itraconazole 200 mg, not 400 mg, did not provide a maximal inhibition effect of CYP3A4 inhibition on flibanserin metabolism.
- Therefore, the Applicant conducted another drug-drug interaction study using ketoconazole 400 mg daily to evaluate the effect of a strong CYP3A4 inhibitor on flibanserin exposure.

Effect of a Strong CYP3A4 Inhibitor, Ketoconazole
The Applicant evaluated the influence of multiple doses of the strong CYP3A4 inhibitor ketoconazole on the PK of flibanserin after a single oral dose of 50 mg flibanserin (Study 511.111). This study was an open-label, randomized, two-period, crossover study. Flibanserin was administered with 240 ml of water in the morning about 1 hr after ketoconazole and light breakfast.

Ketoconazole 400 mg daily for 5 days inhibited flibanserin metabolism leading to a 4.5-fold increase in flibanserin $AUC_{0\text{-}inf}$ and a 1.8-fold increase in Cmax, based on geometric means. Tmax increased slightly from 1.25 to 1.50 hr and t1/2 was significantly prolonged from 8.5 to 15.9 hrs.

The following table summarizes flibanserin PK 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
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1140 (44)	5260 (57)
Cmax (ng/mL)	256 (27)	472 (25)
Tmax (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

Safety Findings:

- 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. In this subject, flibanserin AUC was 1.2-fold higher and Cmax was 1.4-fold higher, compared to the mean values following flibanserin 50 mg alone.
- 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. In this subject, flibanserin AUC was 7.3-fold higher and Cmax was 2.6-fold higher, compared to the mean values following flibanserin 50 mg alone.

Reviewer's Comments:

- 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 Applicant conducted a DDI with moderate CYP3A4 inhibitor fluconazole and grapefruit juice.
- To address the potential inhibition by weak CYP3A4 inhibitors, the conducted and submitted a meta-analysis of phase 1 studies in women taking oral contraceptives.
- An extensive list of prescription drugs and dietary supplements including CYP3A4 inhibitors were prohibited from the two pivotal Phase 3 trials 511.71 and 511.75.
- The study was conducted with 50 mg flibanserin; therefore, the absolute exposures (Cmax and AUC) are expected to be higher at the proposed therapeutic dose of 100 mg. Based on the dose/response relationship, the incidence rate of AEs and events of syncope following co-administration of flibanserin and a strong CYP3A4 inhibitor are likely to be higher than those captured in this study.

Effect of a Moderate CYP3A4 Inhibitor, Fluconazole

The original NDA showed that co-administration of flibanserin 50 mg with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 4.6-fold increase in flibanserin exposure ($AUC_{0\text{-}inf}$) and increased frequency of AEs. The Applicant conducted a DDI study with fluconazole and flibanserin to address the potential effect of a moderate CYP3A4 inhibitor on flibanserin exposure. Fifteen healthy women received one 400 mg loading dose and three daily 200 mg doses of fluconazole, then received a single 100 mg dose of flibanserin co-administered with 200 mg fluconazole. For this study, fluconazole and flibanserin were administered in the morning and subjects fasted 10 hrs prior and through 4 hrs after dosing of a single 100 mg dose flibanserin.

Multiple doses of fluconazole resulted in a 2.2-fold increase in Cmax and 7.0-fold in $AUC_{0\text{-}inf}$ of flibanserin. All subjects had an increase in systemic flibanserin exposure. Mean terminal half-life of flibanserin increased from 10 to 23 hrs. Mean clearance (CL/F) of flibanserin decreased significantly from 75.9 to 9.8 L/hr with fluconazole administration. The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.5-fold increase with ketoconazole, a strong CYP3A4 inhibitor.

Fluconazole is a moderate CYP3A4, moderate CYP2C9, and strong CYP2C19 inhibitor.

Co-administration of single 100 mg dose flibanserin and multiple doses of fluconazole 200 mg resulted in more frequent and profound AEs, compared to flibanserin alone. All 15 subjects who received flibanserin + fluconazole experienced at least 1 AE. Three of fifteen subjects experienced a hypotensive event. One subject who received flibanserin + fluconazole experienced a severe hypotensive event (blood pressure of 64/41 mmHg, heart rate of 50 bpm and unable to speak) and required medical intervention before discontinuation from the study. Another subject described feeling "drugged". The onset of all three (20%) hypotensive events occurred at approximately the time of maximum flibanserin concentration.

The following table summarizes flibanserin pharmacokinetics in healthy 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 under a fasting condition.

	Flibanserin 100 mg under fasting condition	
PK parameter*	Without co-administration of fluconazole	With co-administration of fluconazole
$AUC_{0\text{-}inf}$ (ng.hr/mL)	1756 (52)	11249 (30)
Cmax (ng/mL)	421 (52)	889 (41)
Tmax (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

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/min 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. In this subject, flibanserin AUC was 7.4-fold higher and Cmax was 3.3-fold higher, compared to the mean values following flibanserin 100 mg alone.
  - 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. In this subject, flibanserin AUC was 6.6-fold higher and Cmax was 3.1-fold higher, compared to the mean values following flibanserin 100 mg alone.
  - 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. In this subject, flibanserin AUC was 9.4-fold higher and Cmax was 3.6-fold higher, compared to the mean values following flibanserin 100 mg alone.

Reviewer's Comments:

- Hypotension occurred approximately 1 hour following co-administration of flibanserin and fluconazole (i.e., at about Tmax for flibanserin).
- Due to the hypotensive-related AEs experienced in the three subjects described above, the Applicant 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 could not be explained if we assume that only CYP3A4 pathway was inhibited by fluconazole.

- Fluconazole is a moderate CYP3A4 inhibitor, a moderate CYP2C9 inhibitor and a strong CYP2C19 inhibitor. The in vivo DDI study results with fluconazole suggest other enzymes may be involved in the metabolism of flibanserin.
- The sponsor conducted a phase 1 study with subjects possessing a CYP2C9 or CYP2C19 PM status and taking a single dose of flibanserin 100 mg to address the contribution of CYP2C9 or CYP2C19 to the metabolism of flibanserin.

Effect of a Moderate CYP3A4 Inhibitor, Grapefruit Juice
Due to concerns that grapefruit juice, a moderate CYP3A4 inhibitor, can affect the metabolism of flibanserin, the Applicant 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 Cmax and an increase of 38% in AUC0-inf, compared to flibanserin alone. Median Tmax 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).

The following table summarizes Flibanserin Pharmacokinetics 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.

	Flibanserin 100 mg under a fasting	
PK parameter*	Without co-administration of grapefruit juice	With co-administration of grapefruit juice
AUC0-inf (ng.hr/mL)	1869 (42)	2508 (46)
Cmax (ng/mL)	405 (48)	433 (38)
Tmax (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

Reviewer's Comments:
- 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.

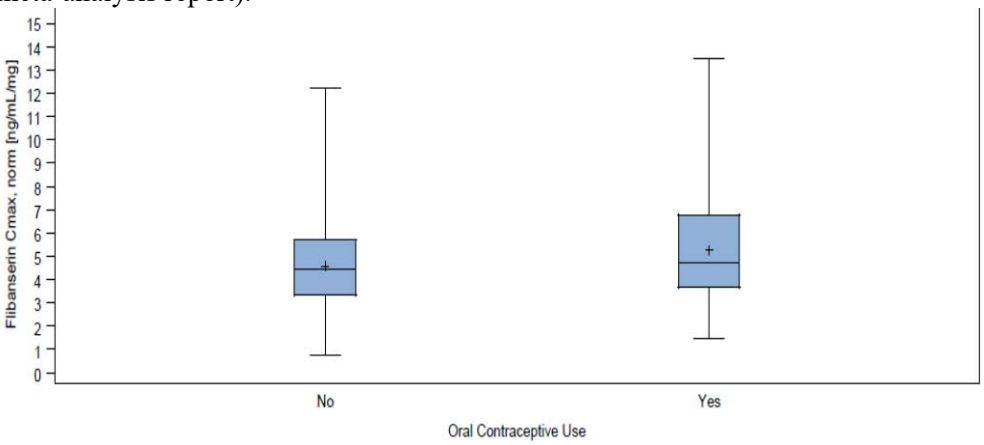
Effect of a Weak CYP3A Inhibitor, Oral Contraceptives (Meta-Analysis)
In the CR issued in August 2010, DBRUP requested the Applicant submitted the final report of a meta-analysis of phase 1 PK data in women who received oral contraceptives and various doses of flibanserin concomitantly. The analysis was requested to exclude subjects with renal or hepatic impairment from the meta-analysis report U10-2254-01.

The meta-analysis is entitled "Amended Statistical comparison of dose normalized PK parameters AUC0-∞,norm, Cmax,norm, AUCτ,ss,norm, Cmax,ss,norm of flibanserin with and

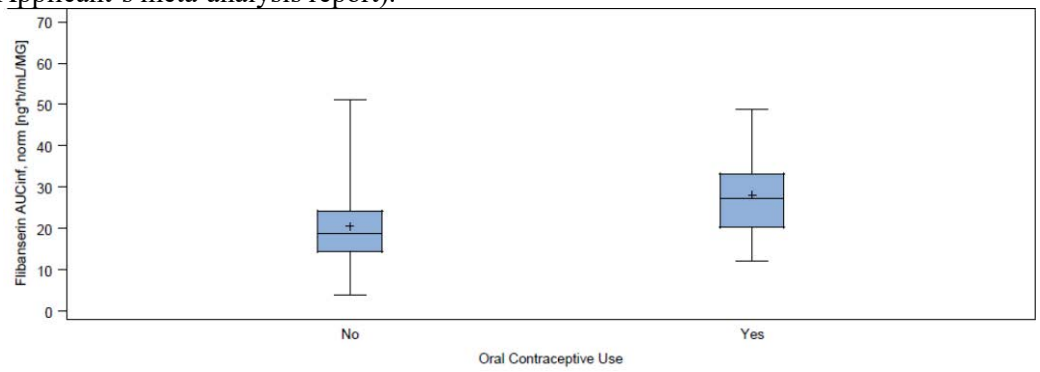
without oral contraceptives across Phase I trials − exclusion of subjects with renal or hepatic impairment".

Subjects were on flibanserin doses ranging from 25 to 100 mg from 7 studies. The adjusted geometric mean ratios for AUC0-inf and Cmax of flibanserin (dose-normalized) were 1.42 and 1.12, respectively, following a single dose flibanserin and oral contraceptives. Flibanserin exposure was affected by oral contraceptives.

Boxplot of Cmax of flibanserin after oral administration of flibanserin in healthy female subjects and HSDD Patients With (n=39) and Without Oral Contraceptives (n=114) (from Applicant's meta-analysis report).



Boxplot of AUC0-inf of flibanserin after oral administration of flibanserin in healthy female subjects and HSDD Patients With (n=39) and Without Oral Contraceptives (n=114) (from Applicant's meta-analysis report).



Effect of a Strong CYP3A Inducer, Rifampin

The Applicant evaluated the influence of rifampin, a strong CYP3A4 inducer, on the PK of flibanserin in an open-label, single center, randomized, two-period cross-over study in healthy females (Study 511.86). Rifampin 600 mg daily was given in the evening for 7 days followed by a morning dose of flibanserin 100 mg on Day 8, and then rifampin 600 mg was given for 2 additional evenings. In the group receiving no rifampin, flibanserin 100 mg was given in the morning of study Day 1. Flibanserin and rifampin were administered with 240 ml of water.

The geometric mean flibanserin exposure AUC0-inf was significantly lower when co-administered with rifampin. Flibanserin AUC0-inf was reduced by 96% with rifampin pre-treatment. Mean flibanserin Cmax was also significantly lowered when co-administered with rifampin. Cmax for

flibanserin was reduced by 91%. Flibanserin metabolism is clearly influenced by the strong CYP3A4 inducer rifampin. Patients should be advised not to use flibanserin with a strong CYP3A4 inducer.

The following table summarizes single dose PK parameters of flibanserin 100 mg with and without co-administration of rifampin 600 mg for 10 days.

	Flibanserin 100 mg under a fasting	
SD PK parameter*	With co-administration of rifampicin	Without co-administration of rifampicin
$AUC_{0\text{-}inf}$ (ng hr/ml)	93.5 (54.8)	2080 (45.0)
Cmax (ng/ml)	371 (57.1)	377 (46.4)
Tmax (hr)[1]	0.75 (0.50 – 1.50)	0.75 (0.50 – 2.00)
$t_{1/2}$ (hr)	5.05 (101)	10.7(34.8)

*arithmetic mean (%CV)
[1] median and range

Effect of a Moderate CYP3A inducer, Etravirine
Flibanserin is proposed for once daily intake at bedtime with or without food. In this study, flibanserin tablets were administered in the morning within 30 min after consumption of a standard breakfast on Days 1 and 16 following an overnight fast of at least 10 hrs. Etravirine should always be taken following a meal because systemic exposure of etravirine decreased by about 50% when administered under fasting conditions. In this study etravirine 200 mg was given twice daily following a meal for 15 consecutive days in healthy female subjects. After 13 days (Days 3 - 15) of etravirine alone administration, flibanserin was co-administered with etravirine on Day 16.

Co-administration of multiple doses of etravirine and a single dose of flibanserin resulted in a decrease of 3.2% in Cmax and 20.6% in $AUC_{0\text{-}inf}$ of flibanserin, compared to flibanserin alone. Median (range) Tmax of flibanserin was delayed by 0.5 hr (3.0 to 2.5) hrs when flibanserin was administered with etravirine. Mean half-life of flibanserin was similar for flibanserin at 9.8 and 9.2 hrs for flibanserin alone and flibanserin + etravirine, respectively. The Applicant is only seeking approval of 100 mg; no other doses were evaluated in their Phase 3 program. In the original NDA, 50 mg dose of flibanserin was found to be ineffective for the treatment of HSDD. With a 20% decrease in exposure and with dose proportionality established only from 50 to 100 mg, concomitant administration of flibanserin and a moderate CYP3A4 inducer may reduce the efficacy of flibanserin. Patients should be advised that efficacy may be reduced when flibanserin is used with a moderate CYP3A4 inducer.

Fatigue, a common AE of flibanserin treatment, was less prominent in the flibanserin + etravirine treatment group (21%), compared to flibanserin alone (47%). Somnolence is common AE of flibanserin therapy and a known, but less common AE of etravirine therapy. The frequency of somnolence increased with co-administration of flibanserin + etravirine (46%), compared with flibanserin alone (20%) group. This suggests that somnolence may be exacerbated when flibanserin is co-administered with somnolence-inducing drugs such as antihistamines and antiparkinson drugs.

The following table summarizes flibanserin pharmacokinetics in healthy female subjects (N=24) following a single 100 mg Dose of flibanserin administered alone and following multiple doses of etravirine.

	Flibanserin 100 mg under a fed condition	
SD PK parameter*	With co-administration of etravirine	Without co-administration of etravirine
$AUC_{0\text{-}inf}$ (ng hr/ml)	1679 (54.8)	2225 (39.0)
Cmax (ng/ml)	286 (39.1)	296 (35.4)
Tmax (hr)[1]	2.5 (1.0 – 4.0)	3.0 (2.0 – 4.0)
$t_{1/2}$ (hr)	9.2 (19.1)	9.8 (24.8)

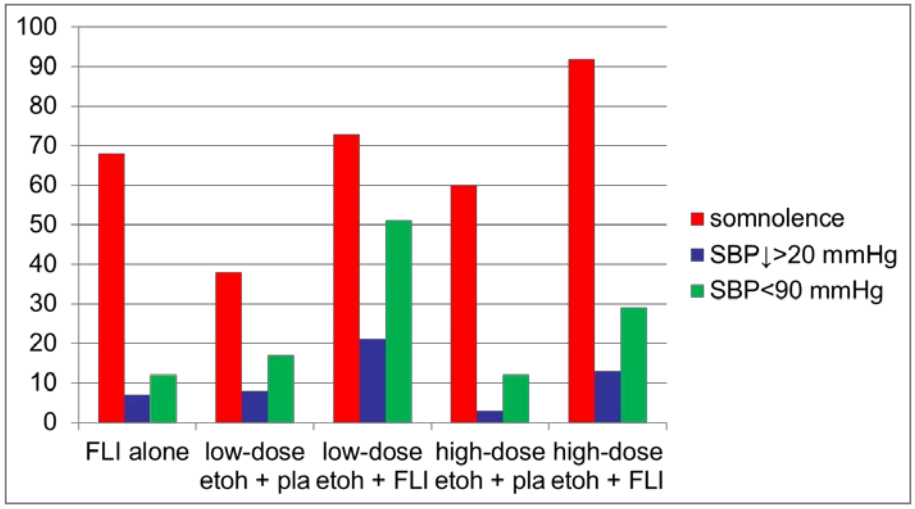
*arithmetic mean (%CV)
[1] median and range

Effect of Alcohol (Ethanol) on Orthostasis
The Applicant 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 Applicant'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 2 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 ($AUC_{0\text{-}4}$) decreased by 11% and 4% when flibanserin 100 mg was administered with 0.4 g/kg ethanol (equivalent to 2 drinks in a 70 kg subject) and 0.8 g/kg ethanol (equivalent to 4 drinks in a 70 kg subject), respectively, compared to flibanserin 100 mg alone.

The following figure summarizes the 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

Safety Findings:

- The most commonly reported AEs were somnolence, headache, and dizziness for subjects in the alcohol and flibanserin or placebo treatment groups. 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 (all with ethanol and flibanserin):
  - 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.

Reviewer's Comments:

- 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.
- The Applicant was encouraged to include women in the study as they are the intended population. However, the majority of subjects in the study were males - 23 healthy men and 2 healthy women.
- 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 (AUC_{0-4}) 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. Considering the variability, it appears that ethanol does not affect flibanserin exposure.

Effect of Flibanserin on Other Drugs

Effect of Flibanserin on Bupropion PK

The Applicant 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. This study was reviewed in the first NDA review cycle.

For bupropion, the AUCτ at steady state increased by 2.2% and Cmax at steady state increased by 2.7% when co-administered with flibanserin 100 mg once daily, compared to bupropion alone.

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.

Reviewer's Comments:

- 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 CYP2B6 substrates.

Effect of Flibanserin on digoxin PK

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. This study was reviewed in the first NDA review cycle.

This was a single center, open-label, randomized, two-way cross-over study in twenty-four healthy male (n=11) and female (n=13) subjects. Subjects were randomized to flibanserin and digoxin (following pre-treatment of flibanserin) or digoxin alone. Flibanserin 100 mg was given once daily over 7 days in 23 subjects (1 subject withdrew from study). On Day 5, a single 0.5 mg dose of digoxin (2 x 0.25 mg) was administered with 100 mg flibanserin.

Digoxin exposure ($AUC_{0\text{-inf}}$) increased 81% and Cmax increased 38% in the group that was co-administered flibanserin and digoxin compared to the group that received digoxin alone.

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 woman with somnolence of severe intensity and recovered without medical intervention.

Reviewer's Comments:

- The Applicant concluded that flibanserin did not inhibit P-gp because the increase in digoxin exposure was moderate based upon digoxin $AUC_{0\text{-}24}$ (25% increase) and digoxin renal clearance ($CL_{R,0\text{-}24}$) (~8% decrease). However, based upon digoxin $AUC_{0\text{-}inf}$, not $AUC_{0\text{-}24}$, digoxin exposure increased 81% with flibanserin co-administration and digoxin Cmax increased 38%. The 8% reduction in digoxin renal clearance was based upon urine samples calculated from 0 to 24 hours. Based on the increased AUC0-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, Cmax 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.

2.7.2 Drug-Drug Interactions

2.7.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

See first cycle Clinical Pharmacology Review (DARRTS August 26, 2010).

2.8.1 GENERAL BIOPHARMACEUTICS

2.8.1 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The formulation of the clinical and the to-be-marketed formulations for the 100 mg tablets are the same. The Applicant did not assess the effect of food with the 100 mg tablet. The Applicant evaluated the effect of different food types on the PK of flibanserin after a single 50 mg dose of flibanserin tablet in an open-label, four-way, cross-over study in 16 healthy male subjects. All the inactive ingredients for the 100 mg dose (total tablet weight is 347 mg) are (b) (4)% more than the inactive ingredients in the 50 mg tablet (total tablet weight is (b) (4)).

Table 13: Composition of flibanserin film-coated tablets (final film-coated tablet formulation)

Ingredient	25 mg tablet mg per tablet	50 mg tablet mg per tablet	100 mg tablet mg per tablet
			(b) (4)
BIMT 17 BS	(b) (4)	(b) (4)	100.000
Lactose monohydrate			(b) (4)
Microcrystalline cellulose			
Hypromellose	(b) (4		
Croscarmellose sodium			
Magnesium stearate			
	(b) (4)		
Titanium dioxide			
Talc			
Ferric oxide	(b) (4		
	(b) (4		
Total			347.000
			(b) (4)

Compared to the fasted condition, the exposure of flibanserin was 17%, 41%, and 53% higher after administration of a light, medium, and high fat/caloric breakfast, respectively. The total flibanserin exposure increased with increasing fat/calorie content.

The Cmax was essentially the same between the light breakfast and fasted groups, with a decrease of 3.9% in the light breakfast group. This is not meaningful considering the level of variability in the data. In the medium and high fat/caloric breakfast groups, Cmax increased by 12 and 14%, respectively, compared with the fasted condition.

Tmax was prolonged slightly from 0.8 hr under fasted condition up to 2 hrs under high fat/caloric meal.

The formulation of the 50 mg tablet evaluated in the food effect study was very similar to the 50 mg tablet formulation used in some phase 3 studies. There are a few minor differences between the two products – (b) (4) titanium dioxide, (b) (4) talc, (b) (4) ferric oxide

The following table summarizes PK parameters of flibanserin 50 mg after administration of food with varying fat/caloric content:

	Meal Type			
PK parameter*	Fasted	Light Fat	Medium fat	High Fat/High Calorie
AUC0-inf (ng.hr/ml)	821 (52.0)	959 (50.1)	1160 (46.6)	1260 (49.1)

Cmax (ng/ml)	207 (34.7)	199 (33.1)	232 (43.9)	236 (38.7)
Tmax (hr)	0.77 (36.7)	1.78 (67.8)	1.19 (65.0)	2.03 (74.1)
$t_{1/2}$ (hr)	7.55 (37.1)	7.79 (33.2)	7.52 (27.0)	7.93 (30.5)

*Arithmetic mean (%CV)

Under the worst case scenario with high fat/caloric breakfast, the exposure increased by 53%. Cmax was influenced less by food, while Tmax was prolonged slightly. The recommendation dose for flibanserin in HSDD women is 100 mg at bedtime.

There was no mention by the Applicant with regard to the administration of food in the pivotal phase 3 studies 511.71, 511.75, and 511.174. The protocol for these studies states that flibanserin tablets were given with 150 ml of fluid. The Applicant proposes in the label that flibanserin be given at bedtime with or without food. The dosing instruction for the phase 3 studies included 150 ml of fluid, not water.

2.9 ANALYTICAL SECTION

(DARRTS August 26, 2010 and August 29, 2013).

For Study SPR-14-06 submitted in this third cycle review, the analytical methods were the same as previously used methods. Plasma flibanserin concentrations were determined using a validated LC-MS/MS method developed by [redacted] (b) (4). The lower and upper limit of quantitation was 0.1 ng/mL and 100 ng/mL, respectively. The QC samples were 0.3, 3, and 80 ng/mL. The precision and accuracy of the control samples are within the acceptable limits as shown in the following table (study report SPR-14-06 table 3).

	Nominal Concentration Level of QC Samples for Flibanserin Analyte				
	0.300 ng/mL	3.00 ng/mL	80.0 ng/mL	QC Dilution 80 ng/mL	QC Dilution 500 ng/mL
Number of QC samples	46	46	46	12	54
Precision (%RSD)	7.1	4.9	11.0	9.9	9.1
Accuracy (%RE)	1.3	1.0	-2.3	14.9	7.8

Abbreviations: %RE = percent relative error, %RSD = percent relative standard deviation, QC = quality control.

3. APPENDIX
Individual Study Review

Study SPR-14-06

Title: Pharmacokinetics of Flibanserin in Relation to CYP2C19 and CYP2C9 Genotypes

Objectives: The primary objective of this study was to evaluate the single dose PK of a 100 mg oral dose of flibanserin in healthy premenopausal women with either CYP2C9 or CYP 2C19 PM genotype as compared to healthy premenopausal women with both CYP2C9 and CYP2C19 EM genotypes. The secondary objective of this study was to evaluate the safety and tolerability of a single 100 mg oral dose of flibanserin in healthy premenopausal women with either CYP2C9 PM or CYP2C19 PM genotype and in healthy premenopausal women with both CYP2C9 and CYP2C19 EM genotypes.

Methods: This was a multi-center (7 centers), open-label study of the PK, safety, and tolerability of a single, 100 mg oral dose of flibanserin in 3 groups of healthy premenopausal female subjects: 1) subjects who had both CYP2C9 EM and CYP2C19 EM genotypes, 2) subjects who had a CYP2C9 PM genotype but who had a CYP2C19 EM genotype, and 3) subjects who had a CYP2C19 PM genotype but who had CYP2C9 EM genotype. The study was planned to include 8 to 12 subjects in each genotype group. Each subject took one 100 mg tablet of flibanserin orally, with 240 mL of room temperature water, after an overnight fast (minimum of 10 hours), at approximately 8 am on the morning of Day 1.

After providing written informed consent, potential study participants were screened for study eligibility during an up to 45-day screening period. The screening procedures included a medical history, a single 12-lead electrocardiogram (ECG), a physical examination, laboratory tests (hematology, serum chemistries, urology, serology, and pregnancy test), an alcohol and drug screen, and genetic testing to ensure that the subjects met the criteria for one of the 3 genotype groups.

Subjects were required to fast and to refrain from lying down for 4 hours after dosing. Subjects remained confined to the clinical research unit for 96 hours post-dose (Day 5).

Main Inclusion Criteria:
Healthy premenopausal female subjects aged 18 years or older who had a body mass index (BMI) between 18 and 35 kg/m2, inclusive, and who met the criteria for one of the following genotypes (based on pharmacogenetic testing results) were eligible for the study:
1) CYP2C9 EM and CYP2C19 EM: *1*1.
2) CYP2C9 PM: *2*2, *2*3, *3*3; or homozygous for *6, *15, and *25; or heterozygous with *6, *15, or *25 could be considered a PM.
3) CYP2C19 PM: *2*2, *2*3, *3*3; or homozygous for *2b, *4, *5, *6, *7, *8; or heterozygous for a combination of *2, *2b, *3, *4, *5, *6, *7, *8 could be considered a PM.

Subjects who were both CYP2C9 PMs and CYP2C19 PMs were excluded from the study (i.e., the PM genotypes were exclusive of each other). Any homozygous or heterozygous combination of *1a and *1b for CYP3A4 was considered to be an EM.

Subjects who met the criteria for inclusion in any one of the genotype groups were excluded from the study if:
• They had a PM status genotype for CYP3A4 or CYP2D6 with any of the following variants: CYP3A4*22, CYP3A4*20, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*11, CYP2D6*15, CYP2D6*36, CYP2D6*40, or CYP2D6*42.

• They had an EM status genotype that was consistent with a CYP2C19*1*17 or CYP2C19*17*17 variant.

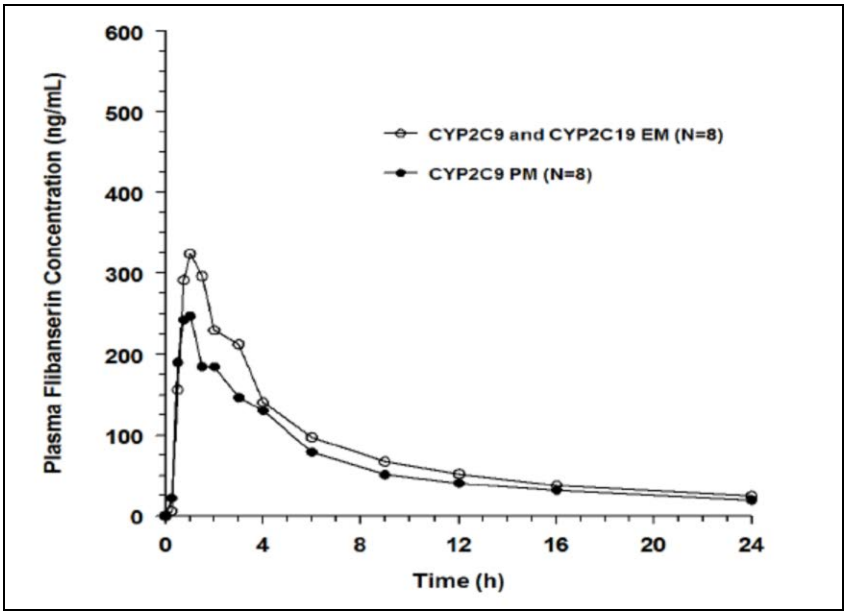
Study Sites (7): Jasper Clinic (An MPI Research Company), Kalamazoo, Michigan; Davita Clinical Research, Lakewood, Colorado; Algorithme Pharma, Mont Royal, Quebec, Canada; Davita Clinical Research, Minneapolis, Minnesota; Celerion, Lincoln, Nebraska; PRA Health Sciences, Salt Lake City, Utah; Celerion, Tempe, Arizona

Study Period: July 23, 2014 to November 7, 2014

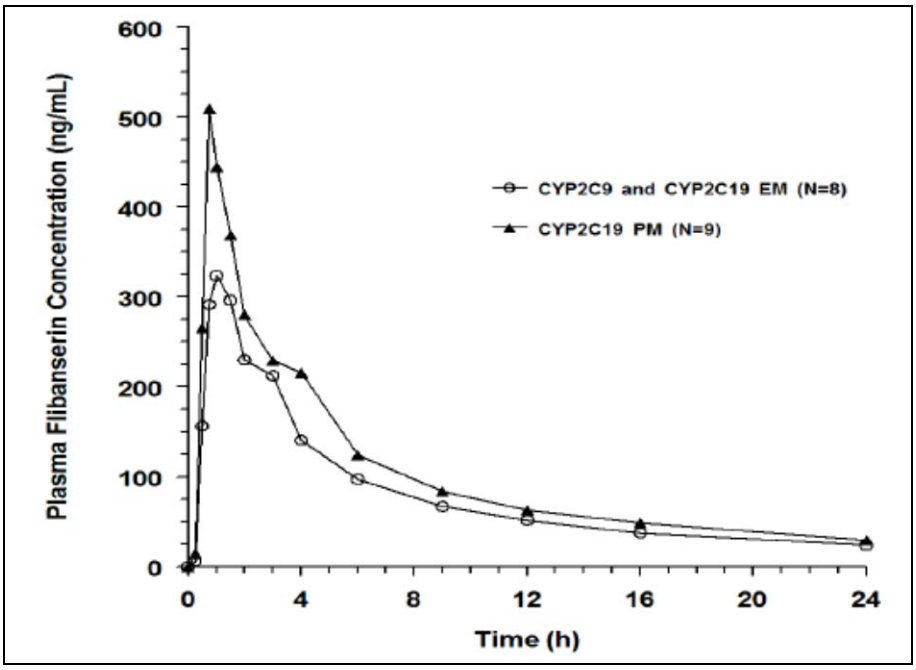
Treatment Products
Flibanserin: 100 mg immediate-release, film-coated tablets, lots X130475D and X130475F

PK Sampling: Blood samples for determination of plasma flibanserin concentrations were obtained within 60 minutes pre-dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, and 96 hours post-dose. Safety and tolerability were assessed by review of adverse event, vital sign (including orthostatic changes), laboratory, ECG, and physical examination data.

The following figure is the concentration-time profile of flibanserin 100 mg in CYP2C9/CYP2C19 EMs (n=8) and CYP2C9 PMs (n=8) (figure 2 from study report).



The following figure is the concentration-time profile of flibanserin 100 mg in CYP2C9/CYP2C19 EMs (n=8) and CYP2C19 PMs (n=9) (figure 4 from study report).



The following table summarizes flibanserin PK following flibanserin 100 mg in CYP2C9/CYP2C19 EMs (n=8), CYP2C9 PMs (n=9), CYP2C19 PMs (n=9), and CYP2C19 PMs without subject 2013 (n=8) (table 8 from study report).

	Flibanserin 100 mg x 1 Dose			
Parameter	CYP2C9/CYP2C19 EM (N=8)	CYP2C9 PM (N=8)	CYP2C19 PM (N=9)	CYP2C19 PM Without Subject 2013 (N=8 [a]
AUC_{0-t} (ng•h/mL)	2343 (1130)	1886 (851)	3117 (1721)	2587 (701)
AUC_{0-inf} (ng•h/mL)	2357 (1146)	1903 (863)	3153 (1771)	2606 (713)
AUC_%Extrap	0.433 (0.450)	0.775 (0.881)	0.824 (0.726)	0.653 (0.549)
C_{max} (ng/mL)	379 (146)	310 (170)	557 (182)	540 (187)
T_{max} (h)[b]	1.00 (0.50 – 2.00)	0.78 (0.50 – 3.00)	0.78 (0.75 – 1.50)	0.767 (0.75 – 1.50)
$t_{½}$ (h)	11.1 (3.54)	10.7 (5.18)	13.5 (4.51)	12.8 (4.32)
CL/F (L/h)	54.5 (30.7)	66.0 (35.1)	39.1 (18.4)	42.3 (16.7)
V_z/F (L)	794 (395)	861 (293)	689 (230)	730 (208)

The following table is the geometric mean ratios and 90% confidence intervals for flibanserin AUC and Cmax in subjects with CYP2C9 and CYP2C19 PM status, compared to CYP2C9/2C19 EM status.

CYP2C9 PM (Test) N=8 / CYP2C9/CYP2C19 EM (Reference) N=8		
Parameter	**Geometric Mean Ratio (Test/Reference)**	**90% CI for Ratio of Least-Squares Means**
Geometric $AUC_{0\text{-}inf}$	0.8169	0.5120-1.3033
Geometric $AUC_{0\text{-}t}$	0.8141	0.5116-1.2954
Geometric C_{max}	0.7749	0.5128-1.1709
CYP2C19 PM (Test) N=9 / CYP2C9/CYP2C19 EM (Reference) N=8		
Parameter	**Geometric Mean Ratio (Test/Reference)**	**90% CI for Ratio of Least-Squares Means**
Geometric $AUC_{0\text{-}inf}$	1.3487	0.8719-2.0861
Geometric $AUC_{0\text{-}t}$	1.3434	0.8719-2.0696
Geometric C_{max}	1.4885	1.0726-2.0658

Safety Findings:

- Subject #1014, a 47 year-old Asian woman with a CYP2C19 PM genotype (weight, 50.4 kg; BMI, 19.2 kg/m^2) 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.

Reviewer's Comments:

- To understand the contribution of CYP2C9 and CYP2C19 to overall flibanserin clearance, the Applicant evaluated the PK of flibanserin in healthy premenopausal women with either CYP2C9 or CYP2C19 PM genotype as compared to healthy premenopausal women with both CYP2C9 and CYP2C19 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 (AUC0-inf) decreased 19% and Cmax decreased 18%, compared to those with a CYP2C9 EM genotype. Half-life (t1/2) was essentially the same, at approximately 11 hours.
- In subjects with a CYP2C19 PM genotype, mean flibanserin exposure (AUC0-inf) increased 1.3-fold and Cmax increased 1.5-fold compared to those with a CYP2C19 EM genotype. Half-life (t1/2) 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.
- Subject #2013 with CYP2C19 PM status had an $AUC_{0\text{-}inf}$ of 7526 ng/mL, C_{max} of 698 ng/mL, and $t_{1/2}$ of 18.8 hrs. The Applicant states that the higher exposure in subject 2013 was the result of a prolonged absorption, not a decrease in metabolic elimination, as observed by a second peak in the PK profile. For this reason, the Applicant conducted their PK analysis without this subject. In this review, Subject 2013 was included in the CYP2C19 PM group for the purpose of PK analysis as she was a confirmed CYP2C19 PM.
- The greatest flibanserin exposure among the nine subjects with a CYP2C19 PM genotype occurred in a 29 year-old Asian subject who had flibanserin AUC0-inf of 7526 ng*hr/mL and Cmax of 698 ng/mL. In this subject, the AUC0-inf was increased 3.2-fold and Cmax 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.
- The findings from this study suggest flibanserin is partially metabolized by CYP219 (not CYP2C9) secondary to CYP3A4.

Study CYP0899 R1 (In Vitro Metabolism Study)

Title: Study to Investigate the Reaction Phenotyping of the Test Compound, Flibanserin, in the Presence of Selective Reversible and Irreversible Inhibitors of Cytochrome P450 Enzymes

Objectives: To determine the rate of metabolism of flibanserin in pooled human liver microsomes (HLM) in the absence and presence of selective reversible and irreversible inhibitors CYP450 enzymes with the aim of identifying which CYP enzyme(s) contribute to flibanserin metabolism. The first part of the study evaluated the effects of CYP2C9, CYP2C19 and CYP3A4/5 inhibitors on flibanserin clearance. The second part of the study evaluated CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 inhibitors on the clearance of flibanserin. The final objective of the study was to compare the effects of three azole antifungals ketoconazole, itraconazole and fluconazole, on the metabolic clearance of flibanserin in pooled HLM.

Methods: Flibanserin solutions were prepared in DMSO. Pooled male and female microsomes from 150 donors were purchased from (b) (4) and were stored at -80 °C prior to use. Microsomes (final protein concentration 0.1 mg/mL), 50 mM potassium phosphate buffer pH 7.4 containing 0.1 mM EDTA and 3 mM MgCl2 and flibanserin (final substrate concentrations 0.2 and 1 µM) were pre-incubated at 37 °C prior to the addition of an NADPH-regenerating system (1 mM NADP, 5 mM glucose-6-phosphate and 1 U/mL glucose-6-phosphate dehydrogenase) to initiate the reaction. The final incubation volume was 600 µL. Three positive control substrates (verapamil for CYP3A4, diclofenac for CYP2C9 and omeprazole for CYP2C19) were included to assess the metabolic competence of the pooled HLM.

The rate of metabolism is based on loss of parent drug.

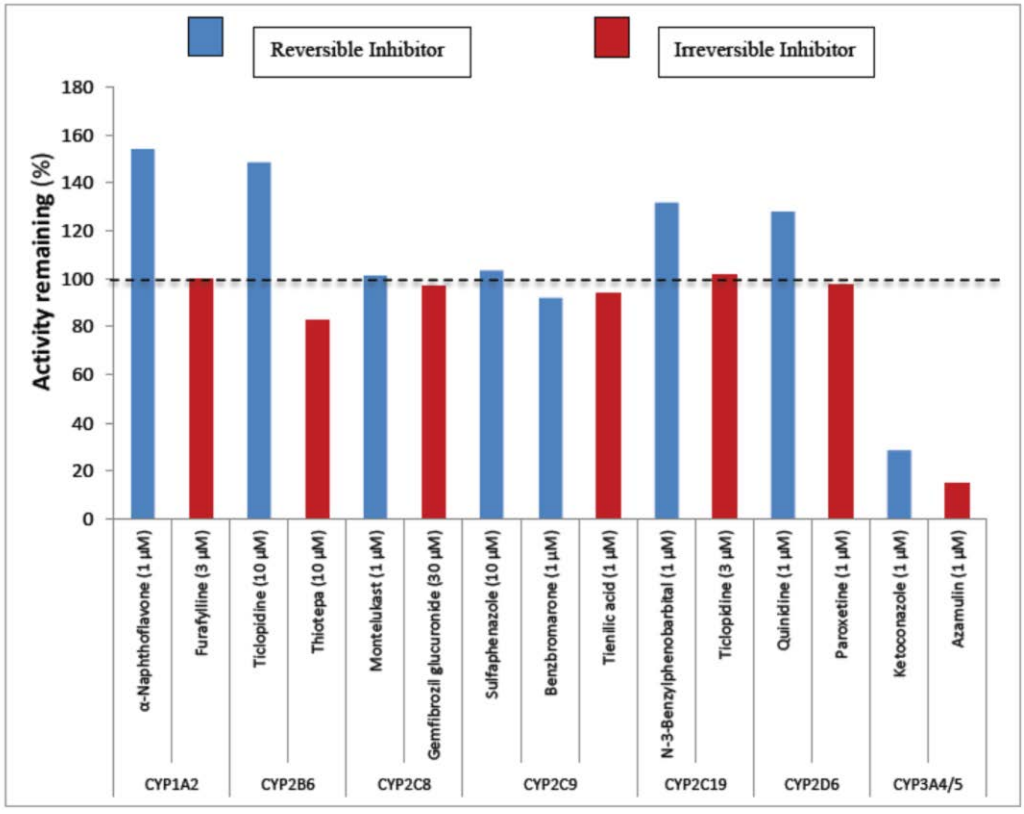
Results:

The following table summarizes the effects of CYP inhibitors on flibanserin metabolism in pooled microsomes (table 7 from study report).

CYP enzyme	Inhibitor (reversible and *irreversible*)	Flibanserin metabolism	
		Percent activity remaining	Percent inhibition
CYP1A2	α-Naphthoflavone (1 µM) *Furafylline* (3 µM)	154 100	-54.0 -0.0922
CYP2B6	Ticlopidine (10 µM) *Thiotepa* (10 µM)	148 82.4	-48.4 17.6
CYP2C8	Montelukast (1 µM) *Gemfibrozil glucuronide* (30 µM)	101 97.0	-1.20 3.03

CYP enzyme	Inhibitor (reversible and *irreversible*)	Flibanserin metabolism	
		Percent activity remaining	Percent inhibition
CYP2C9	Sulfaphenazole (10 µM) Benzbromarone (1 µM) *Tienilic acid* (1 µM)	103 91.8 93.7	-3.30 8.20 6.26
CYP2C19	*N*-3-Benzylphenobarbital (1 µM) *Ticlopidine* (3 µM)	132 102	-31.6 -1.50
CYP2D6	Quinidine (1 µM) *Paroxetine* (1 µM)	128 97.5	-28.0 2.51
CYP3A4/5	Ketoconazole (1 µM) *Azamulin* (1 µM)	28.7 14.8	71.3 85.2

The following figure summarizes the effects of CYP inhibitors on flibanserin metabolism in pooled microsomes (figure 4 from study report).



Reviewer's Comments:

- The study was conducted with human microsomes pool from 150 male and female subjects. This is generally acceptable for in vitro assessment of CYP involvement as microsomes are conveniently available. For CYP2C9 and CYP2C19, the enzymes of interest in this review cycle and subject to genetic polymorphism, in vitro studies with individual hepatocytes may be a more sensitive system.
- The incubation time in this study was 30 min. This duration is shorter than other in vitro metabolism studies that include varying incubation periods. The results from this study may not reflect optimal study condition.
- Acceptable substrates for CYP3A4 are midazolam and testosterone, for CYP2C9 are S-warfarin and diclofenac, and CYP2C19 are A-mephenytoin and omeprazole. The Applicant used acceptable substrates for the assessment of CYP3A4, 2C9 and 2C19.
- Percent metabolism of flibanserin was calculated according to the following equation:

  % metabolism = [(*peak area ratio or concentration at 1 min) – (peak area ratio or concentration at 30 min)] /peak area ratio or concentration at 1 min

  This first part of the numerator and denominator of this equation (peak area ratio or concentration at 1 min) is the drug concentration after 1 min of drug exposure to hepatocytes. Mathematically, it reduces the initial drug concentration (drug not exposed to enzymes) and decrease the final calculated value.
- The percent of metabolic activity remaining in the presence of inhibitor was calculated according to the following equation:

  $$\% \text{ activity remaining} = \frac{\% \text{ metabolism w/o inhibitor} - \% \text{ metabolism with inhibitor}}{\% \text{ metabolism w/o inhibitor}}$$

  This is acceptable.
- The Applicant concluded CYP3A4 is the major contributor to flibanserin clearance. They state the results suggest that CYP2C19 does not contribute flibanserin clearance and that CYP2C9 may be a minor contributor (<10%) to flibanserin clearance by HLM.
- Based upon the negative values for inhibition, there is significant variability in the in vitro study. Assessment of CYP enzymes with HLM does not conclusively exclude its effect in vivo. The in vitro data with HLM does not reverse our prior hypothesis that CYP2C9 and/or CYP2C19 may be involved in flibanserin clearance.
- Evidence for the involvement of CYP3A4 and CYP2C19 comes primarily from in vivo studies SPR-12-01 (DDI with fluconazole) and SPR-14-06 (CYP2C9/CYP2C19 EM/PM). In Study SPR-12-01 flibanserin $AUC_{0\text{-inf}}$ increased 7-fold with concomitant intake of flibanserin and fluconazole, an inhibitor of CYP3A4/2C9/2C19, compared to flibanserin alone. In SPR-14-06, flibanserin exposure increased in subjects with CYP2C19 PM phenotype were 1.3 to 3.1-fold higher (Cmax and AUC), compared to CYP2C19 EM subjects. We conclude flibanserin clearance is mediated by CYP3A4 and, to a lesser extent, CYP2C19.

The table below summarizes the Phase I studies reviewed by the Office of Clinical Pharmacology over three review cycles.

Study No.	Individual Studies Reviewed Under Original NDA Submission (2009) (DARRTS: August 26, 2010)
c-10165-040-0404	Investigation of the passive and active (P-glycoprotein mediated) transport of flibanserin in vitro by means of permeability measurements across confluent Caco-2 cell monolayers
511.1	A single increasing dose-tolerance study in healthy volunteers after oral administration on flibanserin BIMT 17BS (0.1 to 150 mg)
511.2	A study to evaluate the clinical tolerability and pharmacokinetics of BIMT 17 BS after multiple increasing oral dosages of 20 mg tid, 50 mg bid, 50 mg tid, 100 mg bid, and 100 mg tid over 15 days in healthy men and women
511.15	A two-way crossover study investigating the pharmacokinetics and metabolism of flibanserin after administration of a single intravenous dose of 20 mg and a single oral dose of 50 mg [^{14}C]-radiolabelled flibanserin to six healthy male volunteers
511.26	An open-label, four-way, crossover study to evaluate a food effect on the pharmacokinetics of flibanserin after single oral administration of a 50 mg tablet following a light breakfast, a normal breakfast, and a high fat/caloric breakfast, compared with fasted state in healthy male volunteers
511.37	A randomized, open label study to investigate the influence of CYP3A4 inhibitor itraconazole (oral 200 mg qd) on the pharmacokinetics of a single tablet administration of 50 mg flibanserin and the influence of 50 mg tablets flibanserin bid as a putative CYP3A4 inhibitor on the pharmacokinetics of oral administration of 40 mg simvastatin in two independent two way crossover studies in healthy female and male subjects
511.67	Pharmacokinetics of flibanserin in subjects with liver impairment as compared to healthy subjects
511.86	An open, randomized two-period cross-over trial to evaluate the effect of multiple doses of rifampicin on the pharmacokinetics of flibanserin
511.87	Pharmacokinetics and pharmacodynamic of flibanserin in poor and extensive metabolizer of CYP2D6 and in combination with paroxetine
511.88	An open, randomized, two-period crossover trial to evaluate the effect of multiple doses of flibanserin on the steady-state pharmacokinetics of bupropion
511.93	An open-label, randomized, two-way crossover trial to evaluate the effect of multiple doses of flibanserin on the single dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel
511.96	Pharmacokinetics of flibanserin in subjects with renal impairment as compared to healthy subjects
511.105	A Phase I, open-label, parallel, and within-groups sequential trial to evaluate the single dose and steady state pharmacokinetics of flibanserin in premenopausal women with hypoactive sexual desire disorder

511.111	An open-label, randomized two-period crossover trial to evaluate the effect of multiple doses of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of flibanserin
511.117	Safety, tolerability and pharmacokinetics of single rising oral doses (25 and 50 mg) of flibanserin followed by multiple rising oral doses (25, 50, 100 mg per day) in healthy Japanese female volunteers

Study No.	**Individual Studies Reviewed Under Second Review Cycle (2013) (DARRTS: August 29, 2013)**
Report U10-2254-01	Amended Statistical Comparison of Dose Normalized PK Parameters AUC0-∞,norm, Cmax,norm, AUCτ,ss,norm, Cmax,ss,norm of Flibanserin with and Without Oral Contraceptives Across Phase I trials – Exclusion of Subjects with Renal or Hepatic Impairment
SPR-12-01	An Open Label, Sequential Study to Evaluate the Effect of a Single Dose of Grapefruit Juice and Multiple Doses of Fluconazole on the Pharmacokinetics of Flibanserin in Healthy Females
SPR-12-02	An Open Label, Sequential Study to Evaluate the Effect of Multiple Doses of Etravirine on the Pharmacokinetics of Flibanserin in Healthy Females
SPR-12-03	A Randomized, Double-Blind, Single-Dose, Five-Way Crossover Study in Healthy Subjects to Determine the Effects of Simultaneous Administration of Flibanserin 100 mg and Varying Concentrations of Ethanol on the Safety and Pharmacodynamics Characteristics of Flibanserin
SPR-12-04	A Two-Stage, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Evaluation of Standard and Supratherapeutic Single Doses of Flibanserin in Healthy Females
511.146	An Eight Day Open-Label Trial to Evaluate the Single Dose and Steady State Pharmacokinetics of 100 mg Flibanserin Administered Orally Once Daily in Post-Menopausal Women with Hyposexual Desire Disorder
511.158	An Open Two-Way Cross-Over Study to Evaluate the Effect of Multiple Doses of Flibanserin 100 mg Film-Coated Tablets Given Once Daily on the Single Dose Pharmacokinetics of Digoxin 0.5 mg in Healthy Male and Female Volunteers

Study No.	**Individual Studies Reviewed Under Third Review Cycle (2015)**
SPR-14-06	Pharmacokinetics of Flibanserin in Relation to CYP2C19 and CYP2C9 Genotypes
CYP0899 R1	Study to Investigate the Reaction Phenotyping of the Test Compound, Flibanserin, in the Presence of Selective Reversible and Irreversible Inhibitors of Cytochrome P450 Enzymes

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAI M LEE
07/16/2015

MYONG JIN KIM
07/16/2015

EDWARD D BASHAW
07/17/2015

A supervisory memo has been prepared and is linked to this review. While not discounting the serious sedative effects of flibanserin and the severity of the drug-drug interactions with CYP3A4 and CYP2C19 inhibitors, I do believe that the sponsor has addressed the core clinical pharmacology concerns. In my memo I have laid out the logic structure of my position and the linked memo conveys the final determination from the Division of Clinical Pharmacology-3.

Memorandum

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

DATE: July 17th, 2015

TO: Hylton Joffe, MD, MMSc
Director, Division of Bone, Reproductive and Urologic Drug Products
USFDA

From: CAPT Edward D. Bashaw, PharmD.
Director, Division of Clinical Pharmacology-3
USFDA

RE: NDA 022526 (FLIBANSERIN)

This memo transmits the recommendation of the Division of Clinical Pharmacology-3 regarding the acceptability of the Clinical Pharmacology portion of the Flibanserin NDA. The primary reviewer Dr. LaiMing Lee, Ph.D., has completed her review of the application and found it to be unacceptable and recommends a Complete Response (CR) action. This opinion has been concurred with by her Team Leader, Dr. Myong-Jin Kim, PharmD. As this application is a New Molecular Entity (NME), has had two previous CR's, and has been the subject of two separate FDA Advisory Committee meetings, I am exercising my prerogative as the Director of the Division of Clinical Pharmacology-3 to issue a supervisory memo which will convey the Division's final recommendation and the logic structure behind the recommendation. This memo is not intended to replace the review or to encompass all of the issues or detail of the primary review. It is intended to be a weighing of the elements leading to a decision.

Overview of Flibanserin

Flibanserin is a 5-HT1A agonist and a 5-HT2A antagonist with high affinity binding to 5-HT1A and 5-HT2A receptors. Flibanserin also has moderate affinity for dopamine D4, 5-HT2B and 5-HT2C receptors. Flibanserin displays antidepressant-like activity in most animal models sensitive to antidepressants. In clinical studies the antidepressant effects of flibanserin were not clinically detectable vs. placebo.

Much like sildenafil, whose activity was only recognized while it was being developed for high blood pressure, the effect of flibanserin in women was developed from anecdotal reports during its development as a potential antidepressant. The exact mechanism of action for treatment of hypoactive sexual desire disorder (HSDD)[i] is unknown. The Applicant believes the therapeutic benefit is derived from its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system. The definition of HSDD is attached in Appendix 1 of this memo for reference.

Regulatory History/Timeline

Flibanserin was originally under development by Boehringer Ingelheim (BI). The original NDA submission was filed on October 27th, 2009. The efficacy and safety findings were discussed at

the Reproductive Health Drugs Advisory Committee Meeting on June 18th, 2010. At that time the committee members voted 11 to 0 against flibanserin based on the overall benefit/risk profile as presented at that time. Subsequent to the meeting the Division of Bone, Reproductive, and Urologic Products (DBRUP) issued a CR letter on August 27th, 2010 based on a lack of efficacy in the co-primary endpoint of desire in two clinical trials and safety concerns (including dizziness, somnolence, nausea, and syncope), i.e, an unfavorable risk/benefit ratio. At the time of this CR the Clinical Pharmacology portion of the NDA was found to be acceptable, however, additional in vivo Drug-Drug interaction studies with weak and moderate CYP3A4 inhibitors were recommended.

Following the CR letter, BI transferred the drug to Sprout Pharmaceuticals in 2011. Following the completion of a clinical trial that was ongoing at the time of the 2010 Advisory Committee Meeting, Sprout re-submitted the NDA on March 29th, 2013. In addition to the aforementioned clinical trial the re-submission also contained 7 new Phase 1 studies:

- Moderate CYP3A4 inhibitors (fluconazole and grapefruit juice) on flibanserin exposure (Study SPR-12-01)
- Moderate CYP3A4 inducer (etravirine) on flibanserin exposure (Study SPR-12-02)
- Alcohol on orthostasis and syncope (Study SPR-12-03)
- Supratherapeutic doses on safety and orthostasis (Study SPR-12-04)
- Flibanserin in recreational poly-drug users and potential for abuse (Study SPR-12-05)
- Single dose (SD) and multiple dose (MD) administration of flibanserin in postmenopausal women to evaluate the effect of age (Study 511.146)
- Effect of MD of flibanserin on a SD of digoxin in male and female subjects (Study 511.158)

These studies were reviewed and at the time of the second CR action (September 27th, 2013) the Clinical Pharmacology review again concluded that the Clinical Pharmacology package was "acceptable", provided that adequate labeling could be developed. An additional evaluation of the metabolism of flibanserin was requested as the results from the submitted DDI studies in this resubmission suggested that additional metabolizing enzymes were involved in the metabolism of flibanserin. Upon receipt of the CR letter Sprout entered into the Dispute Resolution (DR) process with the Agency. The net result of the DR was that the CR was upheld and the sponsor was advised to address the concerns noted in the CR and re-submit.

The current resubmission (the second) was submitted to the Agency on February 18th, 2015. This submission contained the results of additional in vitro metabolism study and a DDI study in individuals that were classified as having either loss of CYP2C9 or CYP2C19 activity (Study SPR-14-06). From the analysis of the data from this trial CYP2C19 was identified as a relevant metabolizing enzyme.

A Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee was held on June 4, 2015. During this meeting the Division of Clinical Pharmacology-3 made a presentation to the committee highlighting the effect of DDIs on flibanserin (these issues will be discussed in detail in the next section) and alcohol. This second Advisory Committee voted 18 to 6 in favor of approval, with all 18 voting members stating that a Risk Evaluation and Mitigation Strategy (REMS) is needed to ensure benefits outweigh the risks. During the discussion period after this vote many committee members voiced strong support for a REMS that would include prescriber and/or pharmacy certification (elements to assure safe use or ETASU). In addition, the members

of the committee commented that while they were voting in favor of the application, they had misgivings both in regards to its low level of efficacy and significant safety risks, such as sedation, hypotension and syncope[1].

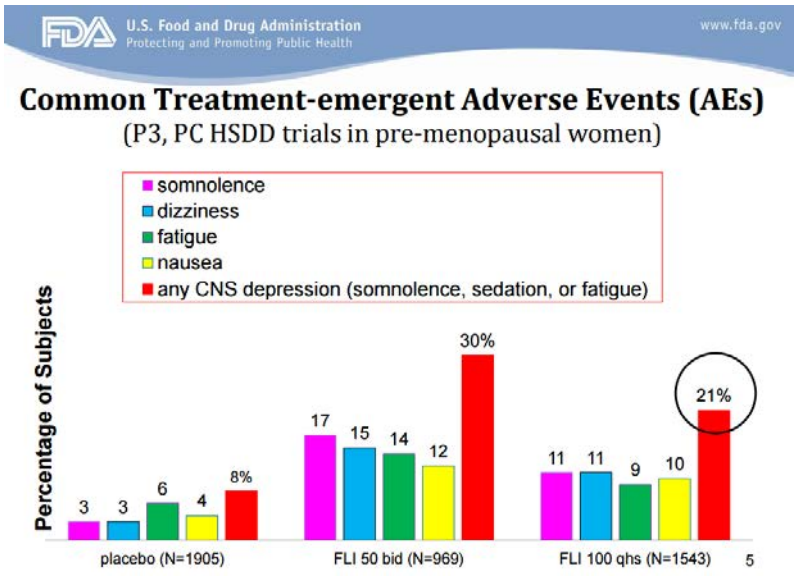
Clinical Pharmacology

The sponsors of the flibanserin (BI and Sprout) have produced a detailed body of information through the original submission and two cycles of re-submission. An adequate review of this information is beyond the scope of this memo. Suffice to say that in terms of the number and types of studies performed, the amount of information is adequate for approval. However, that being said, one of the roles of Clinical Pharmacology is to look at the data not just from a pharmacokinetic or biopharmaceutics point of view, but with a view to the clinical use and the steps that can be taken to maximize the benefit to patients while minimizing risk. The key Clinical Pharmacology issues for flibanserin revolve around the inherent sedative properties of flibanserin, the effect of DDIs, both CYP mediated (PK/PD) and alcohol (PD) mediated, and its overall clinical utility in light of these issues.

Sedative Effect of Flibanserin

As noted in the overview section, flibanserin works on the central nervous system via serotonin and dopamine receptors. In this case the pharmacology of flibanserin is diametrically at odds with its "public" classification as the "pink Viagra®", in that Viagra® acts via a specific physiologic mechanism to produce a physical effect, i.e., erection. Flibanserin, on the other hand works through the CNS to "lower inhibitory signals" and thus allow a psychological response to sexual stimulation. Thus the comparison of flibanserin to Viagra® shows a lack of understanding of the underlying pharmacology of both drugs.

As it works in the CNS, and was originally developed as an antidepressant, it is no surprise that flibanserin is sedating in nature. Reproduced below is slide 5 of Dr. Olivia Easley's presentation at the 2015 Advisory Committee Meeting showing the common treatment emergent adverse events from the Phase 3 trials:

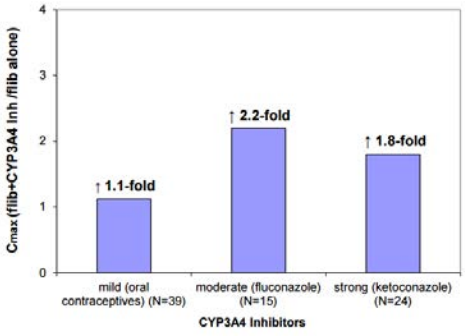
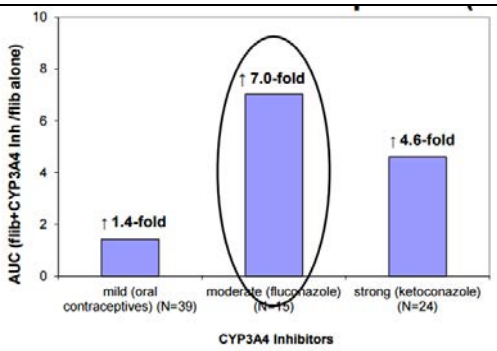


[1] At the time of this memo the transcript of the Advisory Committee was not yet available online. The meeting materials are located at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm446101.htm

Examination of the data shown here reveals a consistent increase of all measures of CNS depression to levels 5-6x those of placebo. Attempts to minimize the sedation effect, much like what is done with alpha-adrenergic blocking agents, by administration as a single dose at night time still show significant effects. It is interesting that the bid administration is actually worse in terms of sedating effects than a larger dose. Without going into a larger discussion on this (defer to the Medical Officer's review), it is very clear that in its own right that flibanserin can cause significant CNS depression.

Effect of DDIs-CYP Mediated

During the development of flibanserin a number of in vivo and in vitro DDI studies were conducted with strong, moderate, and weak CYP3A4 inhibitors and subjects deficient in CYP2C9 and 2C19. The data presented below was adapted from the June 2015 Advisory Committee presentation by Dr. LaiMing Lee (slides 8 & 9).

Extrinsic Factors CPY3A4 DDI Summary Cmax	Extrinsic Factors CPY3A4 DDI Summary AUC
	

meta-analysis of various flibanserin doses with OCs; flibanserin 100 mg + fluconazole; flibanserin 50 mg + ketoconazole

The data from this chart is somewhat unexpected at first glance as the moderate inhibitor (fluconazole) has a markedly higher interaction than the strong 3A4 inhibitor (ketoconazole). This "paradox" is explained by understanding that fluconazole also interferes with the CYP enzyme 2C19. Thus the results here are indicative of a multi-CYP inhibitor affecting more than one enzyme system. It should also be noted that the fluconazole study upon which this data was generated had to be stopped early due to an unacceptable rate of syncope and sedation in patients.

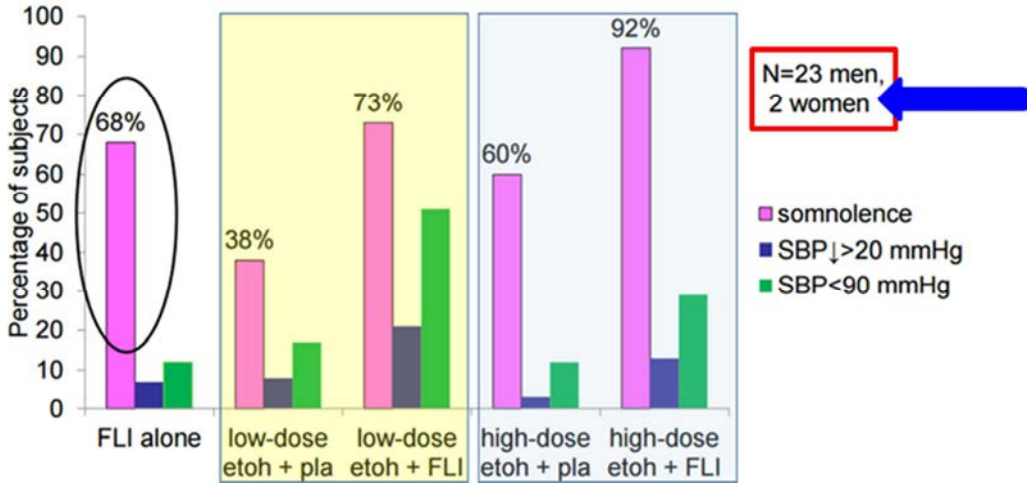
This is concerning in that a number of commonly used drugs including some proton pump inhibitors are also CYP2C19 inhibitors. To further explore this, the sponsor undertook an additional study to compare flibanserin exposures in subjects who were classified as poor metabolizers (PMs) of CYP2C9 and also 2C19 to subjects that were classified as extensive metabolizers (EMs). For 2C19, the results of the EM:PM comparison showed a modest increase in flibanserin levels, the observed Mean Cmax was 1.5-fold higher (range: 0.8 to 2.1-fold ↑), and the Mean AUC0-inf was 1.3-fold higher (range: 0.6 to 3.2-fold ↑).

Thus, flibanserin has the potential to interact with drugs that inhibit either CYP3A4 and/or CPY2C19. The net result of this would be an elevated plasma level of flibanserin with attendant increases in CNS exposure and an elevated pharmacologic response. Whether it would result in enhanced efficacy is unknown but the CNS sedation effects certainly are likely to be concentration/exposure related and concomitant use with such inhibitors would result in enhanced sedation and represent a *significant* safety risk.

Effect of DDIs-Alcohol

The combination of known CNS depressants and alcohol has long been recognized as a significant DDI for which patients are routinely warned. The classic example, of course, is the warning against concomitant use of alcohol and opiates for their potential to cause fatal respiratory depression. For flibanserin, the sequelae is not as dramatic as this, but was still of sufficient concern for the sponsor, at the FDA's direction to undertake an alcohol interaction study.

Adverse Events in Ethanol (ETOH) +
Flibanserin (100 mg) Interaction Study



This figure was adapted from Dr. Olivia Easley's Advisory Committee presentation and is her slide 13. The colored boxes have been added to focus the attention on the relevant comparison showing that, on average, flibanserin ALONE causes 30% more somnolence than low dose alcohol (2 standard drinks in a 70kg person) alone and 8% more than with high dose alcohol (4 standard drinks in a 70kg person) in terms of the absolute risk (based on a total of 25 subjects). When compared head-to-head, flibanserin has an additive effect to alcohol sedation, increasing the percentage of subjects reporting sedation by almost 30% compared to alcohol alone. What is most concerning about these numbers is that the study was poorly conducted in that the study was conducted almost exclusively in males (23 of 25). This is a major failing for a drug that is exclusively to be used in women. Given the difference in both body mass and composition, it is quite possible that the values for somnolence and hypotension seen here are in fact UNDERSTATED.

It is really inexcusable that with the availability and prevalence of alcohol use in this country and the known sedation potential of flibanserin that the sponsor allowed the study to be conducted in such a poor manner. It is hard to believe that they or their investigators could not find a sufficient number of women willing to participate in this trial. Normally, Clinical Pharmacology trials are done in mixed gender groups, however, single gender studies are allowed and encouraged for gender specific indications such as HSDD.

In addition, recent data on the use of alcohol in women sponsored by Substance Abuse and Mental Health Services Administration (2013) reveal that over 50% of women over the age of 18 self-identify as current drinkers and of them a significant portion also self-identify as binge drinkers.

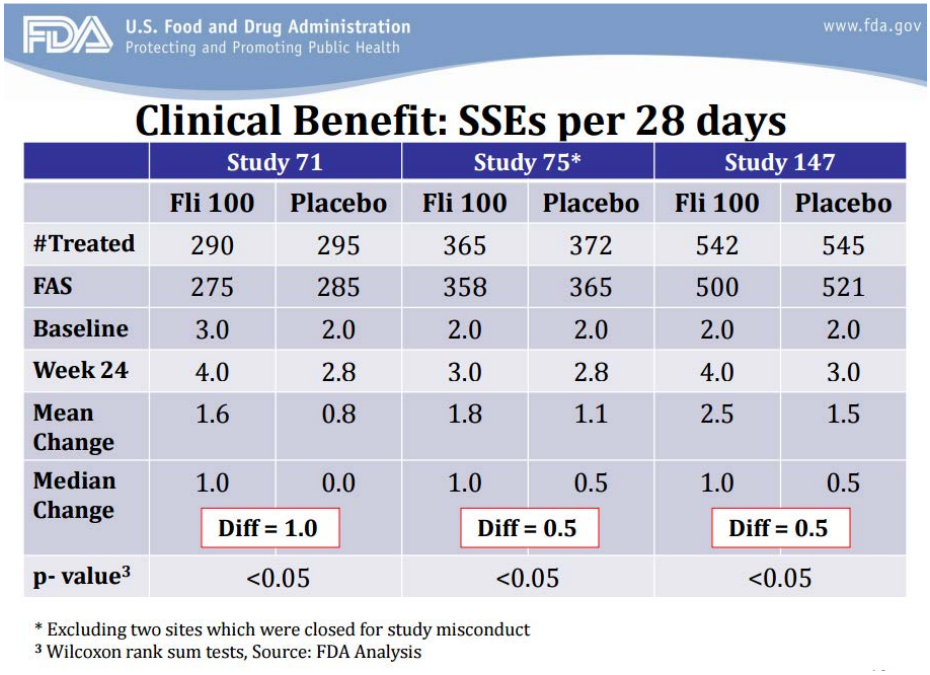
Women Age	% Current Drinker	% Binge Drinker (5 or more drinks on the same occasion)
18 - 25	56.9%	31.4%
26+	50.1%	14.7%

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

Irregardless of the final action on this application at this time, to be able to appropriately quantify the *MAGNITUDE* of the risk, the sponsor will need to conduct an appropriately designed gender-specific trial in an adequate number of subjects.

Clinical Utility

The clinical utility of flibanserin is certainly up to debate. Part of this is related to the drug, but a large part is also due to HSDD itself. It is highly unlikely that there is one cause for HSDD. HSDD is a multi-focal psychological disorder that can manifest itself in different ways. In addition how one deals with and discusses their sexuality is dependent upon extrinsic factors such as social mores of their community, their parents, their peers, and societal images of the body-among others. That being said, a discussion of the clinical endpoints and their assessments-and the pros and cons, is deferred to the Medical Review team as they have the requisite expertise to opine on their utility and or lack of utility. To frame the rest of the discussion and the ultimate conclusion I do refer to Dr. Catherine Sewell's slide 10 from the June 2014 Advisory Committee meeting which presented the data for "satisfying sexual experiences" across all 3 of the placebo controlled clinical trials.



This data rather elequently shows the generally overall low success rate with flibanserin across the 3 trials in over 1300 subjects. Even so, it must be conceeded that the values (although low) were statistically significant. Whether or not it is clinically useful is an entirely different matter. Taking a broader view, the supportive analysis using anchoring found that, when considering a

responder as one who was much improved or very much improved, the absolute difference in the percentage of responders with flibanserin and the percentage of responders with placebo across the three trials was 8-9% for SSEs, 10-13% for Female Sexual Function Index (Desire Domain), and 7-13% for Female Sexual Distress Scale-Revised Question 13[2].

Discussion

This latter question is the crux of the matter. Whether given all of the safety concerns that the Division of Clinical Pharmacology-3 has as they relate to DDIs, Alcohol, and sedation are they counterbalanced by clinical utility (no) or clinical need ("yes"). The overall efficacy of flibanserin is low, however, that is not to say that it is unapprovably low-because there is no standard for that. Flibanserin does work, albeit to a very small degree. It is possible that there are sub-populations in whom it may work well and in others it will not work at all, unfortunately as of now we cannot aprori identify them. Thus we have to consider that the drug once approved will be used by the majority of women who complain of HSDD some of whom will undoubtedly use alcohol and/or be taking concomitant therapy with a metabolic inhibitor-in those women sedation and somnolence will be of major concern.

From a Clinical Pharmacology perspective the following questions need to be answered:

1.) Do we have sufficient PK information to
    a. Describe the pharmacokinetics of flibanserin?
        i. Yes
    b. Understand all of the relevant intrinsic and extrinsic factors affecting the safety and efficacy of flibanserin?
        i. No, the alcohol study needs to be repeated in a female population as a PMC/PMR-(interim labeling until we can fully label the concern)
        ii. No, the final to-be-marketed dosage form lacks a food effect study. During the clinical trials patients were allowed to take their dose without regards to meals. Given that, as intended, the dosing regimen is to be taken at bedtime, this can be handled thru labeling at this time. Additional discussion regarding this issue will be held with the medical review team, especially should a BID regimen ever be proposed.
        iii. No, the drug has to date been studied in pre-menopausal women, post-menopausal women represent a logical extension and likely off-label use in an uncontrolled setting
2.) Do we understand the pharmacology of:
    a. The drug-disease interface
        i. No, the disease is multi-factorial in nature and the clinical instruments are subjective and subject to recall issues.

[2]13. How often did you feel bothered by low desire?
- Never
- Rarely
- Occasionally
- Frequently
- Always

3.) Is the clinical effect measurable and meaningful:
    a. Measurable
        i. Yes, an affect was seen in various scoring tools for female sexual desire/distress.
    b. Meaningful
        i. A qualified "yes", while the improvement over placebo was not large, in some analysis it was statistically significant. Even so the efficacy in general hovers around 10% depending on the analyses performed.
        ii. As there is not an approved treatment for HSDD even a product with low efficacy can be useful to some segment of the affected population.
4.) What are the bars to successful safe use of the drug?
    a. Flibanserin is very sedating
    b. Flibanserin is a victim drug of both CYP3A4 and 2C19, inhibition and poor metabolizer status, respectively
    c. Flibanserin potentiates the CNS depressant effects of alcohol and likely all other CNS depressants (e.g., benzodiazepines, barbiturates, etc.)
5.) Can a label be developed to properly balance these issues?
    a. Although difficult a label can be written laying out these issues
    b. Labeling alone will NOT be sufficient for the safe use of this product.
        i. A Risk Evaluation and Mitigation Strategy will be needed
            1. Include prescriber and pharmacy certification (elements to assure safe use or ETASU)

Conclusion

It is my opinion as the Director of the Division of Clinical Pharmacology-3 that the sponsor has adequately addressed all of the outstanding Clinical Pharmacology concerns that were raised in the previous two review cycles. There are still, however, outstanding issues, namely the need to execute a properly designed and recruited alcohol study and for there to be additional discussing regarding the need for a new food effect study with the to-be-marketed formulation, and the potential development of the drug for use in post-menopausal women. Until this information is available, appropriate labeling will need to be developed consistent with what we have done for other products that are lacking such information.

Having interacted with the review staff, read the review and being present at the June 2015 Advisory Committee, I am well aware of the minimal efficacy and real concern over the sedation and drug-interaction potential of this drug. I do believe that we can develop adequate labeling for the drug which should include a BOX WARNING for sedation, alcohol, and drug-drug interactions. I also recommend that the alcohol warning be broadened to include other CNS depressants as well, i.e. "Do not use with alcohol or other CNS depressants". I also fully support the development of a comprehensive REMS for flibanserin that includes ETASU elements (prescriber and pharmacy certification).

Female Sexual Interest/Arousal Disorder
Diagnostic Criteria 302.72 (F52.22)

A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:

   1. Absent/reduced interest in sexual activity.

   2. Absent/reduced sexual/erotic thoughts or fantasies.

   3. No/reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate.

   4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).

   5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).

   6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.

C. The symptoms in Criterion A cause clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

[i] HSDD is the older term from the Diagnostic and Statistical Manual 4th ed. (DSM-4). In the new DSM-5, it is re-named Female Sexual Interest/Arousal Disorder. As the older terminology was used during the development of flibanserin, this older terminology will be retained.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD D BASHAW

07/17/2015

This documents transmits the final opinion from the Division of Clinical Pharmacology-3 regarding the Clinical Pharmacology portion of the Flibanserin NDA. Based on my examination of the regulatory history, the data, and established precedent, I believe that the Clinical Pharmacology portion of this NDA is acceptable, however, significatn labeling will need to be developed along with a REMS/ETASU.

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 22526	**Biopharmaceutics Reviewer:** Vidula R. Kolhatkar, Ph.D.	
Submission Date:	February 18, 2015		
Division:	Division of Reproductive and Urologic Products	**Acting Biopharmaceutics Lead:** Kelly M. Kitchens, Ph.D.	
Applicant:	Sprout Pharmaceuticals, Inc.	**Acting Supervisor:** Tapash Ghosh, Ph.D.	
Trade Name:	Addyi	**Date Assigned:**	February 18, 2015
Established Name:	Flibanserin Tablets	**Date of Review:**	May 19, 2015
Indication:	Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women	**Type of Submission:** Resubmission after two Complete Response letters	
Formulation/ strengths	Tablet/100 mg		
Route of Administration	Oral		
Type of Review:	Comparative dissolution data to qualify drug product manufacturing site transfer		

SUMMARY:

Background: NDA 22526 for Flibanserin tablets was originally submitted on October 27, 2009. A Complete Response (CR) Letter was issued on August 27, 2010 and a resubmission of the NDA was filed on March 29, 2013. A second CR Letter was issued on September 27, 2013. The two CR letters were issued mainly due to efficacy and safety concerns. There were no outstanding biopharmaceutics issues related to this NDA. Please refer to biopharmaceutics reviews by Dr. Houda Mahayni dated 06/02/2010, 06/23/2010 and 08/07/2013. In the current resubmission, the applicant performed additional clinical trials and changed the manufacturing site from Boehringer Ingelheim Roxane, Inc. (Columbus, Ohio) to (b) (4). The (b) (4) site in (b) (4) will be used exclusively for the manufacture, packaging and testing of flibanserin tablets. This is a Level 3 site change per the SUPAC-IR Guidance, which requires comparative multi-point dissolution data to support the proposed change.

Submission: The applicant has submitted the comparative dissolution data required to qualify the site change.

Review: This Biopharmaceutics review is focused on evaluation and acceptability of the comparative dissolution data supporting the approval of the manufacturing site change.

RECOMMENDATION:

The dissolution data presented in this submission demonstrate that based on the similarity factor (f2) calculated, 76.88, the dissolution profiles of the proposed drug product manufactured at the new site and the approved site are similar. From the Biopharmaceutics perspective, NDA 22526 for Addyi® (flibanserin) Tablets is recommended for approval.

Signature

Vidula R. Kolhatkar, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Quality Assessment Lead
Office of New Drug Products

cc. TGhosh; PSeo

Assessment of Biopharmaceutics information

- Flibanserin Tablets, 100 mg, are film coated tablets.
- The applicant changed the manufacturing site for these tablets from Boehringer Ingelheim Roxane, Inc. (Columbus, OH) to (b) (4). Drug product manufactured at the proposed new site was used for two clinical studies (SPR-14-01 to evaluate next-day residual effects of flibanserin on simulated driving performance and SPR-14-06, to evaluate flibanserin PK in relation to CYP2C19 and CYP2C9 genotypes). The new site will be used for the manufacture, packaging and testing the drug product. The following tables list the previously registered and the proposed manufacturing sites.

Table 1 Previously Registered Manufacturer(s)

Company Name & Address (CFN/FEI Number)	**Operation(s) Performed**
Boehringer Ingelheim Roxane Inc. 1809 Wilson Road Columbus, Ohio 43228 USA (1510690)	Manufacturing, packaging, labeling, testing, stability
(b) (4)	Excipients testing

Table 2 Commercial Manufacturer(s)

Company Name & Address (CFN/FEI Number)	**Operation(s) Performed**
(b) (4)	Manufacturing, packaging, labeling, testing, stability
	Excipients testing

- This is a Level 3 site change per the SUPAC-IR Guidance, and the applicant has provided comparative dissolution data to support this change.

- Along with the site change, batch size is [redacted] from (b) (4) and (b) (4) batch sizes.

- The following table lists a comparison of formulas between the original development company, Boehringer Ingelheim Roxane, Inc. and the proposed new manufacturer, (b) (4).

Table 1
Comparison of Formula

Ingredients	Boehringer Ingelheim Roxane, Inc. Quantity per Unit (mg)	Boehringer Ingelheim Roxane, Inc. Quantity per Batch (kg) (b) (4)	Boehringer Ingelheim Roxane, Inc. Percentage (%)	(b) (4) Quantity per Unit (mg)	(b) (4) Quantity per Batch (kg) (b) (4)	(b) (4) Percentage (%) (b) (4)
Flibanserin	100.00	(b) (4)	(b) (4)	100.00	(b) (4)	(b) (4)
Lactose Monohydrate NF	(b) (4)			(b) (4)		
Microcrystalline Cellulose NF						
Hypromellose USP						
Croscarmellose Sodium NF						
Magnesium Stearate NF						
(b) (4) Pink (b) (4)						
						(b) (4)

- Although the applicant provided the comparative dissolution data in the submission on February 18, 2015 based on the information provided, the applicant did not clearly identify the dissolution method employed, batches manufactured at the approved and the proposed sites, and dates when the dissolution studies were performed. The following IR was sent to the applicant on April 14, 2015:

  Please provide comparative dissolution data between drug product manufactured at Boehringer Ingelheim Roxane Inc. and drug product manufactured at (b) (4) *Include the complete dissolution data (individual, mean, SD, profiles), clearly identify the batches manufactured at the approved site and the new proposed site, and describe the dissolution method employed. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). Also include the dates when the dissolution studies were performed for each batch.*

  We request this information by COB April 23, 2015.

The applicant provided the following information in response to the IR on April 21, 2015.

- Dissolution data generated by the approved site, Boehringer-Ingelheim Roxane, Inc. (BIR), on batch 4001397 for flibanserin 100 mg tablets (reference product).

  Batch number and manufacturing date for the tablets used in the comparative dissolution data.

Table 1 Batch 4001397 Details

Parameter	Relevant Information
Manufacturer/Testing Site	Boehringer-Ingelheim Roxane, Inc.
Manufacturing Date	November 7, 2012
Method Number	A090952 (Dated: January 18, 2008)
Dissolution performed	September 13, 2013

- Dissolution data generated by the proposed new site, (b) (4) on batch F130326 for flibanserin 100 mg tablets (test product).

  Batch number and manufacturing date for the tablets used in the comparative dissolution data.

Table 3 Batch F130326 Details

Parameter	Relevant Information
Manufacturer/Testing Site	(b) (4)
Manufacturing Date	June 27, 2013
Method Number	FPSPMF1189B (Dated: June 26, 2013)
Dissolution performed	November 13, 2013

- The currently approved dissolution method as shown below was employed for comparative dissolution testing.

Media:	Citric Acid/Phosphate Buffer, pH 4.0; 900 mL
Temperature:	37.0 ± 0.5° C
Apparatus II:	50 rpm (paddle)
Time:	30 minutes
Filter:	Membrane filter (e.g., Whatman GF/D, 2.7 µm or Millex PVDF 0.45µm), discarding first 4 mL

- The report for the validation of the analytical procedure for the dissolution test of flibanserin film-coated tablets, 100 mg was provided in the original submission (October, 27, 2009). Samples for the dissolution study are analyzed by UV spectrophotometry. The method was validated for specificity, linearity, accuracy, repeatability, intermediate precision, and robustness (Report/Study No.: 07/244, Document No.: U07-2236). Overall, validation of the analytical method is acceptable. The following table provides a summary of validation results.

Validation Parameter	Method of Determination	Results	
Specificity	Visual evaluation and determination of interference of UV-scans of blank, placebo and sample solutions of flibanserin film-coated tablets 100 mg/tablet	Demonstrated acceptable interference from blank and placebo at the quantification wavelength of flibanserin (278 nm)	
Linearity	Linear regression analysis for linearity data generated in a concentration range from 20 to 130 % and determination of the correlation coefficient	Linear range for flibanserin: 20 – 140 %[a]	
Accuracy	Determination of percent recoveries for spiked samples; percent recoveries were determined for 3 different concentration levels (20, 75 and 130 %) with 3 replicates each	concentration level	recovery rate
		20 %	95.2 % (n = 3)
		75 %	96.8 % (n = 3)
		130 %	97.0 % (n = 3)
		Mean recovery rate: 96.4 %	
Precision / Repeatability	RSD (%) spiked placebo at 3 different concentration levels	RSD: 1.4 %	

a concentration in relation to label claim

Validation Parameter	Method of Determination	Results
Precision / Intermediate Precision	Determination for difference in mean value and overall RSD of dissolution results for 6 replicate analyses of a representative batch including 2 operators, 2 dissolution apparatus, analyses on different days	RSD: 1.4 % Difference in mean: 1 %
Range	Definition of the dissolution range for which linearity, accuracy and precision has been demonstrated	20 – 130 % of label claim
Robustness	Stability of sample and standard preparations	Test and standard solutions are stable for at least 24 hours in amber glass at room temperature (at 20 – 25°C).

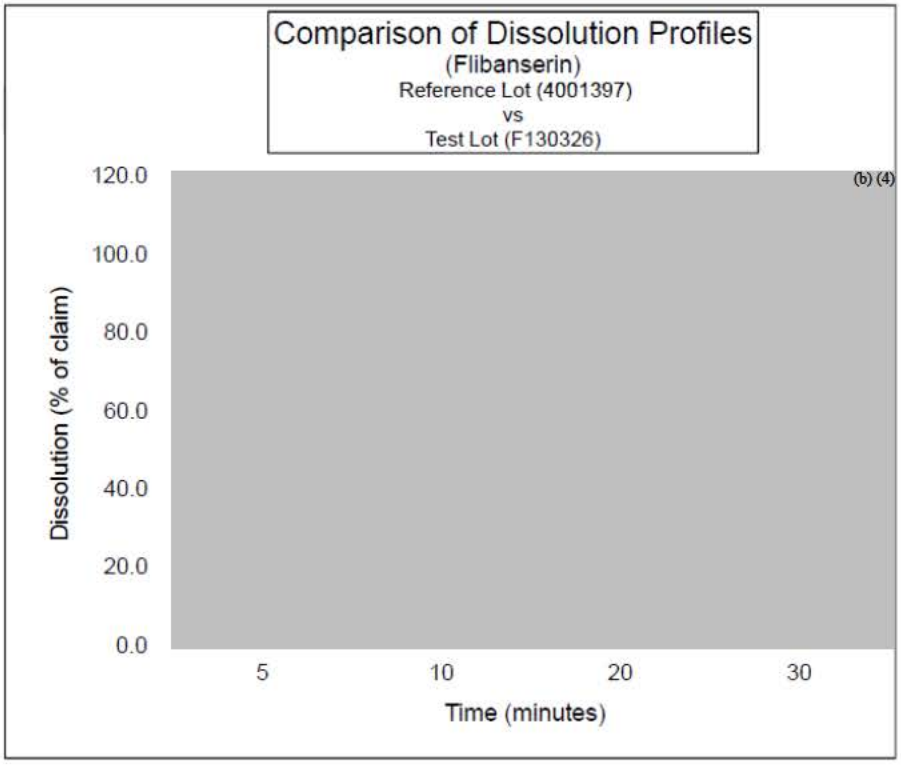
- The applicant provided method transfer report (Code: RbMF1189-MT_Version2) in the current submission (February 18, 2015) to support transfer of assay, degradation products, uniformity of dosage units, and identification and dissolution testing methods from the approved Boehringer Ingelheim site to the proposed (b) (4) This reviewer finds the report acceptable.

- The applicant submitted % dissolved data (individual, mean, SD, profiles) for the dissolution data. Mean comparative dissolution data is included in the following Table:

Mean Comparative Dissolution Data

Time (t) minutes	4001397 Reference Batch (R) % of claim	F130326 Test Batch (T) % of claim
5		(b) (4)
10		
20		
30		

Dissolution profiles of reference and test batches



The similarity factor (f2) was calculated by this Reviewer to be 76.88 (this is similar to the Applicant's f2 value 77), indicating similarity between the two dissolution profiles.

Reviewer's Comments:
The dissolution data submitted to support the proposed change of manufacturing site was reviewed. The applicant submitted reference dissolution data from one batch

manufactured at the approved site for comparison. Dissolution data for the batch manufactured at the approved site and the proposed site were obtained on different occasions. The dissolution data presented in this submission demonstrate that based on the similarity factor (f2) calculated, 76.88, the proposed drug product manufactured at the new site and the approved site have similar dissolution profiles. Therefore, the comparative dissolution data support approval of the proposed new drug product manufacturing site.

RECOMMENDATION

The dissolution data presented demonstrate that based on the similarity factor (f2) calculated, 76.88, the dissolution profiles of proposed drug product manufactured at the new site and the approved site are similar. From the Biopharmaceutics perspective, NDA 22526 for Addyi® (flibanserin) Tablets is recommended for approval.

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA #	022526
Submission Dates	October 27, 2009; March 26, 2010; May 10, 2010; March 29, 2013
Brand Name	Addyi
Generic Name	Flibanserin
Strength and Formulation; Regimen	100 mg tablet; 100 mg taken orally once daily at bedtime with or without food
Sponsor	Sprout Pharmaceuticals
Proposed Indication	Treatment of Hyposexual Desire Disorder
Submission Type	Resubmission NDA Class 2
Relevant IND	(b) (4)
Clinical Pharmacology Reviewer	LaiMing Lee, PhD
Team Leader	Myong-Jin Kim, PharmD
Division Director	E. Dennis Bashaw, Pharm.D
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Bone, Reproductive and Urologic Products

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1 EXECUTIVE SUMMARY

Sprout Pharmaceuticals is seeking approval of flibanserin oral tablets for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women (≥ 18 years of age). The proposed dosing regimen is one 100 mg tablet taken once daily at bedtime (qhs) with or without food. There is currently no FDA-approved pharmacologic therapy for HSDD.

Boehringer Ingelheim (BI) was the original owner of flibanserin and submitted the original NDA on October 27, 2009. The Sponsor received a Complete Response (CR) on August 27, 2010 due to the benefit/risk assessment. There was limited efficacy benefit compared to placebo and safety concerns included dizziness, nausea, fatigue and somnolence.

Flibanserin efficacy and safety findings were discussed at the Reproductive Health Drugs Advisory Committee Meeting on June 18, 2010; the committee members voted 10 to 1 against approval of flibanserin. Following the CR, BI transferred ownership of the flibanserin NDA and associated IND to Sprout Pharmaceuticals. This CR Response was submitted on March 29, 2013 and includes one new Phase 3 study and 7 Phase I studies including drug-drug interaction (DDI) studies to address unresolved DDI concerns highlighted in the CR letter.

The following Phase I studies were submitted in this CR:

- Moderate CYP3A4 inhibitors (fluconazole and grapefruit juice) on flibanserin exposure (Study SPR-12-01)
- Moderate CYP3A4 inducer (etravirine) on flibanserin exposure (Study SPR-12-02)
- Alcohol on orthostasis and syncope (Study SPR-12-03)
- Supratherapeutic doses on safety and orthostasis (Study SPR-12-04)
- Flibanserin in recreational poly-drug users and potential for abuse (Study SPR-12-05)
- Single dose (SD) and multiple dose (MD) administration of flibanserin in postmenopausal women to evaluate the effect of age (Study 511.146)
- MD of flibanserin on a SD of digoxin in male and female subjects (Study 511.158)

With the exception of Study SPR-12-05 (abuse potential study), this Clinical Pharmacology review includes a detailed review of the new studies and some relevant information from the Clinical Pharmacology review of the original NDA (DARRTS August 26, 2010).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 022526 flibanserin 100 mg oral tablets submitted to the Agency on October 27, 2009 (original NDA) and March 29, 2013 (resubmission). We have found the original NDA and this resubmission acceptable from a Clinical Pharmacology perspective pending agreement on the labeling language.

1.2 Post-Marketing Commitment/Post-Marketing Requirement (PMC/PMR)

We recommend the sponsor identify enzymes other than CYP3A4 that contribute to the metabolism of flibanserin as a PMR if the application is approved or in a Resubmission if the NDA is issued a Complete Response.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Flibanserin is extensively metabolized by CY3A4. Data submitted to the original NDA showed that a strong inhibitor of CYP3A4, ketoconazole, significantly increased flibanserin exposure. Hepatic impairment significantly increased systemic flibanserin exposure. Data from the current resubmission showed that a moderate CYP3A4 inhibitor fluconazole significantly increased flibanserin exposure and adverse events (AEs) such as fatigue, dizziness, nausea and hypotension. It also suggested that metabolism of flibanserin may be mediated by other CYP enzymes.

PK characteristics

From this resubmission, following administration of a single 100 mg dose of flibanserin tablet in healthy premenopausal women (N=8), mean (SD) Cmax was 419 (206) ng/mL and mean (SD) $AUC_{0\text{-}inf}$ was 1543 (511) ng.hr/mL. Median (range) Tmax was 0.75 (0.75 – 4.0) hrs and mean (SD) $t_{1/2}$ was 11.7 (1.9) hrs. Cmax of flibanserin appears to be dose proportional from 100 to 250 mg. For flibanserin $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, exposure appears to be greater than dose proportional from 100 to 250 mg.

Dose-Response Relationship

Efficacy Endpoints

For this resubmission, the two co-primary endpoints used to demonstrate clinical efficacy for flibanserin in women with HSDD were change from baseline in number of satisfying sexual events (SSEs) and change from baseline in desire as assessed by Female Sexual Function Index (FSFI) desire domain. A key secondary endpoint was change from baseline in distress assessed by Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R).

Efficacy

The sponsor submitted a new Phase 3 study (511.147) evaluating only 1 dose/dosing regimen (100 mg qhs) to support efficacy. Phase 3 studies submitted to the original NDA evaluated 50 mg and 100 mg qhs, 25 mg twice daily (bid), 50 mg bid (up-titrated from 50 mg qhs), and 100 mg qhs (up-titrated from 50 mg qhs). Efficacy results with the 25 mg bid or 50 mg qhs doses were less positive than those for the 100 mg qhs dose. The sponsor did not explore other doses or dosing regimen in the new Phase 3 study. Sprout is seeking approval of flibanserin 100 mg qhs for the HSDD indication based upon a 24-week, randomized, double-blind, placebo-controlled trial in premenopausal women (mean age of 36.5 yrs) conducted in the United States. The sponsor demonstrated statistically significant changes in the co-primary and secondary endpoints; however, the placebo effect is high and the absolute change in desire, SSEs and distress may not be clinically meaning.

Desire: The mean (SD) baseline data for the FSFI desire score was 1.9 (0.7). Compared with placebo, there were numerical and statistically significant improvements in the FSFI desire score in favor of flibanserin 100 mg qhs. With the mean difference of 0.30 between flibanserin treatment and placebo in the improvement of the FSFI desire score, flibanserin improved sexual desire more compared to placebo, at least based on data collected every 28 days using a 28-day recall with the FSFI instrument.

SSEs: The mean (SD) baseline monthly count for SSEs was 2.6 (2.7). The increase in SSEs with flibanserin 100 mg qhs treatment was a mean of ~2.43 SSEs for the last month of treatment, while the placebo group had an average increase 1.46 SSEs. The mean treatment difference between flibanserin and placebo was 0.97 SSEs during the last 28 days of recorded data.

Distress: The mean baseline scores for distress showed a relatively high level of distress (~32.6 on a scale of 0-52; 3.4 on a scale of 0-4). The flibanserin 100 mg qhs significantly (statistically) improved the FSDS-R Item 13 and FSDS-R total scores.

Safety

The most commonly reported AEs in the pivotal Phase 3 study (Study 511.147) in this resubmission were somnolence (14.2%), dizziness (8.5%), nausea (5.4%), fatigue (4.6%) and insomnia (4.2%). These AEs are the same as previously noted with other Phase 3 studies of flibanserin (original NDA submission). For this resubmission, hypotension was particularly profound in subjects with markedly high flibanserin exposure (e.g., co-administration of flibanserin and fluconazole or supratherapeutic doses of flibanserin alone).

Intrinsic and Extrinsic Factors

Effect of Strong CYP3A4 Inhibitors, Itraconazole and Ketoconazole

Itraconazole 200 mg daily given 8 days then co-administered with flibanserin 50 mg increased flibanserin $AUC_{0\text{-}inf}$ by 2.6-fold and Cmax 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. Ketoconazole 400 mg daily for 5 days inhibited flibanserin 50 mg metabolism leading to a 4.6-fold increase in flibanserin $AUC_{0\text{-}inf}$. Cmax increased 1.8-fold. Tmax increased slightly from 1.25 to 1.50 hr and $t_{1/2}$ was significantly prolonged by 7.4 hrs from 8.5 to 15.9 hrs. Ketoconazole inhibition of CYP3A4 was more significant compared with itraconazole. Based on the observed relationship between dose and AEs, it is likely that patients using a CYP3A4 inhibitor will experience more AEs compared with patients not taking a CYP3A3 inhibitor (see original Clinical Pharmacology review dated August 26, 2010 in DARRTS).

Effect of Moderate CYP3A4 Inhibitor, Fluconazole and Grapefruit Juice

The sponsor conducted a DDI study to address the effect of a moderate CYP3A4 inhibitor on flibanserin. Multiple doses of fluconazole resulted in a 2.2-fold increase in Cmax, 5.6-fold increase in $AUC_{0\text{-}t}$ and 7.0-fold in $AUC_{0\text{-}inf}$ of flibanserin. Mean terminal half-life of flibanserin increased from 10 to 23 hrs. Mean clearance (CL/F) of flibanserin decreased significantly from 75.9 to 9.8 L/hr with fluconazole administration. The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.3-fold increase with ketoconazole, a strong CYP3A4 inhibitor. The exposure change with fluconazole was not anticipated based on the presumed metabolism pathway of flibanserin (mainly through CYP3A4 and to a minor extent CYP2D6 as claimed by the sponsor). Fluconazole is an inhibitor of multiple CYP enzymes (3A4, 2C9 and 2C19). The results of the drug interaction study with flibanserin and fluconazole suggest that flibanserin may be metabolized by additional CYP enzymes.

Due to concerns that grapefruit juice can inhibit CYP3A4 metabolism, the sponsor evaluated the effect of a single administration of grapefruit juice on flibanserin PK. Compared to flibanserin alone, the co-administration of flibanserin and regular strength grapefruit juice resulted in an increase of 10%, 38% and 38% in Cmax, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of flibanserin, respectively. Median Tmax 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 at 10.6 and 9.9 hrs for flibanserin alone and flibanserin + grapefruit juice, respectively.

Co-administration of single dose flibanserin and multiple doses of fluconazole resulted in more frequent and profound AEs, compared to flibanserin alone or flibanserin + grapefruit juice. All 15 subjects who received flibanserin + fluconazole experienced at least 1 AE. Hypotension occurred in the flibanserin + fluconazole group only. One of 15 subjects who received flibanserin and fluconazole experienced a severe hypotensive event and required medical intervention.

Effect of Strong CYP3A4 Inducer, Rifampin
The influence of rifampin 600 mg for 10 days, a strong CYP3A4 inducer, on the PK of flibanserin 100 mg and relevant metabolites was evaluated. The flibanserin exposure $AUC_{0\text{-}inf}$ was significantly lower when co-administered with rifampin. Flibanserin $AUC_{0\text{-}inf}$ was reduced by 96% with rifampin pre-treatment. Mean flibanserin Cmax was also significantly lowered when co-administered with rifampicin. Cmax for flibanserin was reduced by 91%. Flibanserin metabolism is clearly influenced by the strong CYP3A4 inducer rifampin (see original Clinical Pharmacology review dated August 26, 2010 in DARRTS).

Effect of Moderate CYP3A4 Inducer, Etravirine
The sponsor conducted a DDI study between etravirine and flibanserin. In this study etravirine 200 mg was given twice daily following a meal for 15 consecutive days. After 13 days (Days 3 - 15) of etravirine alone administration, flibanserin was co-administered with etravirine on Day 16. Co-administration of multiple doses of etravirine and a single dose of flibanserin resulted in a decrease of 3.2% in Cmax and 20.6% in $AUC_{0\text{-}inf}$ of flibanserin, compared to flibanserin alone. Median (range) Tmax of flibanserin was delayed by 0.5 hr (3.0 to 2.5) hrs when flibanserin was administered with etravirine. Mean half-life of flibanserin was similar for flibanserin at 9.8 and 9.2 hrs for flibanserin alone and flibanserin + etravirine, respectively.

Effect of Ethanol
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 twenty-three healthy adult male and two female subjects. Flibanserin exposure as measured by partial AUC ($AUC_{0\text{-}4}$) decreased by 10.5% and 3.9% when flibanserin 100 mg was administered with 0.4 and 0.8 g/kg ethanol, respectively, compared to flibanserin alone.

Flibanserin alone resulted in approximately 67% of subjects experiencing somnolence. The addition of ethanol to flibanserin intake increased the frequency of somnolence to approximately 74% and 92% with 0.4 and 0.8 g/kg ethanol, respectively. Alcohol, especially notable at high concentrations, increased the somnolence-inducing effect of flibanserin.

Orthostatic hypotension, characterized by an increase of >20 beats per minute (bpm) in sitting to standing pulse rate (3 to 4 time points), was observed when flibanserin was co-administered with ethanol at both concentrations. For flibanserin 100 mg alone, there was no increase in the sitting to standing pulse rate that exceeded 20 bpm. However, there was a trend in increasing pulse rate that approached 20 bpm between 2 and 4 hrs postdose suggesting flibanserin alone possesses hypotensive properties.

Effect of Flibanserin on Digoxin PK
The sponsor evaluated the effect of multiple doses of flibanserin on single dose PK of digoxin. Flibanserin 100 mg was given once daily over 7 days. On Day 5, a single 0.5 mg dose of digoxin (2 x 0.25 mg) was administered with 100 mg flibanserin. Digoxin exposure ($AUC_{0\text{-}inf}$) increased by 96% and Cmax increased by 46% with multiple 100 mg doses of flibanserin co-administered with a single 0.5 mg dose of digoxin. Flibanserin is an inhibitor of P-gp.

Effect of Age
Following a single dose of 100 mg flibanserin, there was an increase of 15%, 42% and 54% in Cmax, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of flibanserin, respectively in young postmenopausal women (mean age of 55, range of 46 - 64, N=16), compared to elderly postmenopausal women (mean age of 69, range of 65 - 75, N=8). Median Tmax of flibanserin was delayed by 0.5 hr (1.0 to 1.5 hrs) in

young postmenopausal women, compared to elderly postmenopausal women. Mean half-life increased by 0.9 hr (10.6 to 11.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women.

Following multiple doses (8 days) of 100 mg flibanserin, there was an increase of 25% in Cmax and 56% in $AUC_{0\text{-}t,\ ss}$ of flibanserin in young postmenopausal women, compared to elderly postmenopausal women. Median Tmax of flibanserin was delayed by 0.1 hr (1.4 to 1.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women. Mean half-life increased by 1.4 hr (13.6 to 15.0 hrs) in young postmenopausal women, compared to elderly postmenopausal women.

It appears that systemic exposure of flibanserin is higher in young compared with elderly postmenopausal women with HSDD. By contrast, the volume of distribution and clearance were higher in the elderly postmenopausal women.

Currently, flibanserin is indicated for the treatment of HSDD in premenopausal women,

2 QUESTION-BASED REVIEW

2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Sprout Pharmaceutical is seeking approval of flibanserin for the treatment of HSDD in premenopausal women (≥ 18 years of age). There is currently no FDA-approved pharmacologic therapy for HSDD. The proposed dose and dosing regimen is one 100 mg oral tablet to be given daily at bedtime with or without food. BI, the original NDA holder, transferred ownership to the NDA and relevant IND to Sprout after receiving a CR letter August 2010.

2.2 GENERAL ATTRIBUTES OF THE DRUG

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

See original Clinical Pharmacology review dated August 26, 2010 in DARRTS.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Flibanserin is a serotonin 5-HT_{1A} agonist and a 5-HT_{2A} antagonist with high affinity binding to 5-HT_{1A} and a 5-HT_{2A} receptors. Flibanserin also has regional, dose-related effects on dopamine receptors. The exact mechanism of action for treatment of HSDD is unknown. The sponsor believes the therapeutic benefit is derived from its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system.

2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and clinical studies used to support dosing or claims?

The proposed clinical dosing regimen 100 mg administered once daily at bedtime. In this NDA submission, the new Phase I studies were conducted with the proposed therapeutic dose.

2.3.2 What are the clinical endpoints in clinical pharmacology and clinical studies?

The two co-primary efficacy endpoints for the 24-week pivotal Phase 3 studies were change from baseline in SSEs and desire (assessed by FSFI desire domain). A key secondary endpoint was change from baseline in distress assessed by Question 13 of the FSDS-R. In clinical pharmacology studies, the endpoints for the majority of studies were PK parameters of flibanserin. In some cases such as DDIs, the endpoints in clinical pharmacology studies were PK parameters of the interacting drug.

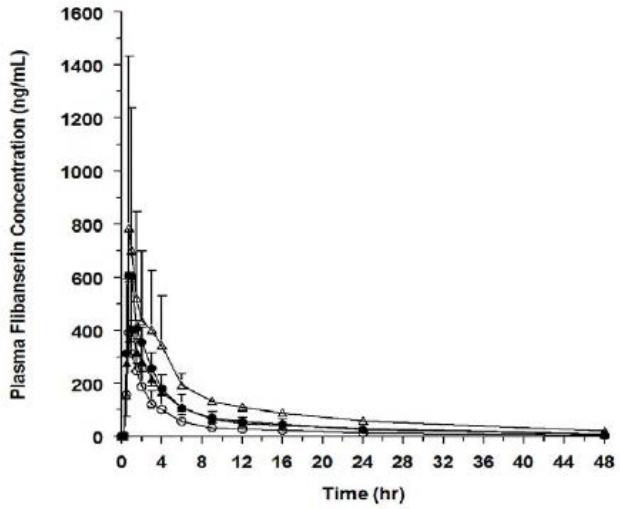
2.3.3 Are the active moieties in the plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In the original NDA, in a two-way crossover study in six healthy male subjects, the sponsor evaluated the metabolism of a single intravenous dose of 20 mg and a single oral solution dose of 50 mg ^{14}C-radiolabelled flibanserin (study 511.15). Flibanserin was well absorbed and extensively metabolized; only detected in trace amounts in urine and feces. After oral dosing of ^{14}C-radiolabelled flibanserin, 44.1% of the total ^{14}C-flibanserin related radioactivity was recovered in urine, and 50.9% in feces. (see original Clinical Pharmacology review dated August 26, 2010 in DARRTS.)

For this resubmission, following a single 100 mg dose of flibanserin in healthy premenopausal women (N=8), mean (SD) Cmax was 419 (206) ng/mL and mean (SD) $AUC_{0\text{-}inf}$ 1543 (511) ng.hr/mL. Median (range) Tmax was 0.75 (0.75 – 4.0) hrs and mean (SD) $t_{1/2}$ was 11.7 (1.9) hrs.

Cmax of flibanserin appears to be dose proportional from 100 to 250 mg following administration of flibanserin tablets. For $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, flibanserin exposure appears to be greater than dose proportional from 100 to 250 mg. In the original NDA and based upon $AUC_{0\text{-}24}$ in healthy male subjects, dose proportionality was observed with flibanserin capsules for doses 0.2 to 150 mg (Study 511.1, see review in DARRTS August 26, 2010).

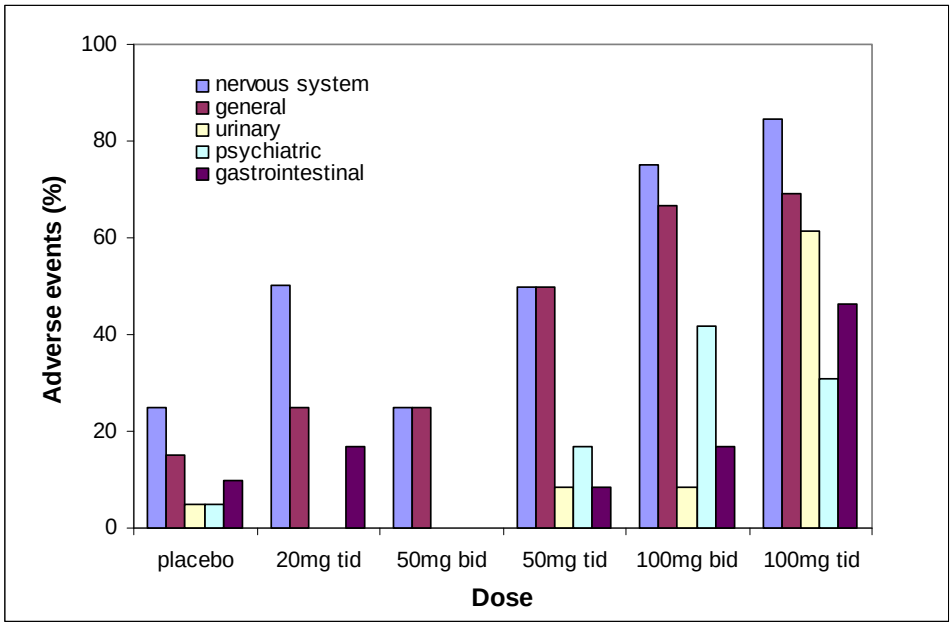
Mean+SD Plasma Flibanserin Concentration-Time Profiles in Healthy Premenopausal Women Following a Single Oral Dose of Flibanserin (sponsor's figure 1, section 12.1.1 of resubmission).



2.3.4. What are the characteristics of the exposure (dose)-response relationships for safety?

The most common treatment-emergent adverse events for subjects treated with flibanserin are dizziness, nausea, fatigue, and somnolence.

In the original NDA, higher incidences of AEs were noted with increased flibanserin dose. The figure below is a dose-adverse events profile from 81 healthy subjects from the clinical tolerability and PK Study 511.2 (see original Clinical Pharmacology review dated August 26, 2010 in DARRTS).



In this resubmission, the exposure-response relationship for safety was clearly observed in the drug interaction study between 100 mg flibanserin and 200 mg fluconazole (a multiple enzyme inhibitor) or regular strength grapefruit juice (a moderate CYP3A4 inhibitor).

Multiple doses of fluconazole resulted in a 2.2-fold increase in Cmax, 5.6-fold increase in AUC_{0-t} and 7.0-fold in AUC_{0-inf} of flibanserin. Following a single 100 mg dose of flibanserin administered with 240 mL of regular strength grapefruit juice resulted in an increase of 10%, 38% and 38% in Cmax, AUC_{0-t} and AUC_{0-inf}, respectively, compared to flibanserin alone.

Flibanserin administered with multiple doses of fluconazole resulted in a 7-fold increase in flibanserin exposure (AUC_{0-inf}), compared to flibanserin alone, and subsequently a greater frequency and severity of AEs. One subject experienced had a blood pressure of 64/41 mmHg, heart rate of 50 bpm and unable to speak. The subject required emergency attention, ammonia inhalant, oxygen and intravenous saline administration. Another subject experienced hypotension that was accompanied with fatigue and euphoria, which she described as feeling "drugged". The onset of all hypotensive events occurred at approximately the time of maximum flibanserin concentration (~0.5 to 2 hrs postdose). Due to severe hypotensive-related AEs experienced by the first 15 subjects in flibanserin + fluconazole treatment group, the sponsor stopped further evaluation of flibanserin + fluconazole co-administration that was scheduled for the second group of 11 subjects.

For fatigue, the percentage of subjects who experienced fatigue was 0% (0/15), 69% (18/26), 85% (22/26) and 93% (14/15) who received fluconazole alone, flibanserin alone, flibanserin + grapefruit juice, and flibanserin + fluconazole, respectively.

For dizziness, the percentage of subjects who experienced dizziness was 0% (0/15), 35% (9/26), 27% (7/26) and 20% (3/15) who received fluconazole alone, flibanserin alone, flibanserin + grapefruit juice, and flibanserin + fluconazole, respectively.

For nausea, the percentage of subjects who experienced nausea was 0% (0/15), 27% (7/26), 19% (5/26) and 73% (11/15) who received fluconazole alone, flibanserin alone, flibanserin + grapefruit juice, and flibanserin + fluconazole, respectively.

Hypotension was observed in 3 of 15 subjects treated with flibanserin + fluconazole. No incidence of hypotension was observed in the other treatment groups.

2.4 INTRINSIC FACTORS

2.4.1 What intrinsic factor (age) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

Age (Study 511.146 of current resubmission)
In this NDA flibanserin is indicated for the treatment of HSDD in premenopausal women, [redacted] the sponsor decided to evaluate the effect of age on flibanserin exposure.

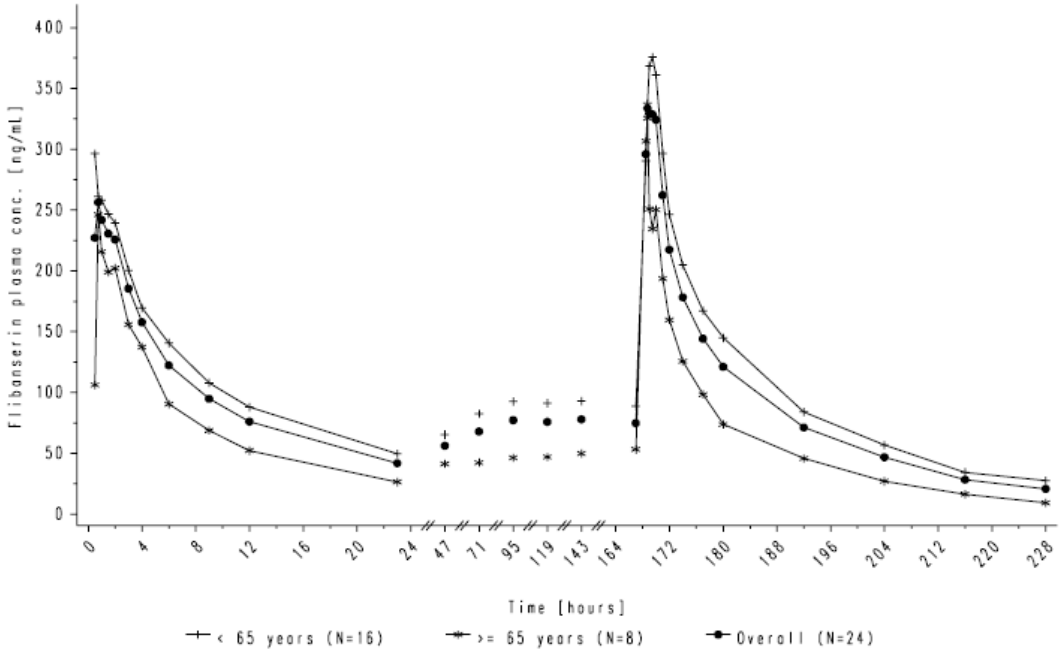
The sponsor compared the systemic exposure of flibanserin between elderly (≥65 years) and younger (<65 years) postmenopausal women with HSDD. The sponsor used the cutoff age of 65 years to distinguish between young and elderly. The mean (range) age for younger postmenopausal patients was 55 (46 - 64; N=16) years and elderly postmenopausal patients was 69 (65 - 75; N=8) years.

Following a single dose of 100 mg flibanserin, there was an increase of 15%, 42% and 54% in Cmax, AUC_{0-t} and AUC_{0-inf} of flibanserin, respectively in young postmenopausal women, compared to elderly postmenopausal women. Median Tmax of flibanserin was delayed by 0.5 hr (1.0 to 1.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women. Mean half-life increased by 0.9 hr (10.6 to 11.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women.

Following multiple doses (8 days) of 100 mg flibanserin tablet, there was an increase of 25% in Cmax and 56% in $AUC_{0-t, ss}$ of flibanserin in young postmenopausal women, compared to elderly postmenopausal women. Median Tmax of flibanserin was delayed by 0.1 hr (1.4 to 1.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women. Mean half-life increased by 1.4 hr (13.6 to 15.0 hrs) in young postmenopausal women, compared to elderly postmenopausal women.

It appears that systemic exposure of flibanserin is higher in young compared with elderly postmenopausal women with HSDD. By contrast, the volume of distribution and clearance were higher in the elderly postmenopausal women.

Arithmetic Mean Plasma Concentration-Time Profiles of Flibanserin Following Multiple Doses (Once Daily for 8 Days) of 100 mg Flibanserin Tablets in Healthy Postmenopausal Women with HSDD (sponsor's figure 15.6.5.3:9, section 15.6).



Geometric Mean PK Parameters of Flibanserin Following Multiple (Once Daily for 8 Days) Doses of 100 mg Dose of Flibanserin Tablet in Postmenopausal Women (sponsor's table 11.5.2.2.2:1, section 11.5.2.2).

Steady-state	<65 years (N=16)		≥65 years (N=8)		All patients (N=24)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	3480	60.8	2230	48.6	3000	60.9
$R_{A,AUC}$ [ ]	1.57	23.5	1.41	13.2	1.51	20.7
$C_{max,ss}$ [ng/mL]	437	59.4	350	64.2	406	60.7
$R_{A,Cmax}$ [ ]	1.46	45.9	1.29	30.2	1.39	40.4
$t_{max,ss}$[a] [h]	1.50	0.500-3.00	1.38	0.500-3.00	1.50	0.500-3.00
$t_{½,ss}$ [h]	15.0	45.1	13.6	25.4	14.5	39.1
$MRT_{po,ss}$ [h]	18.8	47.9	15.9	38.5	17.8	44.9
$CL/F_{,ss}$ [mL/min]	479	60.8	747	48.6	555	60.9
$V_z/F_{,ss}$ [L]	624	44.6	879	25.7	699	42.4

2.5 EXTRINSIC FACTORS

2.5.1 What extrinsic factors (CYP inhibitors, CYP inducers, ethanol and digoxin) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Effect of itraconazole (a strong CYP3A4 inhibitor) (from original NDA)

The sponsor evaluated the influence of multiple doses itraconazole at steady state on the PK of a single dose flibanserin (Study 511.37). This was a randomized, open label, two-way crossover study in male and female subjects to investigate the influence of CYP3A4 inhibitor itraconazole (oral 200 mg qd for 8 days) on the PK of a single tablet administration of 50 mg flibanserin with water.

Itraconazole co-administered with flibanserin increased flibanserin AUC0-inf by 2.6-fold and Cmax by 1.7-fold. $t_{1/2}$ was extended by 4.2 hrs from 7.44 to 11.6 hrs in the presence of itraconazole.

The following table summarizes PK parameters of flibanserin 50 mg single dose with and without itraconazole 200 mg co-administration.

	Flibanserin	
SD PK parameter*	With co-administration of itraconazole	Without co-administration of itraconazole
AUC0-inf (ng.hr/ml)	2810 (76.3)	1090 (57.5)
Cmax (ng/ml)	341 (32.5)	201 (49.8)
Tmax (hr)[1]	1.25 (1.00 – 4.00)	1.25 (0.50 – 3.00)
$t_{1/2}$ (hr)	11.6 (46.5)	7.4 (27.0)

*geometric mean (%CV)

[1] median and range

Effect of ketoconazole (a strong CYP3A4 inhibitor) (from original NDA)

The sponsor evaluated the influence of multiple doses of the strong CYP3A4 inhibitor ketoconazole on the PK of flibanserin after a single oral dose of 50 mg flibanserin (Study 511.111). This study was an open-label, randomized, two-period, crossover study. Flibanserin was administered with 240 ml of water in the morning about 1 hr after ketoconazole and light breakfast.

Ketoconazole 400 mg daily for 5 days inhibited flibanserin metabolism leading to a 4.6-fold increase in flibanserin AUC0-inf. Cmax increased 1.8-fold. Tmax increased slightly from 1.25 to 1.50 hr and $t_{1/2}$ was significantly prolonged from 8.5 to 15.9 hrs.

The following table summarizes PK parameters of flibanserin with and without co-administration of ketoconazole.

	Flibanserin	
SD PK parameter*	With co-administration of ketoconazole	Without co-administration of ketoconazole
AUC0-inf (ng.hr/ml)	5260 (56.5)	1140 (43.5)
Cmax (ng/ml)	472 (24.6)	256 (27.4)
Tmax (hr)[1]	1.50 (0.75 – 4.00)	1.25 (0.75 – 2.00)
$t_{1/2}$ (hr)	15.9 (41.7)	8.5 (29.8)

*geometric mean (%CV)
[1] median and range

Effect of fluconazole (a moderate CYP3A4, moderate CYP2C9 and strong CYP2C19 inhibitor) (Study SPR-12-01 of current resubmission)

The original NDA showed that co-administration of flibanserin 50 mg with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 4.3-fold increase in flibanserin exposure (AUC) and increased frequency of AEs. To address this concern, the sponsor conducted a DDI study between fluconazole and flibanserin. Fifteen healthy women receive one 400 mg loading dose and three daily 200 mg doses of fluconazole, then received a single 100 mg dose of flibanserin co-administered with 200 mg fluconazole. Flibanserin is proposed for once daily intake at bedtime with or without food. For this study, fluconazole and flibanserin were administered in the morning and subjects fasted 10 hrs prior and through 4 hrs after dosing of a single 100 mg dose flibanserin.

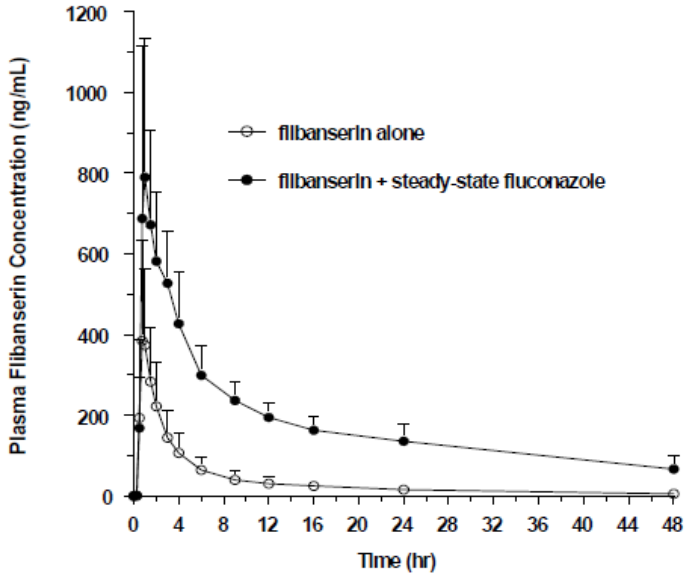
Multiple doses of fluconazole resulted in a 2.2-fold increase in Cmax, 5.6-fold increase in AUC_{0-t} and 7.0-fold in AUC_{0-inf} of flibanserin. All subjects had an increase in systemic flibanserin exposure. Mean terminal half-life of flibanserin increased from 10 to 23 hrs. Mean clearance (CL/F) of flibanserin decreased significantly from 75.9 to 9.8 L/hr with fluconazole administration. The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.3-fold increase with ketoconazole, a strong CYP3A4 inhibitor. The exposure change with fluconazole was not anticipated based on the presumed metabolism pathway of flibanserin (mainly through CYP3A4 and to a minor extent CYP2D6 as claimed by the sponsor).

Fluconazole is identified as an inhibitor of multiple enzymes - CYP3A4 (moderate), CYP2C9 (moderate) and CYP2C19 (strong) - according to the FDA Draft Guidance for Industry: Drug Interactions – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations (February 2012). The in vivo study results suggest that CYP2C9 and/or CYP2C19 may be involved in the metabolism of flibanserin. The sponsor should identify enzymes other than CYP3A4 that potentially contribute to the metabolism of flibanserin; this can be done with their physiologically-based pharmacokinetic model.

Co-administration of single 100 mg dose flibanserin and multiple doses of fluconazole 200 mg resulted in more frequent and profound AEs, compared to flibanserin alone. All 15 subjects who received flibanserin + fluconazole experienced at least 1 AE. Three of fifteen subjects experienced a hypotensive event. One subjects who received flibanserin + fluconazole experienced a severe hypotensive event (blood pressure of 64/41 mmHg, heart rate of 50 bpm and unable to speak) and required medical intervention before discontinuation from the study.

Another subject described feeling drugged. The onset of all three (20%) hypotensive events occurred at approximately the time of maximum flibanserin concentration.

Mean (SD) Plasma Flibanserin Concentration-Time Profiles in Healthy Young Female Subjects (N=15) Following a Single 100 mg Dose of Flibanserin Alone and a Single 100 mg Dose of Flibanserin + Multiple 200 mg Doses of Fluconazole (sponsor's figure 1, section 12.2.1).



Arithmetic Mean (SD) Plasma Flibanserin PK 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 + Multiple 200 mg Doses of Fluconazole (sponsor's table 10, section 12.2.1).

	Sequential Treatments (N=15)	
Pharmacokinetic Parameter	**Flibanserin Alone (Treatment A)**	**Flibanserin + Steady-State Fluconazole[a] (Treatment C)**
AUC(0-t) (hr·ng/mL)	1676 (858)	8401 (1809)
AUC(0-inf) (hr·ng/mL)	1756 (921)	11249 (3422)
fext (%)	3.90 (2.45)	22.4 (13.3)
Cmax (ng/mL)	421 (219)	889 (362)
Tmax (hr)[b]	0.800 (0.750 – 6.00)	1.00 (0.750 – 4.00)
t ½ (hr)	10.0 (3.69)	25.3 (10.8)

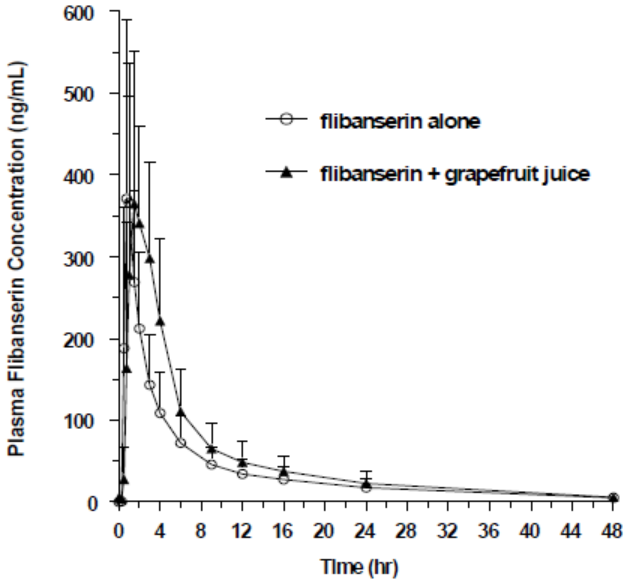
Effect of grapefruit juice (a moderate CYP3A4 inhibitor) (Study SPR-12-01 of current resubmission)

Due to concerns that grapefruit juice inhibit CYP3A4 metabolism, the sponsor evaluated the effect of a single administration of grapefruit juice on flibanserin PK. This study was not conducted at the request of the Division of Bone, Reproductive and Urologic Products (DBRUP) or OCP.

Following a single 100 mg dose of flibanserin administered with 240 mL of regular strength grapefruit juice resulted in an increase of 10%, 38% and 38% in Cmax, AUC_{0-t} and AUC_{0-inf}, respectively, compared to flibanserin alone. Median Tmax 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 at 10.6 and 9.9 hrs for flibanserin alone and flibanserin + grapefruit juice, respectively.

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.

Mean (SD) Plasma Flibanserin Concentration-Time Profiles 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 (sponsor's figure 3, section 12.3.1).



Arithmetic Mean (SD) Plasma Flibanserin PK 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 (sponsor's table 10, section 12.3.2).

	Sequential Treatments (N = 26)	
Pharmacokinetic Parameter	**Flibanserin Alone (Treatment A)**	**Flibanserin + Grapefruit Juice (Treatment B)**
AUC(0-t) (hr·ng/mL)	1752 (741)	2413 (1057)
AUC(0-inf) (hr·ng/mL)	1869 [b] (790)	2508 (1142)
fext (%)	4.04 [b] (2.69)	3.21 (2.35)
Cmax (ng/mL)	405 (195)	433 (163)
Tmax (hr)[a]	0.790 (0.750 – 6.00)	1.53 (1.00 – 4.00)
t ½ (hr)	10.6 [b] (3.43)	9.93 (3.05)

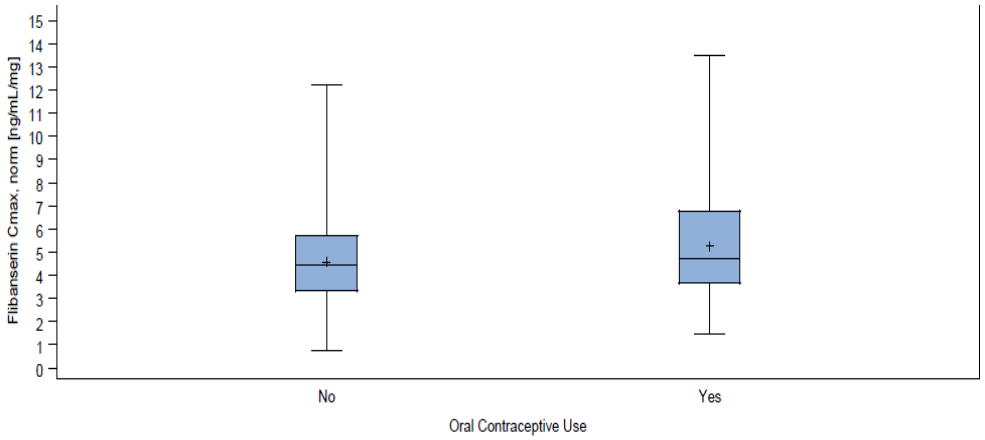
Effect of oral contraceptives (a weak CYP3A inhibitor) (Meta-Analysis Report U10-2254-01 of current resubmission)

In the CR issued in August 2010, DBRUP requested the sponsor submit the final report of a meta-analysis of phase 1 PK data in women who received oral contraceptives and various doses of flibanserin concomitantly. The analysis was requested to exclude subjects with renal or hepatic impairment from the meta-analysis.

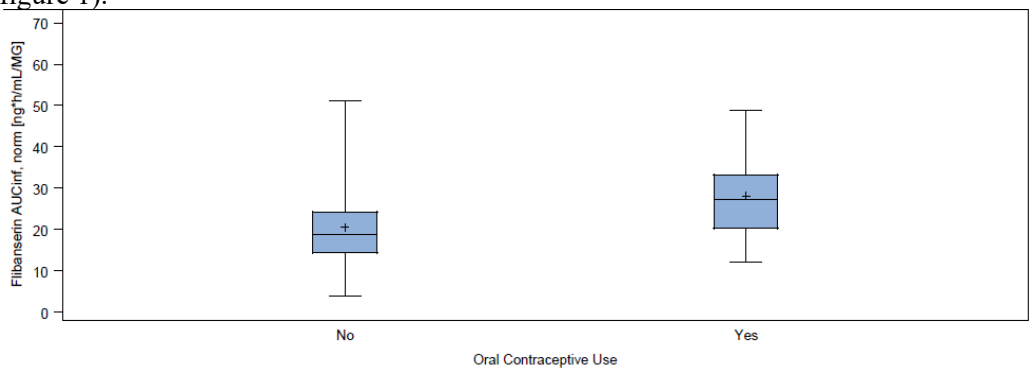
The meta-analysis is entitled "Amended Statistical comparison of dose normalized PK parameters AUC0-∞,norm, Cmax,norm, AUCτ,ss,norm, Cmax,ss,norm of flibanserin with and without oral contraceptives across Phase I trials – exclusion of subjects with renal or hepatic impairment".

Subjects were on flibanserin doses ranging from 25 to 100 mg from 7 studies. The adjusted geometric ratios for $AUC_{0\text{-}inf}$ and Cmax of flibanserin (dose-normalized) were 1.42 and 1.12, respectively, following a single dose flibanserin and oral contraceptives. Flibanserin exposure was not significantly affected by oral contraceptives.

Boxplot of Cmax of flibanserin after oral administration of flibanserin in healthy female subjects and HSDD Patients With (N=39) and Without Oral Contraceptives (N=114) (sponsor's figure 3).



Boxplot of $AUC_{0\text{-inf}}$ of flibanserin after oral administration of flibanserin in healthy female subjects and HSDD Patients With (N=39) and Without Oral Contraceptives (N=114) (sponsor's figure 1).



Effect of rifampin (a strong CYP3A inducer) (from original NDA)

The sponsor evaluated the influence of rifampin, a strong CYP3A4 inducer, on the PK of flibanserin and relevant metabolites in an open-label, single center, randomized, two-period cross-over study in healthy females (Study 511.86). Rifampin 600 mg daily was given in the evening for 7 days followed by a morning dose of flibanserin 100 mg on Day 8, and then rifampin 600 mg was given for 2 additional evenings. In the group receiving no rifampin, flibanserin 100 mg was given in the morning of study Day 1. Flibanserin and rifampin were administered with 240 ml of water.

The geometric mean flibanserin exposure AUC0-inf was significantly lower when co-administered with rifampin. Flibanserin AUC0-inf was reduced by 96% with rifampin pre-treatment. Geometric mean flibanserin Cmax was also significantly lowered when co-administered with rifampin. Cmax for flibanserin was reduced by 91%. Flibanserin metabolism is clearly influenced by the strong CYP3A4 inducer rifampin.

The following table summarizes single dose PK parameters of flibanserin 100 mg with and without co-administration of rifampin 600 mg for 10 days.

	Flibanserin	
SD PK parameter*	With co-administration of rifampin	Without co-administration of rifampin
AUC0-inf (ng.hr/ml)	93.5 (54.8)	2080 (45.0)
Cmax (ng/ml)	37.1 (57.1)	377 (46.4)
Tmax (hr)[1]	0.75 (0.50 – 1.50)	0.75 (0.50 – 2.00)
$t_{1/2}$ (hr)	5.05 (101)	10.7 (34.8)

*geometric mean (%CV)

[1] median and range

Effect of etravirine (a moderate CYP3A inducer) (Study SPR-12-02 of current resubmission)

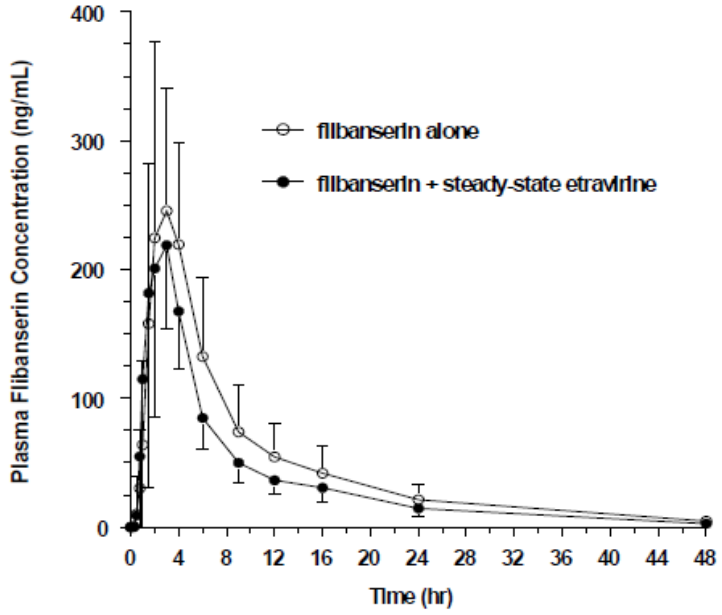
Flibanserin is proposed for once daily intake at bedtime with or without food. In this study, flibanserin tablets were administered in the morning within 30 min after consumption of a standard breakfast on Days 1 and 16 following an overnight fast of at least 10 hrs. Etravirine should always be taken following a meal because systemic exposure of etravirine decreased by about 50% when administered under fasting conditions. In this study etravirine 200 mg was

given twice daily following a meal for 15 consecutive days in healthy female subjects. After 13 days (Days 3 - 15) of etravirine alone administration, flibanserin was co-administered with etravirine on Day 16.

Co-administration of multiple doses of etravirine and a single dose of flibanserin resulted in a decrease of 3.2% in Cmax and 20.6% in $AUC_{0\text{-}inf}$ of flibanserin, compared to flibanserin alone. Median (range) Tmax of flibanserin was delayed by 0.5 hr (3.0 to 2.5) hrs when flibanserin was administered with etravirine. Mean half-life of flibanserin was similar for flibanserin at 9.8 and 9.2 hrs for flibanserin alone and flibanserin + etravirine, respectively. The sponsor is only seeking approval of 100 mg; no other doses were evaluated in their Phase 3 program. In the original NDA, 50 mg dose of flibanserin was found to be ineffective for the treatment of HSDD. With a 20% decrease in exposure and with dose proportionality established only from 100 to 250 mg, concomitant administration of flibanserin and a moderate CYP3A4 inducer may reduce the efficacy of flibanserin.

Fatigue, a common AE of flibanserin treatment, was less prominent in the flibanserin + etravirine treatment group (21%), compared to flibanserin alone (47%). Somnolence is common AE of flibanserin therapy and a known, but less common AE of etravirine therapy. The frequency of somnolence increased with co-administration of flibanserin + etravirine (46%), compared with flibanserin alone (20%) group. This suggests that somnolence may be exacerbated when flibanserin is co-administered with somnolence-inducing drugs such as antihistamines and antiparkinson drugs.

Mean±SD Plasma flibanserin Concentration-Time Profiles in Healthy Female Subjects (N=24) Following a Single 100 mg Dose of Flibanserin Administered Alone and With Multiple Doses of Etravirine (sponsor's figure 1, section 12.2.1).



Arithmetic Mean (SD) Plasma Flibanserin PK Parameters in Healthy Female Subjects (N=24) Following Administration of a Single 100 mg Dose of Flibanserin Alone and With Multiple Doses of Etravirine (sponsor's table 8, section 12.2.2).

	Sequential Treatments (N =24)	
Pharmacokinetic Parameter	Flibanserin Alone	Flibanserin + Steady-State Etravirine[a]
AUC_{0-t} (hr·ng/mL)	2153 (859)	1638 (389)
AUC_{0-inf} (hr·ng/mL)	2225[b] (928)	1679 (415)
f_{ext} (%)	3.00[b] (1.98)	2.21 (1.53)
C_{max} (ng/mL)	296 (104)	286 (96.6)
T_{max} (hr)[c]	3.00 (2.00 – 4.00)	2.50 (1.00 – 4.00)
$t_{½}$ (hr)	9.78[b] (1.97)	9.17 (1.73)

[a] Concomitant flibanserin dosing occurred on 14th day of twice-daily etravirine dosing
[b] N=23
[c] Median (range)

Effect of ethanol (Study SPR-12-02 of current resubmission)

This was a single center, randomized, double-blind, single dose, 5-treatment crossover study in twenty-five healthy adult subjects (23 males and 2 females). Twenty-three subjects completed all 5 treatment arms; two subjects withdrew from the study after completing 0.8 g/kg ethanol + placebo treatment arm. Subjects were randomly assigned to 1 of 5 treatment groups (5 subjects per treatment group).

Treatment A: 0.8 g/kg ethanol diluted to 240 mL with orange juice and administered orally with 1 over-encapsulated flibanserin tablet 100 mg.

Treatment B: 0.8 g/kg ethanol diluted to 240 mL with orange juice and administered orally with 1 matching placebo capsule.

Treatment C: 0.4 g/kg ethanol diluted to 240 mL with orange juice and administered orally with 1 over-encapsulated flibanserin tablet 100 mg.

Treatment D: 0.4 g/kg ethanol diluted to 240 mL 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.

Ethanol (95%) was diluted to 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 (Treatments A, B, C, and D) or orange juice (Treatment E). Subjects were given up to 10 minutes to complete intake of each treatment.

Using a mean weight of 70 kg and US standards for alcohol content, subjects receiving 0.4 g of ethanol/kg of body weight would have been given 28 g of pure alcohol (equivalent to two standard drinks). For subjects receiving 0.8 g of ethanol/kg of body weight, they would have

received 56 g of pure alcohol (equivalent to 4 standard drinks). According to the Dietary Guidelines for Americans, moderate alcohol consumption is defined as having up to 1 drink per day for women and up to 2 drinks per day for men.

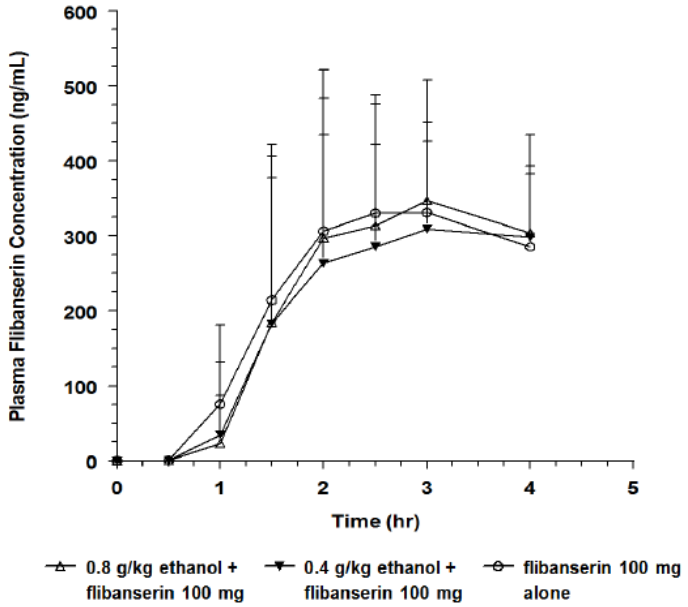
The majority of subjects in this study were males (23 out of 25). For the 0.4 g/kg treatment group, two standard drinks would likely be considered moderate alcohol consumption in males. For the 0.8 g/kg treatment group, four standard drinks would likely be considered high alcohol consumption in males.

Flibanserin exposure as measured by partial AUC (AUC_{0-4}) decreased by 10.5% and 3.9% when flibanserin 100 mg was administered with 0.4 and 0.8 g/kg ethanol, respectively, compared to flibanserin alone. However, considering the inter-subject variability, small number of subjects per treatment group (N=5), and incomplete concentration-time profiles, we have limited data to conclude that ethanol reduces flibanserin exposure.

The most frequently reported AEs were somnolence, headache, and dizziness. The frequency of somnolence, headache, and dizziness was highest in the group receiving the highest concentration of ethanol (0.8 g/kg) with flibanserin (Treatment group A). The frequency of somnolence in subjects who received 0.8 g/kg ethanol + flibanserin was higher compared to 0.8 g/kg ethanol + placebo: 91.7% vs. 60.0%. The frequency of somnolence in subjects who received 0.4 g/kg ethanol + flibanserin was higher compared to 0.4 g/kg ethanol + placebo: 73.9% vs. 37.5%.

Flibanserin alone resulted in approximately 67% of subjects experiencing somnolence. The addition of ethanol to flibanserin intake increased the frequency of somnolence to approximately 74% and 92% with 0.4 and 0.8 g/kg ethanol, respectively. Alcohol, especially notable at high concentrations, increased the somnolence-inducing effect of flibanserin.

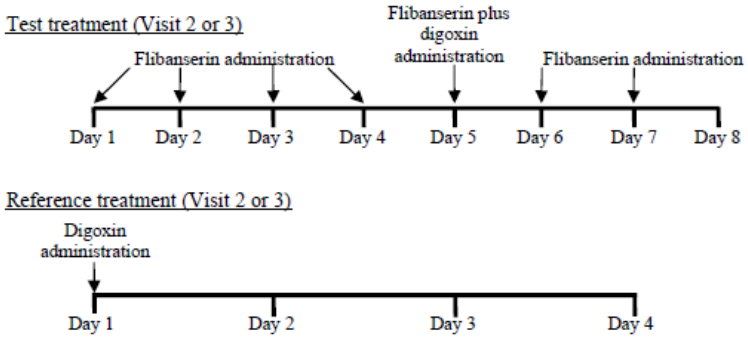
Mean+SD Plasma Flibanserin Concentration-Time Profiles in Healthy Subjects Following a Single Oral 100 mg Dose of Flibanserin Administered With (0.8 or 0.4 g ethanol/kg body weight) and Without Alcohol (sponsor's figure 1, section 12.2.1).



Effect of flibanserin on digoxin PK (Study 511.158 of current resubmission)

Digoxin is commonly used in adults for congestive heart failure and atrial fibrillation. Digoxin has a narrow therapeutic index so its use requires dose titration for efficacy response and monitoring of digoxin toxicity. Digoxin is a substrate P-gp and is commonly used as a probe in drug interaction studies to evaluate potential P-gp substrates and/or inhibitors. Flibanserin is indicated for use in premenopausal women [redacted], the sponsor decided to evaluate the potential in vivo interaction of digoxin and flibanserin.

This was a single center, open-label, randomized, two-way crossover study in twenty-four healthy male (N=11) and female (N=13) subjects. Subjects were randomized to flibanserin and digoxin (following pre-treatment of flibanserin) or digoxin alone.



Flibanserin + Digoxin Group (Test Group): On Days 1 and 2, subjects received 1 dose of flibanserin 100 mg tablet at approximately 8 pm. On Days 3 and 4, subjects received 1 dose of flibanserin 100 mg tablet approximately 8 am. On Day 5, subjects received 1 dose of flibanserin 100 mg and 1 dose of digoxin 0.5 mg at approximately 8 am without food, following an overnight fast of 10 hrs. On Days 6 and 7, subjects received 1 dose of flibanserin 100 mg tablet at approximately 8 am. Flibanserin and digoxin tablets were administered with 240 mL room temperature water.

Digoxin Group (Reference Group): On Day 1, subjects received 1 dose of digoxin 0.5 mg at approximately 8 am with 240 mL room temperature water, following an overnight fast of 10 hrs.

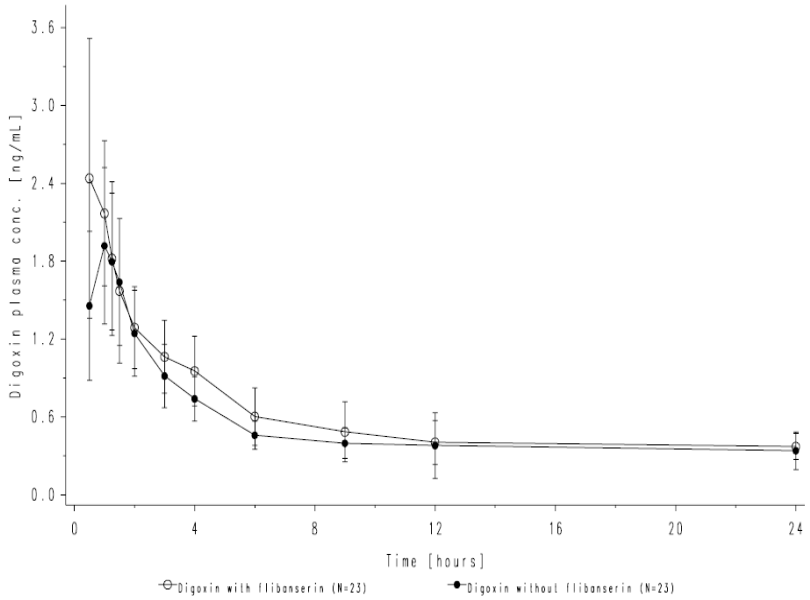
Digoxin exposure increased by 46%, 62% and 96% for Cmax, AUC_{0-t}, and AUC_{0-inf}, respectively, following multiple doses of flibanserin 100 mg co-administered with a single dose of digoxin 0.5 mg. A 96% increase in digoxin AUC suggests flibanserin is a P-gp inhibitor. Due to the narrow margin for efficacy and safety, this increase in digoxin systemic exposure can shift a patient from a safe maintenance dose to a toxic dose. The proposed label should advise monitoring of digoxin toxicity and possible digoxin dose reduction when flibanserin is used in patients on digoxin therapy.

In the original NDA, the sponsor concluded that flibanserin is not a P-gp or multidrug resistance protein (MDR) substrate and that P-gp was not involved in flibanserin absorption, based upon in vitro study in Caco-2 cells. In this resubmission, the sponsor concluded that flibanserin transport is not mediated via P-gp because an increase in digoxin exposure was moderate based upon digoxin AUC_{0-24} (25% increase) and digoxin renal clearance ($CL_{R,0-24}$) (~8% decrease). However, based upon digoxin AUC_{0-inf}, not AUC_{0-24}, digoxin exposure increased by 96% with flibanserin administration and digoxin Cmax increased by 46%. The 8% reduction in digoxin renal

clearance was based upon urine samples calculated from 0 to 24 hrs. Reduction in digoxin renal clearance with flibanserin administration appears to be greater at 72 hrs. In assessing clinical drug interaction between flibanserin and digoxin, use of Cmax and AUC ratio is more direct and sensitive compared to renal clearance ratio due to the nature of sample collection. In conclusion, the in vivo study with flibanserin + digoxin co-administration suggests that P-gp is involved with flibanserin transport and labeling should reflect the findings.

All 24 subjects (100%) 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 common AEs and were mild to moderate in severity. However, two healthy subjects experienced severe AEs - syncope followed by circulatory collapse and somnolence - that occurred around the time of maximum flibanserin concentration (0.5 to 1 hr).

Mean Plasma Concentration-Time Profiles of Digoxin After a Single Oral Dose of Digoxin 0.5 mg With and Without Co-administration of Flibanserin 100 mg (sponsor's figure 15.6.5.3:7, section 15.6.5.3).



Geometric Mean PK Parameters of Digoxin Following a Single Administration of 0.5 mg Digoxin With and Without Multiple Doses of 100 mg Flibanserin (N=23) (sponsor's table 11.5.2.3:1. Section 11.5.2).

			With co-administration of flibanserin (test)		Without co-administration of flibanserin (reference)	
Parameter	Unit	N	gMean	gCV [%]	gMean	gCV [%]
C_{max}	[ng/mL]	[23/23]	2.88	22.1	1.98	29.4
$AUC_{0-\infty}$	[ng·h/mL]	[22/23]	50.0	45.9	25.9	70.5
AUC_{0-tz}	[ng·h/mL]	[23/23]	21.2	55.7	13.2	59.1
AUC_{0-24}	[ng·h/mL]	[23/23]	14.3	21.9	11.5	32.5
t_{max}*	[h]	[23/23]	0.500	(0.483-2.02)	1.00	(0.500-2.00)
$t_{1/2}$	[h]	[22/23]	64.4	59.4	31.3	114
MRT_{po}	[h]	[22/23]	84.4	62.5	40.5	111
CL/F	[mL/min]	[22/23]	167	45.9	322	70.5
V_z/F	[L]	[22/23]	930	38.3	873	39.1
Ae_{0-24}	[µg]	[23/22]	116	20.8	104	26.1
fe_{0-24}	[%]	[23/22]	23.2	20.8	20.8	26.1
$CL_{R,0-24}$	[mL/min]	[23/22]	135	20.5	149	25.1

*For t_{max} the median and range are given

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess drug concentrations? Briefly describe the methods and summarize the assay performance.

In the original NDA, the sponsor used LC-MS/MS for the majority of PK studies and validated the method for the determination of flibanserin (referred to as BIMT 17BS) in human plasma. The method was validated for precision, accuracy, specificity, and recovery; the results are acceptable. The sponsor met the Agency's recommended acceptance criteria of ≤20% for precision (CV%) and within ±20% for accuracy at the lower limit of quantitation and ≤15% or within ±15% at all concentrations. There were 10 calibration standards with concentrations of 0.5, 1, 2.5, 5, 10, 25, 50, 100, 250, and 500 ng/mL. The bioanalytical method was acceptable.

The following table is a summary of the validation results (sponsor's table 1.1, study QA598).

Analyte	BIMT 17 BS		BIMA 23 BS		TFMPP	
Calibration range [ng/mL]	0.500 ng/mL (LLOQ) – 500 ng/mL (ULOQ)					
Required sample volume [µL]	100					
r^2 (mean) of the standard curves	0.99529		0.99863		0.99363	
Recovery Analyte (%)	72.9 – 83.0		75.8 – 83.2		34.4 – 35.8	
Recovery IS (%)	83.4		78.7		32.6	
QC level [ng/mL]	0.500	400	0.500	400	0.500	400
Number of replicates (n)	18	21	18	21	18	21
Precision (cv %) of QC samples	12.50	3.32	9.91	2.98	6.99	3.44
Accuracy (% bias) of QC samples	-8.93	-8.24	4.03	3.49	9.66	4.63

In this resubmission, Sprout Pharmaceuticals used LC-MS/MS method (Zorbax Eclipse Plus C18 column with 10 mM ammonium acetate solution for mobile Phase A and methanol for mobile Phase B) for the analysis of plasma flibanserin concentration collected from 3 mL blood samples. (b) (4) conducted the bioanalyses. The analytical method and calibration range were the same as in the original NDA. There were 10 calibration standards with concentrations of 0.5, 1, 2.5, 5, 10, 25, 50, 100, 250, and 500 ng/mL. The quality controls were prepared to plasma flibanserin concentrations 1.5, 30.0 and 400 ng/mL. Additional diluted QC samples were 750 and 1500 ng/mL.

The following table is a summary of the validation results (sponsor's table; study report N-A BIO-12-020).

Summary of the Performance	Flibanserin
Calibration range	0.500 - 500 ng/mL
Lower Limit of Quantification	0.500 ng/mL
r^2 (mean)	0.99817
% cv at the LLOQ (n=9)	1.3
% bias at the LLOQ (n=9)	1.0
% cv at the lowest QC (n=26)	4.8
% bias at the lowest QC (n=26)	1.8

The following table is the statistics of the back-calculated calibration standards (sponsor's table 9; study report N-A BIO-12-020).

Cal. Std. nominal conc.	0.500	1.00	2.50	5.00	10.0	25.0	50.0	100	250	500
n	9	9	9	9	9	9	9	9	9	9
mean	0.505	0.980	2.48	5.06	10.0	25.4	50.4	99.2	256	480
sd	0.00635	0.0267	0.0442	0.134	0.634	1.42	1.16	2.88	5.85	7.88
cv [%]	1.3	2.7	1.8	2.7	6.3	5.6	2.3	2.9	2.3	1.6
bias [%]	1.0	-2.0	-0.9	1.2	0.5	1.6	0.8	-0.8	2.5	-3.9

The following table is a summary of the inter-assay accuracy and precision for the QC samples (sponsor's table 10; study report N-A BIO-12-020).

Nominal QC conc. [ng/mL]	1.50	30.0	400
number	26	26	26
mean (calc.)	1.53	30.3	403
sd	0.0726	1.09	11.6
cv [%]	4.8	3.6	2.9
bias [%]	1.8	0.9	0.9

The sponsor met the Agency's recommended acceptance criteria of $\leq$20% for precision (CV%) and within $\pm$20% for accuracy at the lower limit of quantitation and $\leq$15% or within $\pm$15% at all concentrations. The bioanalytical method is acceptable.

3 LABELING RECOMMENDATIONS

There are no Clinical Pharmacology labeling recommendations.

4 APPENDIX

4.1 Individual Study Reviews

Table of Contents for Individual Study Reviews

Individual Study Reviews

Study SPR-12-01

Title: An Open Label, Sequential Study to Evaluate the Effect of a Single Dose of Grapefruit Juice and Multiple Doses of Fluconazole on the Pharmacokinetics of Flibanserin in Healthy Females

Objective: The primary objective of this study was to evaluate the effect of multiple daily oral doses (steady-state) of CYP3A4 inhibitor fluconazole on the PK of a single oral 100 mg dose of flibanserin. The secondary objective of this study was to evaluate the effect of a single administration of the CYP3A4 inhibitor grapefruit juice on the PK of flibanserin after a single 100 mg dose. The safety and tolerability of flibanserin with and without concurrent administration of fluconazole or grapefruit juice in healthy female subjects were evaluated.

Methods: This was an open-label, three-period, sequential study in twenty-six healthy young women with a mean (range) age of 33 (18 - 48) years. Twenty-three subjects were white, 2 black and 1 other. Flibanserin 100 mg tablets were administered once daily as over-encapsulated hard gelatin capsules (size 00). Flibanserin tablets (over-encapsulated) and fluconazole tablets were administered with 240 mL of room temperature water. Flibanserin is proposed for once daily intake at bedtime with or without food. For this study, all treatments were administered in the morning and subjects fasted 10 hrs prior and through 4 hrs after dosing of a single 100 mg dose flibanserin on Days 1, 3 and 10.

Thirty subjects were planned for study enrollment with the goal of enrolling 15 subjects in Group 1 and 15 subjects in Group 2. At the end of enrollment period, there were 15 subjects in Group 1 and only 11 subjects in Group 2. Four days after subjects in Group 1 were dosed, subjects in the second group started the study. The staggered design scheme allowed the sponsor to assess treatment response in Group 1 subjects following flibanserin + grapefruit juice or flibanserin + fluconazole co-administration before continuing the study in more subjects.

The sponsor stated that due to hypotensive-related AEs experienced in Period 3 by the first 15 subjects when they received concomitant administration of fluconazole and flibanserin, the second group of 11 subjects only completed Periods 1 and 2. All 15 subjects in Group 1 completed all 3 treatment periods. All 11 subjects in Group 2 completed treatment Period 1 and 2.

Period 1
Day 1: single oral dose of flibanserin 100 mg alone (Treatment A)

Period 2
Day 3: single oral dose of flibanserin 100 mg taken with 240 mL of grapefruit juice (Treatment B)

Period 3
Day 6: a single oral dose of fluconazole 400 mg
Days 7-9: once daily dose of fluconazole 200 mg
Day 10: single oral dose of flibanserin 100 mg and fluconazole 200 mg (Treatment C)
Day 11: oral dose of fluconazole 200 mg

Subjects returned to the clinic on the mornings of Days 6 to 9 for fluconazole dosing, vital signs measurement, blood sampling for safety labs and trough fluconazole concentrations, adverse events (AEs) and concurrent medication recording. Subjects were re-admitted to the clinic during the evening of Day 9, and remained in the clinic until 48 hours after Day 10 dosing. Subjects returned to the clinic 4 to 5 days after discharge for a follow-up visit.

Subjects were required to fast for at least 10 hrs prior to dosing on Days 1, 3 and 10, through 4 hrs postdose. Prior to blood draws, subjects were required to fast for at least 10 hrs.

Study Site: Jasper Clinic, Inc., Kalamazoo, MI
Study Period: January 30, 2012 to February 29, 2012

Treatment Products
Flibanserin: 100 mg tablets were over-encapsulated, lot 013012
Fluconazole: Diflucan® 200 mg tablets, lot Y11898
Grapefruit Juice: one regular strength 8-ounce glass (purchased by the study site)

Pharmacokinetic Sampling: Blood samples for determination of flibanserin plasma concentrations were taken on Day 1, Day 3 and Day 10: predose (within 10 min before dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24 and 48 hrs postdose. Blood samples for determination of fluconazole trough plasma concentrations were collected just prior to fluconazole dosing on Days 6, 7, 8, 9, 10 and 11. The analyses of flibanserin and fluconazole concentrations were performed by (b) (4) using a validated LC-MS/MS method.

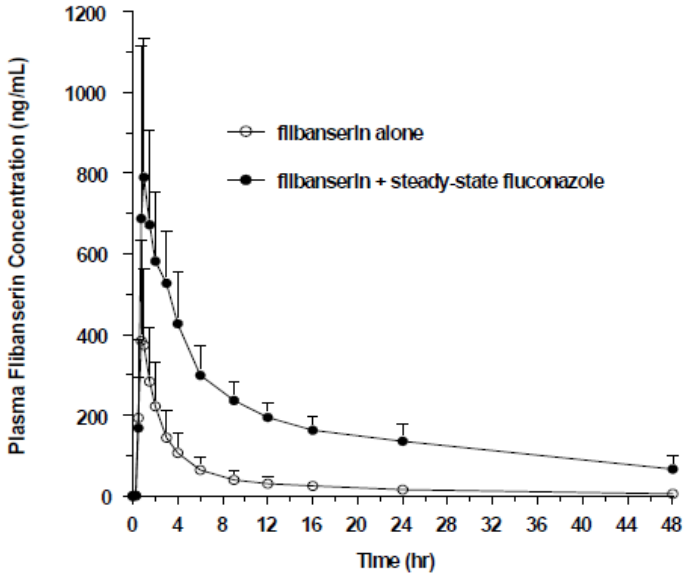
Results and Reviewer's Comments:
Flibanserin + Fluconazole
In the Complete Response (CR) letter issued August 27, 2010 the Office of Clinical Pharmacology (OCP) recommended the sponsor conduct a drug-drug interaction study to evaluate the PK profile and safety of flibanserin 100 mg when co-administered with moderate CYP3A4 inhibitors. This recommendation was generated in response to data from the original NDA showing that co-administration of flibanserin 50 mg with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 4.3-fold increase in flibanserin exposure and increased frequency of AEs.

To address this concern, the sponsor conducted a drug-drug interaction study and submitted the new study results in the current resubmission. The sponsor selected fluconazole as the moderate CYP3A4 inhibitor. Fluconazole (Diflucan®) is an antifungal. It is approved under NDA 019949 for the treatment of vaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis and crytococcal meningitis. It is available in 50, 100, 150 and 200 mg tablets. According to the product label, elimination half-life of fluconazole is approximately 30 hrs and steady-state is reached within 5-10 days following oral doses of 50-400 mg given once daily. For treatments that require multiple dose therapy, a loading dose is recommended on the first day of therapy to get the plasma concentrations close to steady state concentrations by the second day of therapy. Fluconazole exposure is not affected by food and therefore can be taken without regard to meals. After one 400 mg loading dose and three daily 200 mg doses, it appears that fluconazole was near steady-state concentration (mean (SD) of 6.7 (1.1) mcg/mL) by Day 10 when flibanserin was co-administered.

Multiple doses of fluconazole resulted in a 2.2-fold increase in Cmax, 5.6-fold increase in AUC_{0-t} and 7.0-fold in AUC_{0-inf} of flibanserin. All subjects had an increase in systemic flibanserin exposure. Mean terminal half-life of flibanserin increased from 10 to 23 hrs. Mean clearance (CL/F) of flibanserin decreased significantly from 75.9 to 9.8 L/hr with fluconazole administration. The 7-fold increase in flibanserin exposure with fluconazole, a moderate CYP3A4 inhibitor, exceeded the 4.3-fold increase with ketoconazole, a strong CYP3A4 inhibitor. The exposure change with fluconazole was not anticipated based on the presumed metabolism pathway of flibanserin (mainly through CYP3A4 and to a minor extent CYP2D6 as claimed by the sponsor).

Fluconazole is identified as an inhibitor of multiple enzymes - CYP3A4 (moderate), CYP2C9 (moderate) and CYP2C19 (strong) - according to the FDA Draft Guidance for Industry: Drug Interactions – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations (February 2012). The in vivo study results suggest that CYP2C9 and/or CYP2C19 may be involved in the metabolism of flibanserin. The sponsor should identify enzymes other than CYP3A4 that potentially contribute to the metabolism of flibanserin; this can be done with their physiologically-based pharmacokinetic model.

Mean (+SD) Plasma Flibanserin Concentration-Time Profiles in Healthy Young Female Subjects (N=15) Following a Single 100 mg Dose of Flibanserin Alone and a Single 100 mg Dose of Flibanserin + Multiple 200 mg Doses of Fluconazole (sponsor's figure 1, section 12.2.1).



Arithmetic Mean (SD) Plasma Flibanserin PK 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 + Multiple 200 mg Doses of Fluconazole (sponsor's table 10, section 12.2.1).

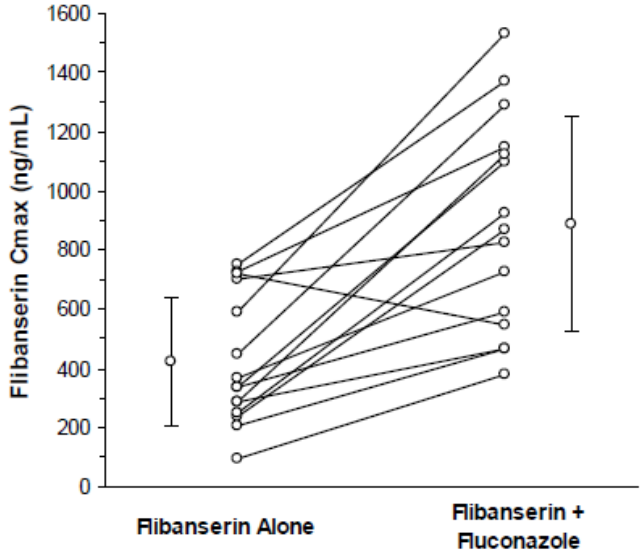
	Sequential Treatments (N=15)	
Pharmacokinetic Parameter	Flibanserin Alone (Treatment A)	Flibanserin + Steady-State Fluconazole[a] (Treatment C)
AUC(0-t) (hr·ng/mL)	1676 (858)	8401 (1809)
AUC(0-inf) (hr·ng/mL)	1756 (921)	11249 (3422)
fext (%)	3.90 (2.45)	22.4 (13.3)
Cmax (ng/mL)	421 (219)	889 (362)
Tmax (hr)[b]	0.800 (0.750 – 6.00)	1.00 (0.750 – 4.00)
t ½ (hr)	10.0 (3.69)	25.3 (10.8)

[a] Concomitant flibanserin dosing occurred with fifth daily oral dose of fluconazole; 400 mg on first day followed by 200 mg
[b] Median (range)

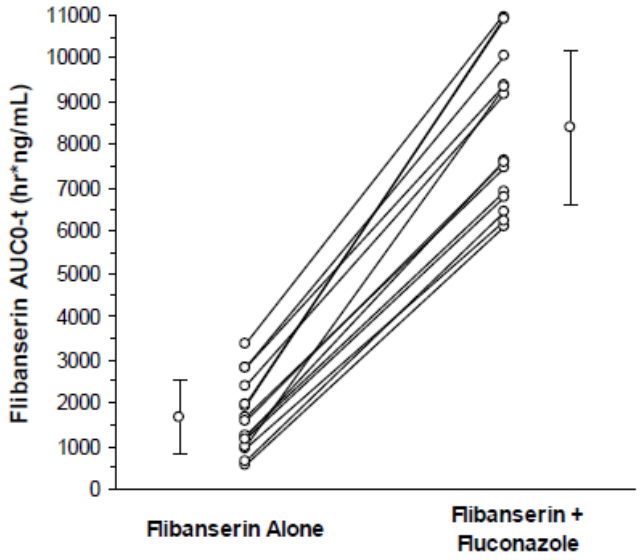
Plasma Flibanserin PK Parameters in Healthy Young Female Subjects (N=15) Following a Single 100 mg Dose of Flibanserin Alone and a Single 100 mg Dose of Flibanserin + Multiple 200 mg Doses of Fluconazole (sponsor's table 10, section 12.2.1).

Parameter	Statistics	Day 1 (N=15)	Day 10 (N=15)
CL/F (L/hr)	n	15	15
	Mean	75.901	9.756
	SD	45.1084	3.1343
	%CV	59.43	32.13
	Median	62.858	8.769
	Min, Max	27.72, 185.10	6.04, 14.79
	Geometric Mean	65.356	9.305
	%CV for Geometric Mean	60.75	32.55

Mean (SD) and Individual Flibanserin Cmax in Healthy Female Subjects (N=15) Following a Single 100 mg Dose of Flibanserin Administered With and Without Fluconazole (sponsor's figure 4, section 12.3.1).



Mean (SD) and Individual Flibanserin AUC_{0-t} in Healthy Female Subjects (N=15) Following a Single 100 mg Dose of Flibanserin Administered With and Without Fluconazole (sponsor's figure 4, section 12.3.1).



Statistical Analysis of Plasma Flibanserin AUC and Cmax 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 + Multiple 200 mg Doses of Fluconazole (sponsor's table 11, section 12.2.3).

Parameter	Geometric Mean Ratio (C/A)	90% Confidence Interval for Ratio of Geometric Means
Geometric $AUC_{(0-t)}$	5.59	4.68 – 6.69
Geometric $AUC_{(0-inf)}$	7.02	6.02 – 8.20
Geometric C_{max}	2.24	1.80 – 2.80

Fluconazole Trough Concentrations in Healthy Young Female Subjects (N=15) Following Multiple 200 mg Doses of Fluconazole (sponsor's table 14.2.3, section 14.2).

Table 14.2.3
Summary Statistics for Plasma Fluconazole Concentrations (µg/mL) Pre-Dose on Days 6-11
Pharmacokinetic Population

Visit	Statistics	All Subjects (N=15)
Day 6	n	15
	Mean	0.000
	SD	0.0000
	%CV	0
	Median	0.000
	Min, Max	0.00, 0.00
Day 7	n	15
	Mean	5.645
	SD	0.5765
	%CV	10.2134
	Median	5.570
	Min, Max	4.46, 6.45
Day 8	n	15
	Mean	6.214
	SD	0.9062
	%CV	14.5824
	Median	5.930
	Min, Max	5.01, 7.83
Day 9	n	15
	Mean	6.514
	SD	1.2169
	%CV	18.6820
	Median	6.170
	Min, Max	4.99, 8.78
Day 10	n	15
	Mean	6.709
	SD	1.1571
	%CV	17.2456
	Median	6.370
	Min, Max	4.84, 8.52
Day 11	Mean	7.123
	SD	1.0724
	%CV	15.0548
	Median	6.840
	Min, Max	5.07, 8.98

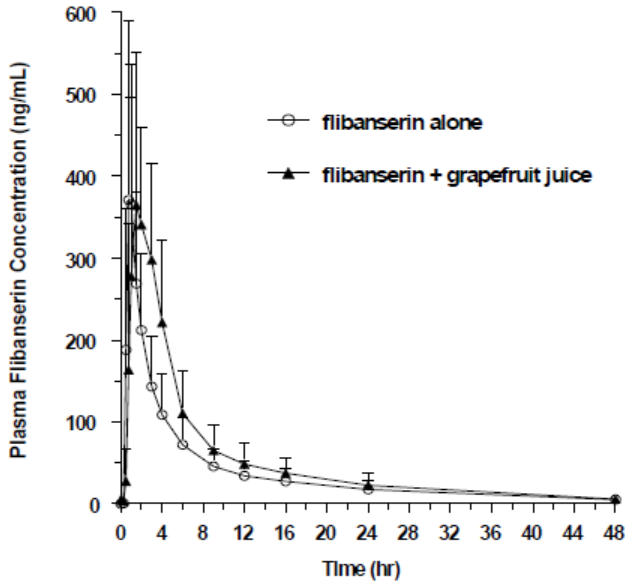
<u>Flibanserin + Grapefruit Juice</u>

Due to concerns that grapefruit juice can inhibit CYP3A4 metabolism, the sponsor evaluated the effect of a single administration of grapefruit juice on flibanserin PK. This study was not conducted at the request of the Division of Bone, Reproductive and Urologic Products or Office of Clinical Pharmacology.

A total of 26 subjects (15 from Group 1 and 11 from Group 2) received a single dose of flibanserin 100 mg with 240 mL of regular strength grapefruit juice. Compared to flibanserin alone, the co-administration of flibanserin and regular strength grapefruit juice resulted in an increase of 10%, 38% and 38% in Cmax, AUC_{0-t} and AUC_{0-inf} of flibanserin, respectively. Median Tmax 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 at 10.6 and 9.9 hrs for flibanserin alone and flibanserin + grapefruit juice, respectively.

The effect of grapefruit juice as a CYP3A4 inhibitor can vary widely due to variability in concentration, dose and preparation. According to the FDA drug interaction guidance, grapefruit juice can be classified as a strong CYP3A4 inhibitor when the juice is high dose/double strength or as a moderate CYP3A4 inhibitor when it is low dose/single strength. Regular strength grapefruit juice was used in this study. For the purpose of potency classification, grapefruit juice is considered a moderate CYP3A4 inhibitor in this study. Subjects in this study received a single administration of regular strength grapefruit juice. For patients who intermittently consumes double strength grapefruit juice or regularly consumes regular or double strength grapefruit juice may observe AEs of greater frequency and/or magnitude.

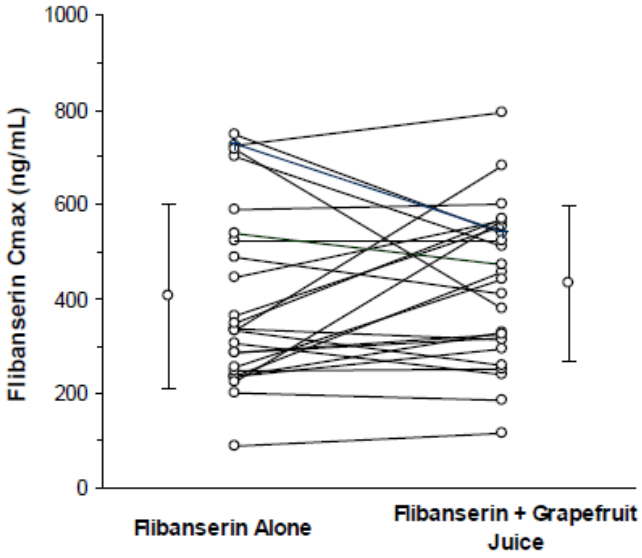
Mean (+SD) Plasma Flibanserin Concentration-Time Profiles in Healthy Young Female Subjects (N=26) Following a Single 100 mg dose of Flibanserin Alone and a Single 100 mg dose of Flibanserin + 240 mL of Grapefruit Juice Administered in the Morning (sponsor's figure 3, section 12.3.1).



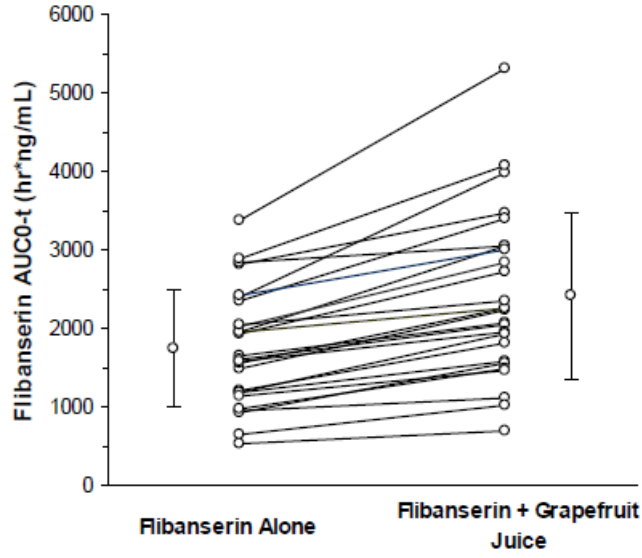
Arithmetic Mean (SD) Plasma Flibanserin PK Parameters in Healthy Young Female Subjects (N=26) Following a Single 100 mg dose of Flibanserin Alone and a Single 100 mg dose of Flibanserin + 240 mL of Grapefruit Juice (sponsor's table 10, section 12.3.2).

	Sequential Treatments (N = 26)	
Pharmacokinetic Parameter	**Flibanserin Alone (Treatment A)**	**Flibanserin + Grapefruit Juice (Treatment B)**
$AUC_{(0\text{-}t)}$ (hr·ng/mL)	1752 (741)	2413 (1057)
$AUC_{(0\text{-}inf)}$ (hr·ng/mL)	1869 [b] (790)	2508 (1142)
f_{ext} (%)	4.04 [b] (2.69)	3.21 (2.35)
C_{max} (ng/mL)	405 (195)	433 (163)
T_{max} (hr)[a]	0.790 (0.750 – 6.00)	1.53 (1.00 – 4.00)
t ½ (hr)	10.6 [b] (3.43)	9.93 (3.05)

Mean(±SD) and Individual Flibanserin Cmax in Healthy Female Subjects (N=26) Following a Single 100 mg Dose of Flibanserin Administered With and Without Grapefruit Juice (sponsor's figure 4, section 12.3.1).



Mean(±SD) and Individual Flibanserin AUC_{0-t} in Healthy Female Subjects (N=26) Following a Single 100 mg Dose of Flibanserin Administered With and Without Grapefruit Juice (sponsor's figure 4, section 12.3.1).



Statistical Analysis of Plasma Flibanserin AUC and Cmax 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 (sponsor's table 13, section 12.2.3).

Parameter	Geometric Mean Ratio (B/A)	90% Confidence Interval for Ratio of Geometric Means
Geometric $AUC_{(0-t)}$	1.38	1.32 – 1.44
Geometric $AUC_{(0-inf)}$	1.38	1.32 – 1.44
Geometric C_{max}	1.10	0.975 – 1.25

Safety Findings

Overall, co-administration of single dose flibanserin and multiple doses of fluconazole resulted in more frequent and profound AEs, compared to flibanserin alone or flibanserin + grapefruit juice. All 15 subjects who received flibanserin + fluconazole experienced at least 1 AE. Hypotension occurred in the flibanserin + fluconazole group only. One of 15 subjects who received flibanserin and fluconazole experienced a severe hypotensive event and required medical intervention. The onset of all three (20%) hypotensive events occurred at approximately the time of maximum flibanserin concentration.

For fatigue, the percentage of subjects who experienced fatigue was 0% (0/15), 69% (18/26), 85% (22/26) and 93% (14/15) who received fluconazole alone, flibanserin alone, flibanserin + grapefruit juice, and flibanserin + fluconazole, respectively.

For dizziness, the percentage of subjects who experienced dizziness was 0% (0/15), 35% (9/26), 27% (7/26) and 20% (3/15) who received fluconazole alone, flibanserin alone, flibanserin + grapefruit juice, and flibanserin + fluconazole, respectively.

For nausea, the percentage of subjects who experienced nausea was 0% (0/15), 27% (7/26), 19% (5/26) and 73% (11/15) who received fluconazole alone, flibanserin alone, flibanserin + grapefruit juice, and flibanserin + fluconazole, respectively.

Hypotension was observed in 3 of 15 subjects treated with flibanserin + fluconazole. No hypotension was observed in the other treatment groups. The following provides details on the hypotension events observed in the three affected subjects:

- Subject #1001 became unresponsive approximately 1 hr postdose when flibanserin was administered with fluconazole on Day 10 on Feb. 20, 2012. She experienced a severe drug-related adverse reaction and had a blood pressure of 64/41 mmHg, heart rate of 50 bpm and unable to speak. She required emergency attention, ammonia inhalant, oxygen and intravenous saline administration. The subject was healthy otherwise and eventually improved with time and became awake and alert.

- Subject #1004 experienced hypotension that lasted approximately 1 hr and was considered mild in severity. It was accompanied by euphoric mood, pallor, nausea, hiccups, and fatigue. The events occurred 36 min to 2 hrs of flibanserin + fluconazole administration.

- Subject #1013 experienced hypotension that lasted approximately 8 min and was considered moderate in severity. The hypotension was accompanied by fatigue and euphoric mood described as "drugged". The subjects AEs occurred within 45 to 67 min of flibanserin + fluconazole administration.

Number of Treatment-Emergent Adverse Events by Treatment Group (sponsor's table 9, section 11.2).

MedDRA SOC Preferred Term	Flibanserin Alone N=26	Flibanserin + Grapefruit Juice N=26	Fluconazole Alone N=15	Flibanserin + Fluconazole N=15
Total Number of Subjects with AEs	22 (84.6)	24 (92.3)	4 (26.7)	15 (100.0)
General disorders and administration site conditions	19 (73.1)	22 (84.6)	1 (6.7)	14 (93.3)
Fatigue	18 (69.2)	22 (84.6)	0 (0.0)	14 (93.3)
Feeling cold	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	10 (38.5)	9 (34.6)	1 (6.7)	6 (40.0)
Dizziness	9 (34.6)	7 (26.9)	0 (0.0)	3 (20.0)
Headache	2 (7.7)	3 (11.5)	1 (6.7)	1 (6.7)
Gastrointestinal disorders	8 (30.8)	6 (23.1)	2 (13.3)	11 (73.3)
Nausea	7 (26.9)	5 (19.2)	0 (0.0)	11 (73.3)
Psychiatric disorders	6 (23.1)	2 (7.7)	2 (13.3)	6 (40.0)
Euphoric mood	4 (15.4)	1 (3.8)	0 (0.0)	4 (26.7)
Respiratory, thoracic and mediastinal disorders	2 (7.7)	0 (0.0)	1 (6.7)	4 (26.7)
Hiccups	2 (7.7)	0 (0.0)	0 (0.0)	4 (26.7)
Vascular disorders	2 (7.7)	0 (0.0)	1 (6.7)	5 (33.3)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	3 (20.0)
Pallor	2 (7.7)	0 (0.0)	0 (0.0)	3 (20.0)

Study SPR-12-02

Title: An Open Label, Sequential Study to Evaluate the Effect of Multiple Doses of Etravirine on the Pharmacokinetics of Flibanserin in Healthy Females

Objectives: The primary objective of this study was to evaluate the effect of multiple daily oral doses (steady-state conditions) of CYP3A4 inducer etravirine on the PK of a single oral 100 mg dose of flibanserin. The secondary objective of this study was to evaluate the safety and tolerability of flibanserin with and without concurrent administration of etravirine in healthy female subjects.

Methods: This was a single center, open-label, sequential study in thirty healthy white young women with a mean (range) age of 33 years (19 - 48), mean (SD) weight of 70 (12) kg, and mean (SD) BMI of 25.8 (4.0) kg/m^2. Subjects were divided into 2 groups of 15 subjects. Subjects in the second group were dosed 8 days after Group 1. Twenty-four subjects completed the study: 4 subjects with protocol violations, 1 subject with BMI of 32.5 (inclusion limit was 32 kg/m^2) and 1 subject took over-the-counter supplements within 12 days of study entry (exclusion criteria prohibited use of medications within 2 weeks of first dose of study drug).

Flibanserin 100 mg tablets were administered as over-encapsulated hard gelatin capsules (size 00). Flibanserin and etravirine tablets were administered orally with 240 mL of room temperature water. Flibanserin is proposed for once daily intake at bedtime with or without food. In this study, flibanserin tablets were administered in the morning within 30 min after consumption of a standard breakfast on Days 1 and 16 following an overnight fast of at least 10 hrs. Etravirine should always be taken following a meal because systemic exposure of etravirine decreased by about 50% when administered under fasting conditions. In this study, etravirine was administered within 30 min after breakfast or dinner.

Period 1
Day 1: single oral dose of flibanserin 100 mg (over-encapsulated) alone in the morning within 30 min after breakfast (Treatment A)

Period 2
Days 3-17: oral dose of etravirine 200 mg (2x100 mg) was given twice daily (every 10-12 hrs). Morning doses were given at the clinic site within 30 min after breakfast. On Days 3-14, the evening dose was taken at home after dinner (approximately 10-12 hrs after the morning dose). Etravirine dosing occurred inpatient beginning on the morning of Day 15 and continued through Day 17.
Day 16: single oral dose of flibanserin 100 mg (over-encapsulated) was taken with morning dose of etravirine within 30 min after breakfast at the clinic (Treatment B)

Study Site: Jasper Clinic, Inc., Kalamazoo, MI
Study Period: March 13, 2012 to May 4, 2012

Treatment Products
Flibanserin: 100 mg tablets were over-encapsulated, lot 013012
Etravirine: Intelence® 100 mg tablets, lot BEL4R00

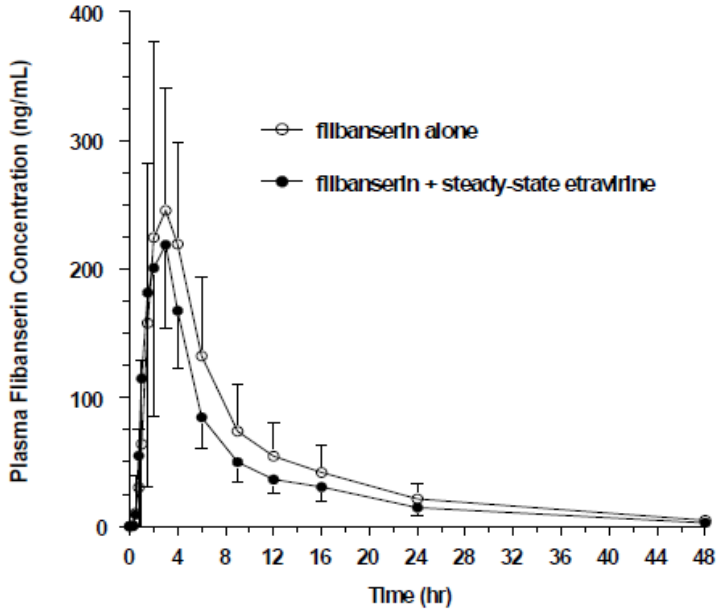
Pharmacokinetic Sampling: Blood samples for determination of flibanserin plasma concentrations were taken on Day 1 and Day 16: predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24 and 48 hrs postdose. The analyses of flibanserin concentrations were performed by (b) (4) using a validated LC-MS/MS method. Blood samples for etravirine trough concentrations were not taken so there is no confirmation steady-state conditions were achieved; however, 13 days of etravirine administration is sufficient to reach steady state prior to flibanserin co-administration.

Results and Reviewer's Comments:
In the CR letter issued August 27, 2010, the OCP noted that co-administration of flibanserin with a strong CYP3A4 inducer resulted in markedly reduced flibanserin plasma concentrations and may compromise the flibanserin efficacy in HSDD patients co-administered strong CYP3A4 inducers. We recommended that the sponsor conduct a drug-drug interaction study to evaluate the effect of co-administration of a moderate CYP3A4 inducer on the PK of flibanserin 100 mg. This recommendation was generated in response to data from the original NDA showing that co-administration of flibanserin 50 mg with multiple doses of rifampin, a strong CYP3A4 inducer, resulted in a 95% decrease in flibanserin exposure.

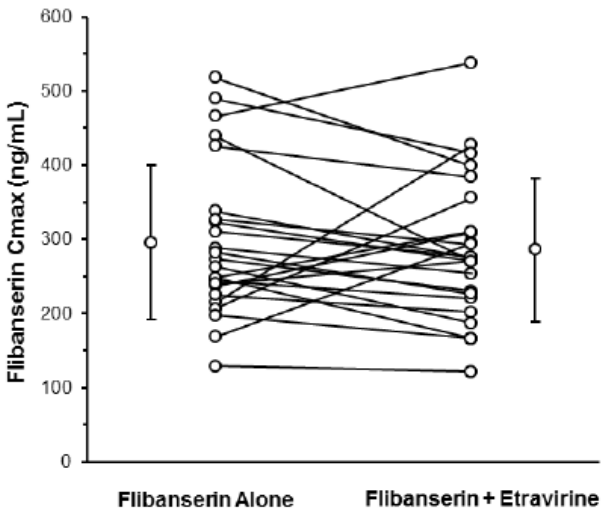
To address this concern, the sponsor conducted a drug-drug interaction study and submitted the new study results in the current resubmission. The sponsor selected etravirine as the moderate CYP3A4 inducer. Etravirine (Intelence®) is approved under NDA 022187 (January 18, 2008) for the treatment of HIV-1 infection. It is available in 25, 100 and 200 mg tablets. According to the etravirine product label, the Tmax is about 2.5 to 4 hrs and elimination half-life is about 41 ($\pm$20) hrs. Etravirine should always be taken following a meal because systemic exposure of etravirine decreased by about 50% when administered under fasting conditions. The recommended oral dose of etravirine in adult patients is 200 mg twice daily following a meal. In this study etravirine 200 mg was given twice daily following a meal for 15 consecutive days. After 13 days (Days 3 - 15) of etravirine alone administration, flibanserin was co-administered with etravirine on Day 16 (within 30 min after breakfast). In general, the study appears to be appropriately designed to maximize CYP3A4 induction.

Co-administration of multiple doses of etravirine and a single dose of flibanserin resulted in a decrease of 3.2% in Cmax and 20.6% in $AUC_{0\text{-inf}}$ of flibanserin, compared to flibanserin alone. Median (range) Tmax of flibanserin was delayed by 0.5 hr (3.0 to 2.5) hrs when flibanserin was administered with etravirine. Mean half-life of flibanserin was similar for flibanserin at 9.8 and 9.2 hrs for flibanserin alone and flibanserin + etravirine, respectively.

Mean$\pm$SD Plasma Flibanserin Concentration-Time Profiles in Healthy Female Subjects (N=24) Following a Single 100 mg Dose of Flibanserin Administered Alone and With Multiple Doses of Etravirine (sponsor's figure 1, section 12.2.1).



Mean+SD and Individual Flibanserin Cmax and AUC0-inf in Healthy Female Subjects (N=24) Following a Single 100 mg Dose of Flibanserin Administered Alone and With Multiple Doses of Etravirine (sponsor's figure 2 section 12.2.2).



Arithmetic Mean (SD) Plasma Flibanserin PK Parameters in Healthy Female Subjects (N=24) Following Administration of a Single 100 mg Dose of Flibanserin Alone and With Multiple Doses of Etravirine (sponsor's table 8, section 12.2.2).

	Sequential Treatments (N =24)	
Pharmacokinetic Parameter	**Flibanserin Alone**	**Flibanserin + Steady-State Etravirine[a]**
AUC0-t (hr·ng/mL)	2153 (859)	1638 (389)
AUC0-inf (hr·ng/mL)	2225[b] (928)	1679 (415)
fext (%)	3.00[b] (1.98)	2.21 (1.53)
Cmax (ng/mL)	296 (104)	286 (96.6)
Tmax (hr)[c]	3.00 (2.00 – 4.00)	2.50 (1.00 – 4.00)
t½ (hr)	9.78[b] (1.97)	9.17 (1.73)

[a] Concomitant flibanserin dosing occurred on 14th day of twice-daily etravirine dosing
[b] N=23
[c] Median (range)

Statistical Analysis of a Single 100 mg Dose Flibanserin + Multiple Dose of Etravirine Versus Flibanserin Alone (sponsor's table 9, section 12.2.3)

Parameter	Geometric Mean Ratio (B/A)	90% Confidence Interval for Ratio of Least-Squares Means
Geometric $AUC_{0\text{-inf}}$	0.794	0.691 – 0.913
Geometric C_{max}	0.968	0.871 – 1.08

Safety Findings

Fatigue, a common AE of flibanserin treatment, was less prominent in the flibanserin + etravirine treatment group (21%), compared to flibanserin alone (47%). Somnolence is common AE of flibanserin therapy and a known, but less common AE of etravirine therapy. The frequency of somnolence increased with co-administration of flibanserin + etravirine (46%), compared with flibanserin alone (20%) group. This suggests that somnolence may be exacerbated when flibanserin is co-administered with somnolence-inducing drugs such as antihistamines and antiparkinson drugs.

Treatment-Emergent Adverse Events by Treatment Group (sponsor's table 7, section 11.2.2).

MedDRA SOC Preferred Term[a]	Flibanserin Alone N=30	Etravirine Alone N=30	Flibanserin + Etravirine N=24
Total Number of Subjects with AEs (%)	22 (73.3)	19 (63.3)	18 (75.0)
General disorders and administration site conditions	15 (50.0)	6 (20.0)	7 (29.2)
Fatigue	14 (46.7)	3 (10.0)	5 (20.8)
Nervous system disorders	10 (33.3)	5 (16.7)	13 (54.2)
Dizziness	3 (10.0)	1 (3.3)	3 (12.5)
Headache	3 (10.0)	5 (16.7)	2 (8.3)
Somnolence	6 (20.0)	0 (0.0)	11 (45.8)
Gastrointestinal disorders	5 (16.7)	10 (33.3)	2 (8.3)
Abdominal distension	0 (0.0)	3 (10.0)	0 (0.0)
Abdominal pain	0 (0.0)	3 (10.0)	0 (0.0)
Psychiatric disorders	1 (3.3)	3 (10.0)	0 (0.0)
Anxiety	0 (0.0)	3 (10.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	6 (20.0)	0 (0.0)
Rash	0 (0.0)	6 (20.0)	0 (0.0)

Study SPR-12-03

Title: A Randomized, Double-Blind, Single-Dose, Five-Way Crossover Study in Healthy Subjects to Determine the Effects of Simultaneous Administration of Flibanserin 100 mg and Varying Concentrations of Ethanol on the Safety and Pharmacodynamic Characteristics of Flibanserin.

Objectives: The primary objective of this study was to evaluate the effect of flibanserin 100 mg administered with ethanol at two different concentrations on seated blood pressure, orthostatic vital signs (when subjects moved from a sitting to a standing position) and oxygen saturation. The secondary objective of this study was to evaluate the safety and tolerability of flibanserin 100 mg with ethanol at two different concentrations.

Methods: This was a single center, randomized, double-blind, single dose, 5-treatment crossover study in twenty-five healthy adult subjects (23 males and 2 females). Twenty-three subjects completed all 5 treatment arms; two subjects withdrew from the study after completing 0.8 g/kg ethanol + placebo treatment arm. Subjects were randomly assigned to 1 of 5 treatment groups (5 subjects per treatment group). The mean (range) age was 30 (21 - 52) years, mean (SD) weight was 80 (13) kg, and mean (SD) BMI was 26 (3.4) kg/m^2. The racial make-up of the subjects were White (76%; N=19); African-American (16%; N=4), Asian (4%; N=1) and Other (4%; N=1).

Treatment A: 0.8 g/kg ethanol diluted to 240 mL with orange juice and administered orally with 1 over-encapsulated flibanserin tablet 100 mg.

Treatment B: 0.8 g/kg ethanol diluted to 240 mL with orange juice and administered orally with 1 matching placebo capsule.

Treatment C: 0.4 g/kg ethanol diluted to 240 mL with orange juice and administered orally with 1 over-encapsulated flibanserin tablet 100 mg.

Treatment D: 0.4 g/kg ethanol diluted to 240 mL 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.

Ethanol (95%) was diluted to 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 (Treatments A, B, C, and D) or orange juice (Treatment E). Subjects were given up to 10 minutes to complete intake of each treatment.

Study Site: Jasper Clinic, Inc, 526 Jasper Street, Kalamazoo, MI 49007

Study Period: June 16, 2012 to July 3, 2012

Treatment Products:
Flibanserin: flibanserin100 mg tablets were over-encapsulated, lot 4000225 (capsule lot 050912B)
Placebo: placebo tablets were over-encapsulated to match the appearance of the active treatment
Ethanol: 95% ethanol (Everclear®) was procured from the study site
Orange juice: orange juice was procured from study site

Safety Monitoring: Safety monitoring included AEs, vital signs, orthostatic vital signs, and clinical laboratory parameters.

Pharmacokinetic Sampling: Blood samples for determination of flibanserin plasma concentrations were taken on Day 1: predose, 0.5, 1, 1.5, 2, 2.5, 3, and 4 hrs following flibanserin administration. The PK endpoint for this study was partial area under the concentration-time curve of flibanserin from 0 to 4 hrs (AUC_{0-4}). The analyses of flibanserin concentrations were performed by (b) (4) using a validated LC-MS/MS method.

Pharmacodynamic Measurements: Vital signs (blood pressure, heart rate and respiration rate), orthostatic vital signs and oxygen saturation were measured at (1) screening; (2) Day -1 of each period; (3) Day 1 of each period at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs postdose; and (4) end of study visit.

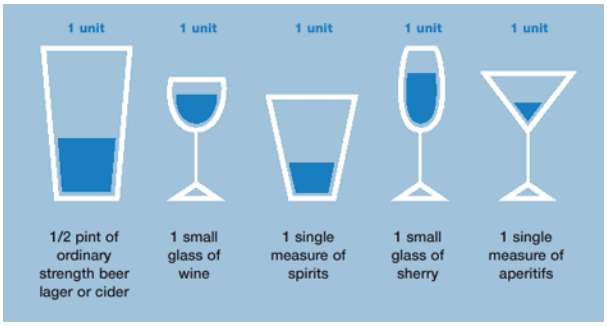
Visual Analog Scale: A Visual Analog Scale was completed by each subject on Day 1 of each period at 0 (predose), 0.5, 1, 1.5, 2, and 4 hrs postdose.

Results and Reviewer's Comments:
The definition of a "standard drink" (also referred to as a "unit") differs from country to country. In Australia and United Kingdom, a standard drink is equal to 10 g of ethanol. In Canada, a standard drink contains approximately 14 g of alcohol. According to the United States' Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/alcohol/faqs.htm#standDrink), a standard drink contains 14 g of pure alcohol. Generally, 14 g of pure alcohol is found in

- 12 oz of beer
- 8 oz of malt liquor
- 5 oz wine
- 1.5 oz or a shot of 80-proof distilled spirits or liquor (e.g., gin, rum, vodka, or whiskey)

Using a mean weight of 70 kg and US standards for alcohol content, subjects receiving 0.4 g of ethanol/kg of body weight would have been given 28 g of pure alcohol (equivalent to two standard drinks). For subjects receiving 0.8 g of ethanol/kg of body weight, they would have received 56 g of pure alcohol (equivalent to 4 standard drinks). According to the Dietary Guidelines for Americans, moderate alcohol consumption is defined as having up to 1 drink per day for women and up to 2 drinks per day for men.

The majority of subjects in this study were males (23 out of 25). For the 0.4 g/kg treatment group, two standard drinks would likely be considered moderate alcohol consumption in males. For the 0.8 g/kg treatment group, four standard drinks would likely be considered high alcohol consumption in males.

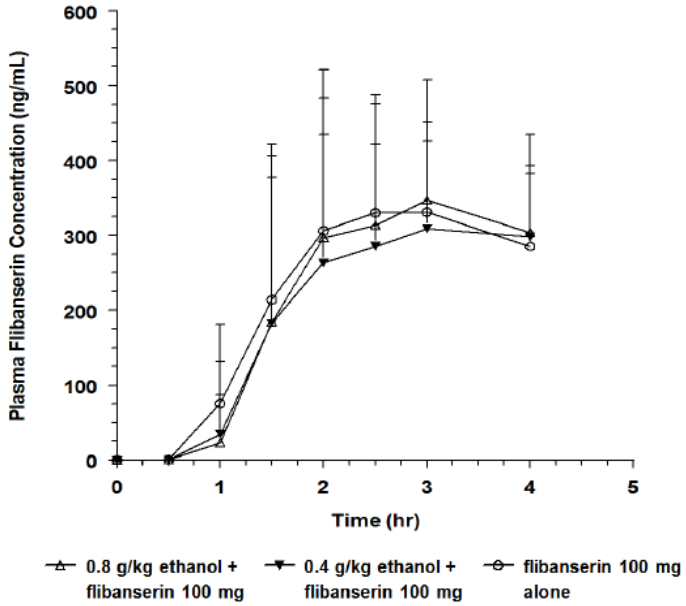


Flibanserin Pharmacokinetics

Flibanserin exposure as measured by partial AUC (AUC_{0-4}) decreased by 10.5% and 3.9% when flibanserin 100 mg was administered with 0.4 and 0.8 g/kg ethanol, respectively, compared to flibanserin

alone. However, considering the inter-subject variability, small number of subjects per treatment group (N=5), and incomplete concentration-time profiles, we have limited data to conclude that ethanol reduces flibanserin exposure.

Mean+SD Plasma Flibanserin Concentration-Time Profiles in Healthy Subjects Following a Single Oral 100 mg Dose of Flibanserin Administered With (0.8 or 0.4 g ethanol/kg body weight) and Without Alcohol (sponsor's figure 1, section 12.2.1).



Arithmetic Mean (SD) Plasma Flibanserin AUC_{0-4} in Healthy Subjects Following a Single 100 mg Dose of Flibanserin Administered With and Without Ethanol (sponsor's table 14, section 12.2.2).

Pharmacokinetic Parameter	Treatment A 0.8 g/kg ethanol + flibanserin 100 mg N=24	Treatment C 0.4 g/kg ethanol + flibanserin 100 mg N=23	Treatment E flibanserin 100 mg N=24
AUC0-4 (hr·ng/mL)	821 (431)	764 (313)	854 (345)

Safety Findings

Treatment-Emergent Adverse Events

The most frequently reported AEs were somnolence, headache, and dizziness. The frequency of somnolence, headache, and dizziness was highest in the group receiving the highest concentration of ethanol (0.8 g/kg) with flibanserin (Treatment group A). The frequency of somnolence in subjects who received 0.8 g/kg ethanol + flibanserin was higher compared to 0.8 g/kg ethanol + placebo: 91.7% vs. 60.0%. The frequency of somnolence in subjects who received 0.4 g/kg ethanol + flibanserin was higher compared to 0.4 g/kg ethanol + placebo: 73.9% vs. 37.5%.

Flibanserin alone resulted in approximately 67% of subjects experiencing somnolence. The addition of ethanol to flibanserin intake increased the frequency of somnolence to approximately 74% and 92% with 0.4 and 0.8 g/kg ethanol, respectively. Alcohol, especially notable at high concentrations, increased the somnolence-inducing effect of flibanserin.

Frequency of Treatment-Emergent Adverse Events by Organ Class Occurring in Three or More Subjects (sponsor's table 13, section 11.6.2).

	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
MedDRA SOC Preferred Term[a]	0.8 g/kg ethanol + flibanserin 100 mg N=24	0.8 g/kg ethanol + placebo N=25	0.4 g/kg ethanol + flibanserin 100 mg N=23	0.4 g/kg ethanol + placebo N=24	flibanserin 100 mg N=24
Total Number (%) of Subjects with AEs	23 (95.8)	17 (68.0)	22 (95.7)	15 (62.5)	19 (79.2)
Nervous System Disorders	22 (91.7)	17 (68.0)	18 (78.3)	12 (50.0)	17 (70.8)
Dizziness	5 (20.8)	3 (12.0)	5 (21.7)	3 (12.5)	4 (16.7)
Headache	6 (25.0)	5 (20.0)	2 (8.7)	5 (20.8)	2 (8.3)
Somnolence	22 (91.7)	15 (60.0)	17 (73.9)	9 (37.5)	16 (66.7)
General Disorders	2 (8.3)	1 (4.0)	4 (17.4)	2 (8.3)	2 (8.3)
Fatigue	1 (4.2)	1 (4.0)	3 (13.0)	2 (8.3)	2 (8.3)
Gastrointestinal Disorders	7 (29.2)	4 (16.0)	5 (21.7)	1 (4.2)	0 (0.0)
Nausea	6 (25.0)	2 (8.0)	5 (21.7)	1(4.2)	0 (0.0)
Stomach Discomfort	1 (4.2)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (8.3)	1 (4.0)	1 (4.3)	1 (4.2)	0 (0.0)
Psychiatric Disorders	3 (12.5)	3 (12.0)	2 (8.7)	1 (4.2)	0 (0.0)
Disorientation	3 (12.5)	2 (8.0)	1 (4.3)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	2 (8.3)	0 (0.0)	1 (4.3)	1 (4.2)	0 (0.0)
Hyperhidrosis	2 (8.3)	0 (0.0)	1 (4.3)	1 (4.2)	0 (0.0)
Vascular Disorders	5 (20.8)	2 (8.0)	3 (13.0)	3 (12.5)	0 (0.0)
Flushing	3 (12.5)	1 (4.0)	1 (4.3)	2 (8.3)	0 (0.0)
Pallor	2 (8.3)	1 (4.0)	1 (4.3)	1 (4.2)	0 (0.0)

Sitting Vital Signs

Of the sitting vital signs measured, the sitting systolic blood pressure was most affected when ethanol was administered with flibanserin. Flibanserin alone decreased sitting systolic blood pressure; however, ethanol had an additive effect on sitting systolic blood pressure. Flibanserin 100 mg alone decreased the maximum sitting systolic blood pressure by 6.6 mmHg. Sitting systolic blood pressure decreased a maximum of 7.6 and 12 mmHg from the baseline when 0.4 and 0.8 g/kg ethanol, respectively, and flibanserin 100 mg were co-administered.

Ethanol also had an additive effect on sitting pulse rate. Flibanserin 100 mg alone increased the maximum sitting pulse rate by 10.1 bpm. Sitting pulse rate increased a maximum of 13.5 and 18.1 bpm from the baseline when 0.4 and 0.8 g/kg ethanol, respectively, and flibanserin 100 mg were co-administered.

The maximum changes from baseline in sitting systolic blood pressure, sitting diastolic blood pressure and sitting pulse rate are highlighted in **yellow** in the table below.

The mean changes from baseline in sitting vital signs are presented in the following table (sponsor's table 7, section 11.2).

	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
	0.8 g/kg ethanol + flibanserin 100 mg	0.8 g/kg ethanol + placebo	0.4 g/kg ethanol + flibanserin 100 mg	0.4 g/kg ethanol + placebo	flibanserin 100 mg
	N=24	N=25	N=23	N=24	N=24
Systolic Blood Pressure					
Baseline[a] Mean, mmHg (SD)	118.5 (11.3)	118.5 (11.3)	118.5 (11.3)	118.5 (11.3)	118.5 (11.3)
Mean Change[b], mmHg (SD)					
Day 1, Hour 0.5	11.7 (11.6)	11.5 (13.9)	8.4 (13.7)	10.2 (13.3)	6.6 (12.7)
Day 1, Hour 1	6.6 (14.6)	8.0 (16.1)	3.7 (11.9)	1.7 (12.6)	2.2 (10.8)
Day 1, Hour 1.5	2.7 (12.8)	3.1 (13.8)	-2.8 (11.2)	0.5 (17.6)	3.1 (11.3)
Day 1, Hour 2	-0.5 (16.1)	-0.2 (13.6)	-3.0 (13.5)	-4.0 (15.1)	2.2 (12.8)
Day 1, Hour 3	-4.6 (16.2)	-4.0 (12.9)	-3.7 (13.0)	-3.7 (15.6)	0.0 (10.9)
Day 1, Hour 4	-5.5 (13.0)	-6.9 (11.6)	-6.5 (11.8)	-4.1 (12.5)	-2.5 (11.2)
Day 1, Hour 6	-12.0 (12.4)	-8.1 (15.8)	-7.6 (13.3)	-5.9 (14.3)	-6.1 (11.6)
Day 1, Hour 8	-10.8 (12.2)	-7.0 (13.2)	-4.9 (13.4)	-5.8 (11.4)	-6.6 (11.5)
Day 1, Hour 12	-4.4 (11.8)	-1.6 (16.5)	-4.4 (11.6)	-2.5 (8.68)	-4.3 (11.0)
Day 1, Hour 24	-3.6 (12.3)	-1.6 (13.5)	-5.6 (11.3)	-4.6 (10.8)	-4.5 (10.8)
Diastolic Blood Pressure					
Baseline[1] Mean, mmHg (SD)	75.2 (8.93)	75.2 (8.93)	75.2 (8.93)	75.2 (8.93)	75.2 (8.93)
Mean Change, mmHg (SD)					
Day 1, Hour 0.5	0.7 (6.95)	0.8 (7.72)	0.2 (6.98)	0.5 (9.63)	0.9 (8.78)
Day 1, Hour 1	-3.1 (7.58)	-3.1 (6.19)	-4.9 (6.54)	-4.4 (9.04)	-2.3 (8.16)
Day 1, Hour 1.5	-3.5 (6.98)	-3.8 (7.90)	-6.5 (7.64)	-6.0 (10.2)	-2.5 (8.29)
Day 1, Hour 2	-4.1 (9.15)	-5.4 (6.77)	-4.4 (8.09)	-6.5 (9.62)	-1.3 (8.58)
Day 1, Hour 3	-5.6 (7.23)	-6.2 (8.29)	-3.7 (6.67)	-5.0 (9.80)	-1.3 (8.98)
Day 1, Hour 4	-2.5 (8.90)	-6.6 (8.39)	-3.3 (6.57)	-1.2 (10.7)	-1.3 (11.0)
Day 1, Hour 6	-9.1 (9.91)	-11.1 (11.1)	-9.3 (8.71)	-9.0 (11.4)	-9.5 (10.2)
Day 1, Hour 8	-10.8 (8.36)	-8.3 (9.66)	-8.1 (10.4)	-7.9 (7.89)	-8.1 (8.95)
Day 1, Hour 12	-6.8 (9.30)	-7.6 (10.6)	-8.1 (9.15)	-7.8 (9.90)	-8.1 (9.17)
Day 1, Hour 24	-4.2 (8.62)	-4.2 (9.38)	-5.4 (8.57)	-5.8 (9.06)	-4.8 (7.81)
Pulse Rate					
Baseline[1] Mean, bpm (SD)	63.9 (9.63)	63.9 (9.63)	63.9 (9.63)	63.9 (9.63)	63.9 (9.63)
Mean Change, bpm (SD)					
Day 1, Hour 0.5	11.9 (12.7)	11.9 (12.7)	8.6 (12.3)	10.0 (13.4)	4.5 (7.62)
Day 1, Hour 1	16.1 (14.1)	13.8 (11.1)	12.3 (10.2)	12.5 (15.2)	7.0 (9.57)
Day 1, Hour 1.5	18.1 (13.7)	17.8 (11.8)	12.1 (9.75)	13.9 (11.0)	10.1 (9.16)
Day 1, Hour 2	14.5 (12.1)	13.4 (8.90)	13.5 (9.79)	11.0 (11.5)	6.3 (10.2)
Day 1, Hour 3	8.0 (10.6)	7.9 (10.4)	6.4 (11.8)	5.9 (10.5)	1.5 (12.7)
Day 1, Hour 4	9.8 (14.1)	5.9 (9.79)	2.9 (12.9)	1.2 (10.3)	-3.7 (10.7)
Day 1, Hour 6	12.7 (12.2)	18.6 (11.4)	6.7 (11.7)	7.2 (8.97)	7.3 (12.4)
Day 1, Hour 8	7.6 (10.7)	9.7 (10.5)	4.5 (11.7)	3.4 (8.40)	1.9 (9.22)
Day 1, Hour 12	9.5 (10.6)	10.2 (8.61)	7.0 (11.1)	6.6 (10.7)	6.6 (11.1)
Day 1, Hour 24	3.2 (12.9)	3.8 (10.7)	4.2 (13.3)	2.6 (10.1)	2.4 (11.9)

Source: Section 14, Table 14.3.4.1

Abbreviations: bpm = beats per minute, SD = standard deviation, N = number of subjects included in mean change from baseline.

[a]Baseline was defined as predose on Period 1, Day 1; N=25 at Baseline for all treatments.

[b] Mean change and standard deviation shown with a maximum of 3 significant figures.

Orthostasis Vital Signs

Orthostatic hypotension as characterized by a decrease of ≥20 mmHg in sitting to standing systolic or diastolic blood pressure was not noted in any of the treatment groups. On the other hand, orthostatic hypotension as characterized by an increase of ≥20 beats per minute (bpm) in sitting to standing pulse rate (3 to 4 time points) was observed when flibanserin was co-administered with ethanol at both concentrations. For flibanserin 100 mg alone, there was no increase in the sitting to standing pulse rate that exceeded 20 bpm. However, there was a trend in increasing pulse rate that approached 20 bpm between 2 and 4 hrs postdose suggesting flibanserin alone possesses hypotensive properties (highlighted in **yellow** in the table below).

Mean changes from sitting to standing pulse rate (sponsor's table 8, section 11.3).

	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E
	0.8 g/kg ethanol + flibanserin 100 mg	0.8 g/kg ethanol + placebo	0.4 g/kg ethanol + flibanserin 100 mg	0.4 g/kg ethanol + placebo	flibanserin 100 mg
	N=24	N=25	N=23	N=24	N=24
Systolic Blood Pressure, mmHg, mean change (SD)[b]					
Baseline[a]	3.7 (11.0)	3.7 (11.0)	3.7 (11.0)	3.7 (11.0)	3.7 (11.0)
Day 1, Hour 0.5	0.1 (11.2)	2.0 (9.53)	4.4 (10.1)	1.6 (12.8)	4.0 (9.03)
Day 1, Hour 1	-1.5 (15.8)	1.1 (10.4)	1.7 (12.7)	2.7 (15.8)	2.2 (9.54)
Day 1, Hour 1.5	-2.7 (14.0)	3.8 (14.3)	0.2 (15.1)	4.0 (12.1)	1.5 (9.17)
Day 1, Hour 2	-1.1(19.4)[c]	0.8 (10.1)	-3.5 (16.4)[e]	2.0 (9.86)	1.8 (14.6)
Day 1, Hour 3	0.9 (10.9)	3.3 (10.6)	-3.7 (18.3)	0.3 (11.0)	1.4 (9.63)
Day 1, Hour 4	-0.0 (13.4)	4.7 (9.01)	0.1 (13.8)	3.8 (11.1)	0.8 (11.3)
Day 1, Hour 6	3.5 (8.38)	5.3 (10.6)[d]	7.6 (11.4)	5.2 (10.2)	5.0 (8.08)
Day 1, Hour 8	4.0 (8.44)	5.0 (12.0)	2.4 (12.8)	4.8 (10.5)	5.5 (7.75)
Day 1, Hour 12	6.4 (10.3)	4.8 (10.8)	8.3 (12.0)	5.5 (11.5)	4.5 (9.45)
Day 1, Hour 24	3.7 (6.95)	3.9 (9.14)	2.5 (8.73)	6.5 (9.78)	6.0 (9.36)
Diastolic Blood Pressure, mmHg, mean change (SD)[b]					
Baseline[a]	5.4 (6.02)	5.4 (6.02)	5.4 (6.02)	5.4 (6.02)	5.4 (6.02)
Day 1, Hour 0.5	4.2 (7.37)	4.6 (5.87)	2.9 (7.24)	4.4 (9.22)	1.5 (7.23)
Day 1, Hour 1	4.7 (9.85)	4.1 (7.10)	6.3 (7.86)	6.3 (8.46)	5.2 (6.51)
Day 1, Hour 1.5	1.9 (7.60)	2.8 (8.94)	3.1 (8.70)	6.1 (9.08)	4.8 (5.88)
Day 1, Hour 2	3.9 (8.74)[c]	3.3 (6.80)	1.7 (14.8)[e]	5.4 (7.98)	5.0 (6.05)
Day 1, Hour 3	4.5 (9.11)	4.9 (5.61)	2.2 (9.74)	6.2 (8.86)	5.5 (9.31)
Day 1, Hour 4	1.4 (8.11)	5.4 (5.65)	3.8 (7.98)	4.5 (5.63)	7.0 (6.37)
Day 1, Hour 6	3.8 (6.31)	5.6 (7.19)[d]	6.0 (5.10)	6.2 (5.27)	8.1 (7.45)
Day 1, Hour 8	6.3 (5.81)	6.2 (5.64)	3.6 (7.60)	6.8 (6.54)	4.5 (5.98)
Day 1, Hour 12	5.3 (5.98)	6.9 (4.74)	6.6 (5.61)	7.0 (3.71)	8.0 (5.60)
Day 1, Hour 24	5.3 (7.74)	7.2 (7.30)	5.3 (6.33)	7.6 (5.37)	6.0 (5.57)
Pulse Rate, bpm, mean change (SD)[b]					
Baseline[a]	11.8 (8.18)	11.8 (8.18)	11.8 (8.18)	11.8 (8.18)	11.8 (8.18)
Day 1, Hour 0.5	12.6 (7.83)	11.4 (14.2)	13.4 (8.21)	13.4 (8.15)	10.5 (7.29)
Day 1, Hour 1	17.4 (10.7)	18.5 (9.55)	17.3 (9.28)	18.0 (9.99)	13.9 (10.7)
Day 1, Hour 1.5	19.6 (9.32)	17.6 (10.6)	20.2 (9.35)	18.2 (12.5)	14.1 (8.17)
Day 1, Hour 2	23.2 (9.51)[c]	19.8 (11.8)	17.2 (17.8)[e]	18.8 (10.3)	17.2 (10.0)
Day 1, Hour 3	28.9 (13.5)	21.7 (11.2)	21.4 (15.4)	17.2 (11.4)	19.1 (13.2)
Day 1, Hour 4	22.9 (13.4)	18.5 (11.3)	20.4 (9.47)	14.4 (9.00)	18.8 (9.32)
Day 1, Hour 6	16.3 (9.20)	12.8 (15.1)[d]	13.0 (7.21)	13.8 (8.68)	11.7 (6.97)
Day 1, Hour 8	12.4 (6.65)	13.2 (6.60)	10.5 (7.70)	13.5 (8.66)	9.8 (6.63)
Day 1, Hour 12	10.8 (6.37)	13.8 (8.30)	8.3 (7.24)	12.4 (9.69)	11.3 (7.63)
Day 1, Hour 24	10.9 (5.51)	14.8 (9.49)	10.1 (8.52)	13.6 (8.77)	15.4 (8.07)

Source: Section 14, Table 14.3.4.3a
Abbreviations: bpm = beats per minute, SD = standard deviation, N = number of subjects.
[a] Baseline was defined as predose on Day 1 of Period 1. N=25 at baseline for all treatments.
[b] Mean change and standard deviation are shown with a maximum of 3 significant figures.
[c] N = 23
[d] N = 24
[e] N = 21

Study SPR-12-04

Title: A Two-Stage, Double-Blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Evaluation of Standard and Supratherapeutic Single Doses of Flibanserin in Healthy Females

Objectives: The primary objective of the study was to evaluate orthostatic changes following therapeutic dose and supratherapeutic single oral doses of flibanserin. The secondary objective was to evaluate the PK of flibanserin following therapeutic and supratherapeutic single oral doses of flibanserin in healthy premenopausal female subjects.

Methods: This was a single center, 2-stage, 3-treatment, double-blind, placebo-controlled, single dose study in twelve healthy female subjects. The mean (range) age was 31 (18 - 45) years, mean (SD) weight was 75 (12) kg, and mean (SD) BMI was 28.2 (3.8) kg/m^2. All subjects were White. Flibanserin was administered at approximately 9 am with 240 mL room temperature water after an overnight fast of at least 10 hrs.

Stage 1 was a sequential, ascending dose (100, 150 and 200 mg), cross-over study that included 3 cohorts (4 subjects each). Dosing within a period was staggered by 24 hrs: 2 subjects from each cohort received treatment and the remaining 2 subjects in the respective cohort received treatment 24 hrs later. Subjects were confined to the clinical site from Day -1 until the morning of Day 3 for each period and were discharged from the clinical site between periods. There were 7 days separating Day 1 of each period for each subject during Stage 1.

Stage 1: Planned Sequential Ascending Dose Crossover

Cohort (Sequence)	Number of Subjects	Flibanserin Single Dose Treatment		
		Period 1	Period 2	Period 3
1	4	100 mg	Placebo	200 mg
2	4	Placebo	150 mg	200 mg
3	4	100 mg	150 mg	Placebo

Stage 2 was a randomized, double-blind, placebo-controlled, sequential, single, ascending-dose (250 and 300 mg) study that included 2 cohorts (8 subjects each). Dosing within a period was staggered by 24 hrs: 2 subjects from each cohort received treatment and the remaining 6 subjects in the respective cohort received treatment 24 hrs later. Cohorts 4 and 5 each consisted of 6 subjects (flibanserin) and 2 subjects (placebo).

Stage 2: Planned Sequential Ascending Dose Cohorts

Cohort	Number of Subjects	Treatment (Flibanserin Single Dose or Placebo)
4	6	250 mg
	2	Placebo
5	6	300 mg
	2	Placebo

The sponsor and clinical investigator evaluated the blinded safety results from Cohort 4 before dosing of Cohort 5. If 3 or 8 subjects (~38%) experienced moderate to severe AEs related to drug treatment, then dose escalation to 300 mg would not occur.

Study Site: Jasper Clinic, Inc, 526 Jasper Street, Kalamazoo, MI 49007

Study Period: May 22, 2012 to June 22, 2012

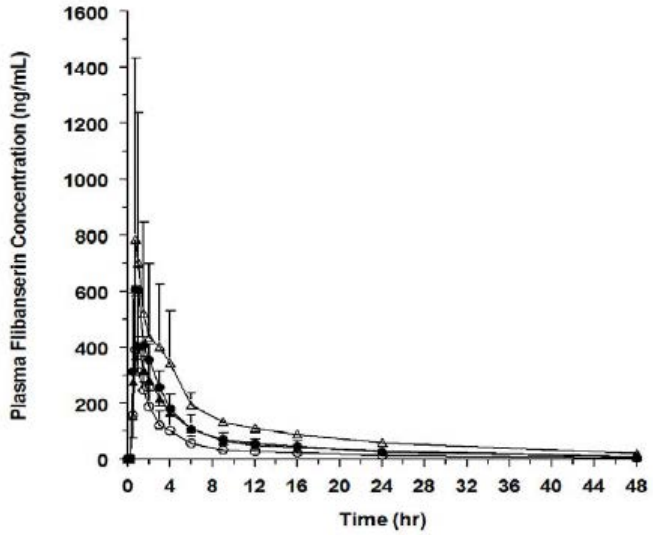
Treatment Products:
Flibanserin: flibanserin 50 and 100 mg tablets were over-encapsulated in size 00 hard, gelatin capsules, lots 4000224 and 4000225 (capsule lots 050912A and 050912B)
Placebo: placebo tablets were over-encapsulated to match the appearance of the active treatment

Pharmacokinetic Sampling: Blood samples for determination of flibanserin plasma concentrations were taken on Day 1 of each period or cohort: predose (within 10 min of dosing), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24 and 48 hrs following flibanserin administration. The analyses of flibanserin concentrations were performed by (b) (4) using a validated LC-MS/MS method.

Results and Reviewer's Comments:
Following a single 100 mg dose of flibanserin in healthy premenopausal women (N=8), mean (SD) Cmax was 419 (206) ng/mL and mean (SD) $AUC_{0\text{-}inf}$ 1543 (511) ng.hr/mL. Median (range) Tmax was 0.75 (0.75 – 4.0) hrs and mean (SD) $t_{1/2}$ was 11.7 (1.9) hrs.

Cmax of flibanserin appears to be dose proportional from 100 to 250 mg following administration of flibanserin tablets. For $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, flibanserin exposure appears to be greater than dose proportional from 100 to 250 mg. In the original NDA and based upon $AUC_{0\text{-}24}$ in healthy male subjects, dose proportionality was observed with flibanserin capsules for doses 0.2 to 150 mg (Study 511.1, see review in DARRTS August 26, 2010).

Mean+SD Plasma Flibanserin Concentration-Time Profiles in Healthy Premenopausal Women Following a Single Oral Dose of Flibanserin (sponsor's figure 1, section 12.1.1).



Arithmetic Mean (SD) Plasma Flibanserin PK Parameters in Healthy Premenopausal Women Following a Single Oral Dose of Flibanserin (sponsor's table 24, section 12.1.2).

	Stage 1 (Cohorts 1-3) [a] Ascending Dose Crossover (N=12)			Stage 2 [a] Cohort 4
Pharmacokinetic Parameter	**Flibanserin 100 mg (n=8)**	**Flibanserin 150 mg (n=8)**	**Flibanserin 200 mg (n=7)**	**Flibanserin 250 mg (n=6)**
$AUC_{0\text{-}t}$ (hr·ng/mL)	1485 (503)	2516 (969)	2809 (606)	4842 (1355)
$AUC_{0\text{-}inf}$ (hr·ng/mL)	1543 (511)	2674 (1099)	2982 (724)	5390 (1580)
fext (%)	4.02 (2.79)	4.79 (4.11)	5.15 (5.80)	9.58 (7.91)
Cmax (ng/mL)	419 (206)	529 (246)	675 (241)	822 (615)
Tmax (hr)[b]	0.750 (0.75 – 4.00)	1.00 (0.50 – 4.00)	1.00 (0.50 – 1.10)	0.875 (0.75 – 6.00)
t ½ (hr)	11.7 (1.94)	11.2 (3.94)	11.5 (5.02)	15.3 (6.62)
CL/F (L/hr)	72.0 (25.5)	68.2 (35.7)	71.6 (22.5)	49.9 (14.8)
Vz/F (L)	1236 (556)	1005 (425)	1154 (538)	1057 (400)
$AUC_{0\text{-}t}$/D (hr·ng/mL/mg)	14.85 (5.03)	16.77 (6.46)	14.05 (3.03)	19.37 (5.42)
$AUC_{0\text{-}inf}$/D (hr·ng/mL/mg)	15.43 (5.11)	17.83 (7.32)	14.91 (3.62)	21.56 (6.32)
Cmax/D (ng/mL/mg)	4.19 (2.06)	3.53 (1.64)	3.37 (1.21)	3.29 (2.46)

Safety Findings:

For Stage 1, the most commonly reported AEs were dizziness, somnolence, and nausea. Somnolence occurred frequently in all flibanserin treatment periods: 75.0% (6/8) of subjects who received 100 mg flibanserin; 62.5% (5/8) of subjects who received 150 mg flibanserin; 85.7% (6/7) of subjects who received 200 mg flibanserin, and 41.7% (5/12) of subjects who received placebo.

Treatment-Emergent Adverse Events Reported in >2% Subjects for all Treatment Groups in Stage 1 (sponsor's table 20, section 11.3.2).

	Flibanserin			
MedDRA SOC Preferred Term	**100 mg N=8**	**150 mg N=8**	**200 mg N=7**	**Placebo N=12**
Total Number (%) of Subjects with AEs	8 (100.0%)	8 (100.0%)	7 (100.0%)	5 (41.7%)
Nervous system disorders				
Dizziness	1 (12.5%)	3 (37.5%)	6 (85.7%)	1 (8.3%)
Somnolence	6 (75.0%)	5 (62.5%)	6 (85.7%)	5 (41.7%)
Gastrointestinal disorders				
Nausea	1 (12.5%)	1 (12.5%)	4 (57.1%)	1 (8.3%)
Vomiting	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)
Psychiatric disorders				
Disorientation	3 (37.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)

For Stage 2, 100% of subjects reported at least 1 AE. The most commonly reported AEs were dizziness (83%), somnolence (83%), and nausea (67%). All 6 subjects who received a single 250 mg dose of flibanserin reported moderate to severe AEs (fatigue, somnolence and disorientation). The stopping criteria were at least 3 of 8 subjects experiencing moderate to severe drug-related AEs. Due to the

number of subjects reporting moderate to severe AEs, dose escalation stopped after 250 mg. The 300 mg dose was not evaluated.

Treatment-Emergent Adverse Events Reported in >2% Subjects for all Treatment Groups in Stage 2 (sponsor's table 21, section 11.3.2).

	Cohort 4	
MedDRA SOC **Preferred Term**	**250 mg Flibanserin** **N=6**	**Placebo** **N=2**
Total Number (%) of Subjects with AEs	6 (100.0%)	0 (0.0%)
Nervous system disorders		
Dizziness	5 (83.3%)	0 (0.0%)
Somnolence	5 (83.3%)	0 (0.0%)
Gastrointestinal disorders		
Nausea	4 (66.7%)	0 (0.0%)

Study 511.158

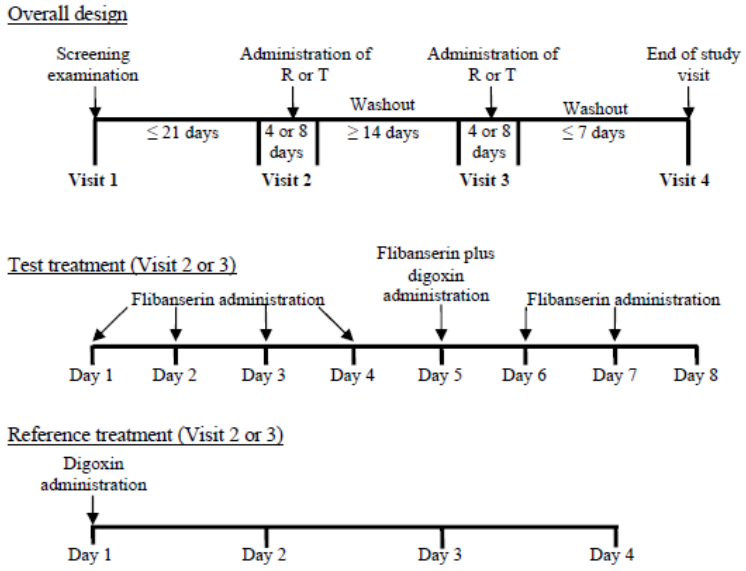
Title: An Open-Label Two-Way, Cross-Over Study to Evaluate the Effect of Multiple Doses of Flibanserin 100 mg film-coated Tablets Given Once Daily on the Single Dose Pharmacokinetics of Digoxin 0.5 mg in Healthy Male and Female Volunteers.

Objective: To evaluate the effect of multiple doses of flibanserin on the single dose PK of digoxin.

Methods: This was a single center, open-label, randomized, two-way crossover study in twenty-four healthy male (N=11) and female (N=13) subjects. The mean (range) age was 38 (18 - 55) years, mean (SD) weight was 70 (12) kg, and mean (SD) BMI was 23.5 (3.1) kg/m^2. All subjects were White. According to Lanoxin label, "When LANOXIN Tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged". In order to capture the effect of flibanserin on digoxin PK, digoxin should be administered without food. In this study, digoxin was given without food. The overall study design is acceptable.

Flibanserin + Digoxin Group (Test Group): On Days 1 and 2, subjects received 1 dose of flibanserin 100 mg tablet at approximately 8 pm. On Days 3 and 4, subjects received 1 dose of flibanserin 100 mg tablet approximately 8 am. On Day 5, subjects received 1 dose of flibanserin 100 mg and 1 dose of digoxin 0.5 mg (2 x 0.25 mg tablets) at approximately 8 am without food, following an overnight fast of 10 hrs. Water was permitted ad lib except for 1 hr before and 1 hr after flibanserin + digoxin administration. On Days 6 and 7, subjects received 1 dose of flibanserin 100 mg tablet at approximately 8 am. All tablets were administered with 240 mL room temperature water.

Digoxin Group (Reference Group): On Day 1, subjects received 1 dose of digoxin 0.5 mg (2 x 0.25 mg tablets) at approximately 8 am without food, following an overnight fast of 10 hrs. Water was permitted ad lib except for 1 hr before and 1 hr after digoxin administration.



Study Site: Boehringer Ingelheim Pharma GmbH & Co KG, Human Pharmacology Centre, Birkendorfer Strasse 65, 88397 Biberach, Germany

Study Period: June 8, 2010 to July 15, 2010

Treatment Products:
Flibanserin: flibanserin 100 mg film-coated tablets (batch no. 059056)
Digoxin: digoxin 0.25 mg tablets (batch no. 0701 [redacted].)
Placebo: placebo tablets were over-encapsulated to match the appearance of the active treatment

Pharmacokinetic Sampling: For determination of digoxin plasma concentrations blood samples were taken on Day 1 of each period or cohort: -0.5 (predose), 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, 24, 48 and 72 hrs following digoxin administration in both treatment and reference arms. For determination of flibanserin plasma concentrations, blood samples were taken -0.5 hr before flibanserin administration on Days 1 and 4. On Day 5, blood samples were taken for determination of flibanserin plasma concentrations at -0.5, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 48 and 72 hrs after flibanserin and digoxin co-administration on Day 5.

The analysis of digoxin was conducted by [redacted] using LC-MS/MS.
The analysis of flibanserin concentrations was performed by [redacted] using a validated LC-MS/MS method.

Results and Reviewer's Comments:
Digoxin is commonly used in adults for congestive heart failure and atrial fibrillation. Digoxin has a narrow therapeutic index so its use requires dose titration for efficacy response and monitoring of digoxin toxicity. Digoxin is a substrate P-glycoprotein (P-gp) and is commonly used as a probe in drug interaction studies to evaluate potential P-gp substrates and/or inhibitors. Flibanserin is indicated for use in premenopausal women but use in postmenopausal women is being explored. Therefore, the sponsor decided to evaluate the potential in vivo interaction of digoxin and flibanserin.

Digoxin is available in 0.125 and 0.25 mg tablets. The recommended maintenance dose in adults is 3.4 to 5.1 µg/kg/day given once daily. For an average man of 70 kg, the maintenance dose is approximately is 0.2 to 0.4 mg per day. Peak digoxin concentrations occur 1 to 3 hrs postdose and digoxin has a half-life of approximately 36 to 48 hrs. Food affects Tmax and Cmax, but not AUC. Based upon the known PK of flibanserin and digoxin, the study design is acceptable.

Digoxin exposure increased by 46%, 62% and 96% for Cmax, AUC_{0-t}, and AUC_{0-inf}, respectively, following multiple doses of flibanserin 100 mg co-administered with a single dose of digoxin 0.5 mg. A 2-fold increase in digoxin AUC suggests flibanserin may be a P-gp inhibitor. Due to the narrow margin for efficacy and safety, this increase in digoxin systemic exposure can shift a patient from a safe maintenance dose to a toxic dose. The sponsor is silent about this drug interaction in their proposed label. This reviewer recommends inclusion of these results in the label and advise monitoring of digoxin toxicity and possible digoxin dose reduction when flibanserin is used in patients on digoxin therapy. The label should state that flibanserin may be a substrate/inhibitor of P-gp.

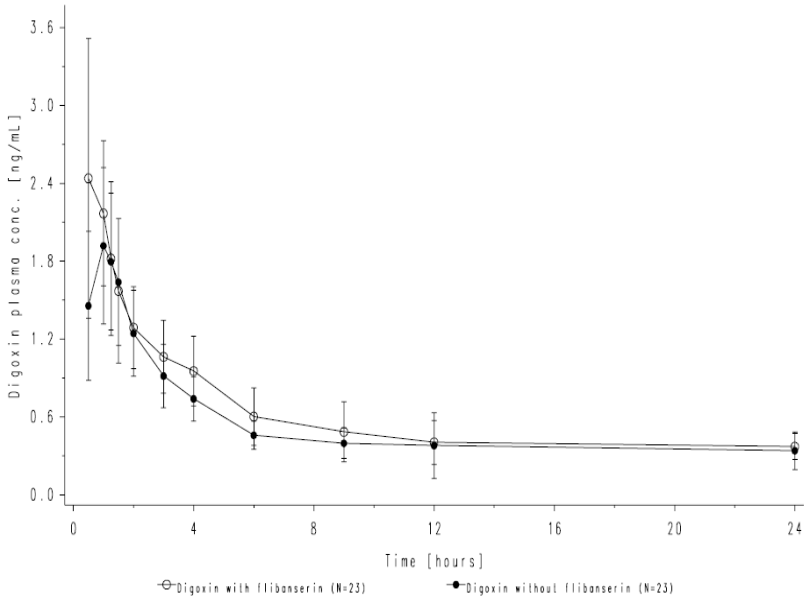
In the original NDA, the sponsor concluded that flibanserin is not a P-gp or multidrug resistance protein (MDR) substrate and that P-gp was not involved in flibanserin absorption, based upon in vitro study in Caco-2 cells. From Study U05-1240 in the original NDA, the sponsor concluded that flibanserin (60 µM; target concentration) partly increased the apical-to-basal transport of digoxin without affecting the basolateral to apical transport of digoxin. The sponsor concluded that increase of digoxin transport is not related to P-gp inhibition because flibanserin did not inhibit both a-b and b-a transport commonly observed with known P-gp inhibitors such as cyclosporine A and verapamil.

In this resubmission, the sponsor claimed that the shape of the digoxin plasma concentration-time profiles were similar for both treatment groups and concluded the increase in digoxin exposure was moderate based upon digoxin AUC_{0-24} (25% increase). The sponsor stated flibanserin transport is not mediated via

P-gp because an 8% reduction in digoxin renal clearance ($CL_{R,0-24}$) was observed and was considered not relevant.

This reviewer disagrees with the sponsor. Although the shapes of the PK profiles are similar, there was clearly an increase in digoxin exposure when flibanserin was administered with digoxin. Based upon digoxin AUC_{0-inf}, not AUC_{0-24}, digoxin exposure increased by 96% with flibanserin administration. Digoxin Cmax increased by 46%. The 8% reduction in digoxin renal clearance was based upon urine samples calculated from 0 to 24 hrs. Based upon figure 11.5.2.2:1, the reduction in digoxin renal clearance with flibanserin administration appears to be greater at 72 hrs. Finally, in assessing clinical drug interaction between flibanserin and digoxin, use of Cmax and AUC ratio is more direct and sensitive compared to renal clearance ratio due to the nature of sample collection (plasma versus urine). In conclusion, the in vivo study with flibanserin + digoxin co-administration suggests that P-gp is involved with flibanserin transport and labeling should reflect the findings.

Mean Plasma Concentration-Time Profiles of Digoxin After a Single Oral Dose of Digoxin 0.5 mg With and Without Co-administration of Flibanserin 100 mg (sponsor's figure 15.6.5.3:7, section 15.6.5.3).



Geometric Mean PK Parameters of Digoxin Following a Single Administration of 0.5 mg Digoxin With and Without Multiple Doses of 100 mg Flibanserin (N=23) (sponsor's table 11.5.2.3:1. Section 11.5.2).

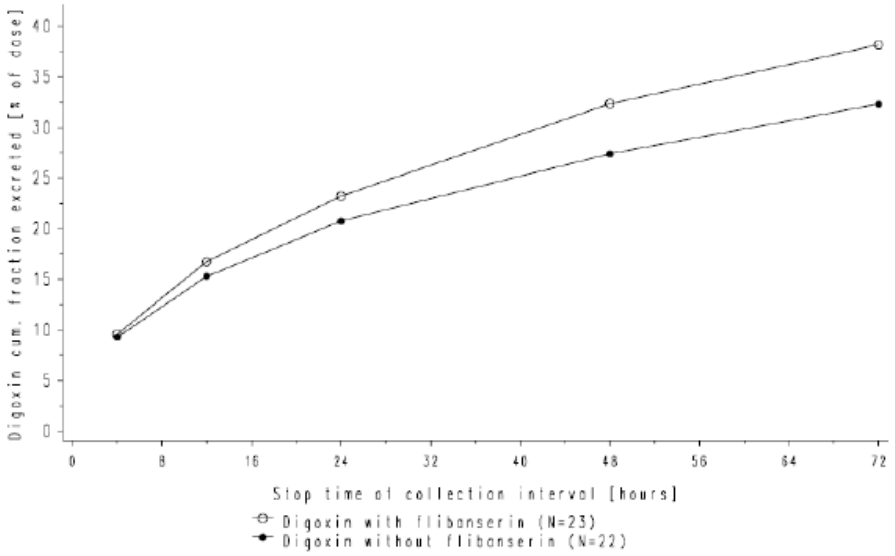
			With co-administration of flibanserin (test)		Without co-administration of flibanserin (reference)	
Parameter	Unit	N	gMean	gCV [%]	gMean	gCV [%]
C_{max}	[ng/mL]	[23/23]	2.88	22.1	1.98	29.4
$AUC_{0-\infty}$	[ng·h/mL]	[22/23]	50.0	45.9	25.9	70.5
AUC_{0-tz}	[ng·h/mL]	[23/23]	21.2	55.7	13.2	59.1
AUC_{0-24}	[ng·h/mL]	[23/23]	14.3	21.9	11.5	32.5
t_{max}*	[h]	[23/23]	0.500	(0.483-2.02)	1.00	(0.500-2.00)
$t_{1/2}$	[h]	[22/23]	64.4	59.4	31.3	114
MRT_{po}	[h]	[22/23]	84.4	62.5	40.5	111
CL/F	[mL/min]	[22/23]	167	45.9	322	70.5
V_z/F	[L]	[22/23]	930	38.3	873	39.1
Ae_{0-24}	[µg]	[23/22]	116	20.8	104	26.1
fe_{0-24}	[%]	[23/22]	23.2	20.8	20.8	26.1
$CL_{R,0-24}$	[mL/min]	[23/22]	135	20.5	149	25.1

*For t_{max} the median and range are given

Statistical Analysis of Digoxin Following a Single Administration of 0.5 mg Digoxin With and Without Multiple Doses of 100 mg Flibanserin (N=23) (sponsor's table 11.5.2.5:1. Section 11.5.2).

Parameter	Test		Reference		Ratio	2-sided 90% CI		Intra-indiv.
	N	Adjusted gMean	N	Adjusted gMean	Test/Ref. [%]	Lower limit [%]	Upper limit [%]	gCV [%]
C_{max} [ng/mL]	23	2.88	23	1.98	145.54	130.42	162.42	21.9
$AUC_{0-\infty}$ [ng·h/mL]	22	50.03	23	25.58	195.55	151.19	252.93	53.3
$CL_{R.0-24}$ [mL/min]	23	135.42	22	146.99	92.13	84.59	100.34	16.6
AUC_{0-tz} [ng·h/mL]	23	21.22	23	13.10	162.00	133.70	196.30	39.2
AUC_{0-24} [ng·h/mL]	23	14.32	23	11.44	125.14	112.20	139.56	21.7

Geometric Mean Cumulative Fractions of Digoxin Excreted in Urine Over 72 hrs following Digoxin + Flibanserin and Digoxin Alone Administration in Healthy Male and Female Subjects (N=23) (sponsor's figure 11.5.2.2:1, section 11.5.2).



Safety Findings

Flibanserin Only Treatment

All 24 subjects (100%) who received once daily administration of flibanserin 100 mg (4 doses) experienced at least 1 drug-related AE between Day 1 (flibanserin administration) until Day 5 co-administration of flibanserin + digoxin (84-hr period). Fatigue, dizziness, somnolence, and headache were the most common AEs and were mild to moderate in severity. However, two healthy subjects (Subject #5 and Subject #6) experienced severe AEs - syncope followed by circulatory collapse and somnolence - that occurred around the time of maximum flibanserin concentration (0.5 to 1 hr). Details of the severe AEs observed in the two subjects follow:

- 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 at 29 min after flibanserin administration and continued for 2 hrs. The subject required medical treatment consisting of 500 mL intravenous (IV) glucose with electrolytes. Severe vomiting was reported 54 min after flibanserin administration and occurred twice in a period of 15 min. The subject was treated with 10 mL IV dimenhydrinate for severe vomiting. The subject also suffered severe fatigue and mild asthenia. The subject was discontinued from the study.

- Subject #6 was a 48 year-old women with somnolence of severe intensity and recovered without medical intervention.

Flibanserin + Digoxin Treatment

Twenty-two of 23 (96%) subjects who received flibanserin 100 mg + digoxin 0.5 mg experienced drug-related AEs during a 72-hr period after flibanserin + digoxin dosing. Fatigue, dizziness, somnolence, headache, hiccups and nausea were the most common AEs and were mild to moderate in severity. Two healthy subjects (Subject #1 and Subject #13) experienced severe nausea; they recovered without medical intervention.

Digoxin Only Treatment

Three of 23 (13%) subjects who received a single dose of digoxin 0.5 mg experienced AEs during a 72-hr period after digoxin dosing. Hematoma, diarrhea and back pain were reported most frequently and were considered mild in intensity. Only diarrhea was considered drug related.

Table 12.2.2: 1 Frequency of subjects with adverse events by treatment and primary system organ class - Treated set

System organ class/ preferred term	Flib[1]	Flib+Digo[2]	Digo[3]	Washout/ post-treatment	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Subjects treated	24 (100.0)	23 (100.0)	23 (100.0)	24 (100.0)	24 (100.0)
Total with any AE	24 (100.0)	22 (95.7)	3 (13.0)	1 (4.2)	24 (100.0)
Psychiatric disorders/	5 (20.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (20.8)
Insomnia	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)
Restlessness	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)
Euphoric mood	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Nervous system disorders/	17 (70.8)	12 (52.2)	0 (0.0)	0 (0.0)	19 (79.2)
Dizziness	12 (50.0)	8 (34.8)	0 (0.0)	0 (0.0)	14 (58.3)
Somnolence	5 (20.8)	6 (26.1)	0 (0.0)	0 (0.0)	9 (37.5)
Headache	4 (16.7)	1 (4.3)	0 (0.0)	0 (0.0)	5 (20.8)
Paraesthesia	1 (4.2)	1 (4.3)	0 (0.0)	0 (0.0)	2 (8.3)
Disturbance in attention	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Eye disorders/	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)
Eye pain	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Eyelid disorder	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Cardiac disorders/	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.2)
Palpitations	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.2)
Vascular disorders/	1 (4.2)	0 (0.0)	1 (4.3)	0 (0.0)	2 (8.3)
Haematoma	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.2)
Circulatory collapse	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Respiratory, thoracic, and mediastinal disorders/	0 (0.0)	5 (21.7)	0 (0.0)	0 (0.0)	5 (20.8)
Hiccups	0 (0.0)	5 (21.7)	0 (0.0)	0 (0.0)	5 (20.8)
Gastrointestinal disorders/	5 (20.8)	3 (13.0)	1 (4.3)	1 (4.2)	9 (37.5)
Diarrhoea	2 (8.3)	0 (0.0)	1 (4.3)	1 (4.2)	4 (16.7)
Nausea	1 (4.2)	3 (13.0)	0 (0.0)	0 (0.0)	4 (16.7)
Dysphagia	1 (4.2)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.2)
Dry mouth	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Vomiting	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
Skin und subcutaneous tissue disorders/	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.2)
Hyperhidrosis	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	1 (4.2)
Musculoskeletal and connective tissue disorders/	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.2)
Back pain	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.2)
General disorders and administration site conditions/	23 (95.8)	18 (78.3)	0 (0.0)	0 (0.0)	24 (100.0)
Fatigue	23 (95.8)	18 (78.3)	0 (0.0)	0 (0.0)	24 (100.0)
Asthenia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)

Study 511.146

Title: An Eight Day Open-Label Trail to Evaluate the Single Dose and Steady State Pharmacokinetics of 100 mg Flibanserin Administered Orally Once Daily in Post-Menopausal Women with Hyposexual Desire Disorder

Objectives: The objectives of the study were to assess the single dose and multiple dose PK of flibanserin and metabolites in postmenopausal women with HSDD and to compare the systemic exposure of flibanserin and metabolites between elderly (≥65 years) and younger (<65 years) patients.

Method: This study was a multi-center, multiple dose, open-label study in twenty-four naturally postmenopausal women with HSDD. For all twenty-four subjects, the mean (range) age was 60 (46 - 75) years, mean (SD) weight was 73 (16) kg, and mean (SD) BMI was 28 (5.3) kg/m^2. The racial make-up of the subjects were White (92%; N=22); African-American (4%; N=1) and Hawaiian/Pacific Islander (4%; N=1). The sponsor stratified the study population by age with 65 years as the cutoff. The mean (range) age for younger and elderly patients was 55 (46 - 64; N=16) and 69 (65 - 75; N=8) years, respectively.

The treatment period consisted of eight days. Patients remained in the clinic overnight on Day 1. In the evening of Days 2 to 7, patients returned to the clinical site for predose PK sampling and assessment of concomitant therapy, AEs and vital signs. In the evening of Day 8, patients stayed overnight at the clinical site for assessment of concomitant therapy, AEs, vital signs, and PK sampling (pre- and postdose). Patients were permitted to leave the clinical site after the 12-hr postdose PK sampling and returned to the clinical site on Days 9 to 11 for assessment of concomitant medications, AEs and vital signs.

Each patient was instructed to take each dose with 150 mL of fluid (no specific type indicated) once daily in the evening as close as possible to the same time each day.

Study Site: New Orleans Center for Clinical Research – Knoxville, University of Tennessee Medical Center, 1928 Alcoa Highway, Suite G50, Knoxville, TN 37920

Study Period: July 16, 2010 to October 28, 2010

Treatment Products: Flibanserin film-coated tablet (batch number PR10/30089 (bulk drug batch no. 4000225) from (b) (4)

Pharmacokinetic Sampling: Blood samples for determination of flibanserin plasma concentrations were taken on Day 1: predose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9 and 12 hrs following the first flibanserin administration. Blood samples for determination of flibanserin trough plasma concentrations were collected one hour (± 15 min) prior to evening flibanserin dose on Days 2 to 7. On Day 8, blood samples for determination of flibanserin plasma concentrations were taken -1, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48 and 60 hrs following the last flibanserin dose. The analyses of flibanserin concentrations were performed by (b) (4) using a validated LC-MS/MS method.

Results and Reviewer's Comments:

Single and Multiple Dose PK in Postmenopausal Women with HSDD

In postmenopausal women with HSDD and a mean (range) age of 60 (46 - 75 years; N=22), the median (range) Tmax was 1.5 (0.5 - 6.0) hrs, mean (SD) $t_{1/2}$ was 12.3 (5.6), mean (SD) Cmax was 343 (200) ng/mL, and mean (SD) $AUC_{0\text{-inf}}$ was 3150 (2140) ng.hr/mL following a single 100 mg flibanserin tablet.

In postmenopausal women with HSDD and a mean (range) age of 60 (46 - 75 years; N=24), the median (range) Tmax was 1.5 (0.5 - 3.0) hrs, mean (SD) $t_{1/2}$ was 15.5 (5.7), mean (SD) Cmax was 472 (268) ng/mL, and mean (SD) $AUC_{0\text{-}t,ss}$ was 4930 (3530) ng.hr/mL following once daily dosing of multiple doses (8 days) of 100 mg flibanserin tablet. Accumulation ratio (R_A) is 1.54 for both for AUC and Cmax.

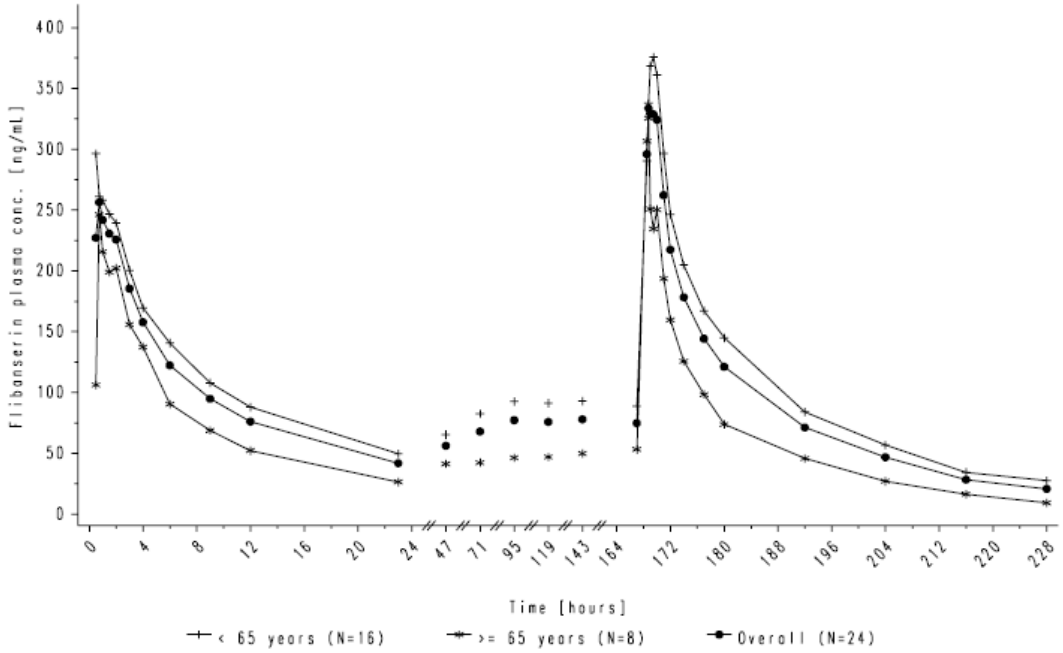
Young vs. Elderly Postmenopausal Women with HSDD: Effect on PK of Flibanserin
The sponsor reported the mean (range) age for younger postmenopausal patients was 55 (46 - 64; N=16) years and for elderly postmenopausal patients was 69 (65 - 75; N=8) years.

Following a single 100 mg dose of flibanserin, there was an increase of 15%, 42% and 54% in Cmax, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of flibanserin, respectively in young postmenopausal women, compared to elderly postmenopausal women. Median Tmax of flibanserin was delayed by 0.5 hr (1.0 to 1.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women. Mean half-life increased by 0.9 hr (10.6 to 11.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women.

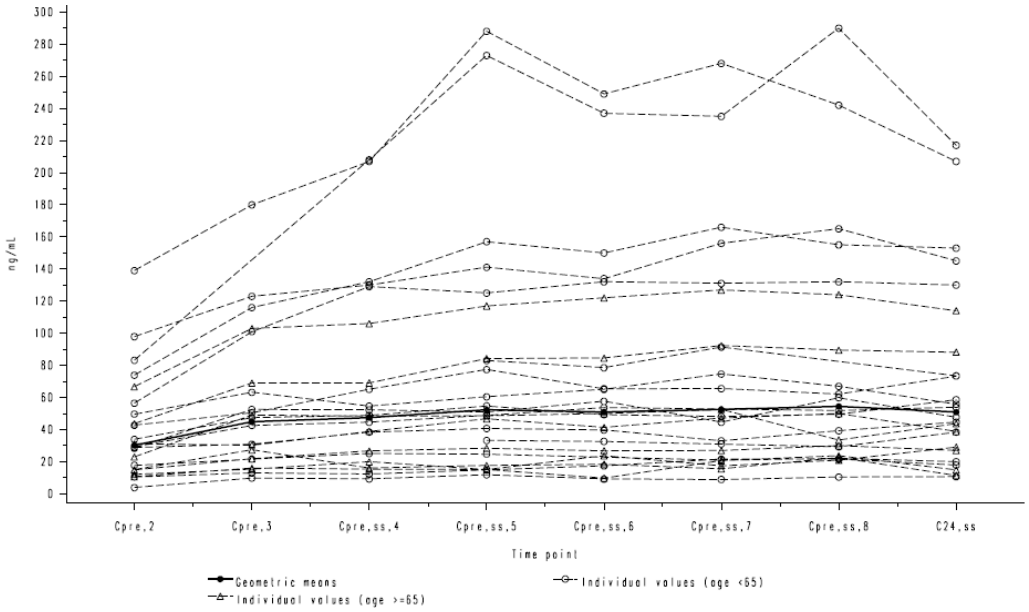
Following multiple doses (8 days) of 100 mg flibanserin tablet, there was an increase of 25% in Cmax and 56% in $AUC_{0\text{-}t,\,ss}$ of flibanserin in young postmenopausal women, compared to elderly postmenopausal women. Median Tmax of flibanserin was delayed by 0.1 hr (1.4 to 1.5 hrs) in young postmenopausal women, compared to elderly postmenopausal women. Mean half-life increased by 1.4 hr (13.6 to 15.0 hrs) in young postmenopausal women, compared to elderly postmenopausal women.

It appears that systemic exposure of flibanserin is higher in young compared with elderly postmenopausal women with HSDD. By contrast, the volume of distribution and clearance were higher in the elderly postmenopausal women.

Arithmetic Mean Plasma Concentration-Time Profiles of Flibanserin Following Multiple Doses (Once Daily for 8 Days) of 100 mg Flibanserin Tablets in Healthy Postmenopausal Women with HSDD (sponsor's figure 15.6.5.3:9, section 15.6).



Individual Patient and Mean Trough Plasma Concentrations (sponsor's figure 15.5.5:1, section 15.5).



Based on the individual trough profiles above, two young elderly patients had relatively higher flibanserin concentrations compared to the elderly postmenopausal women with HSDD.

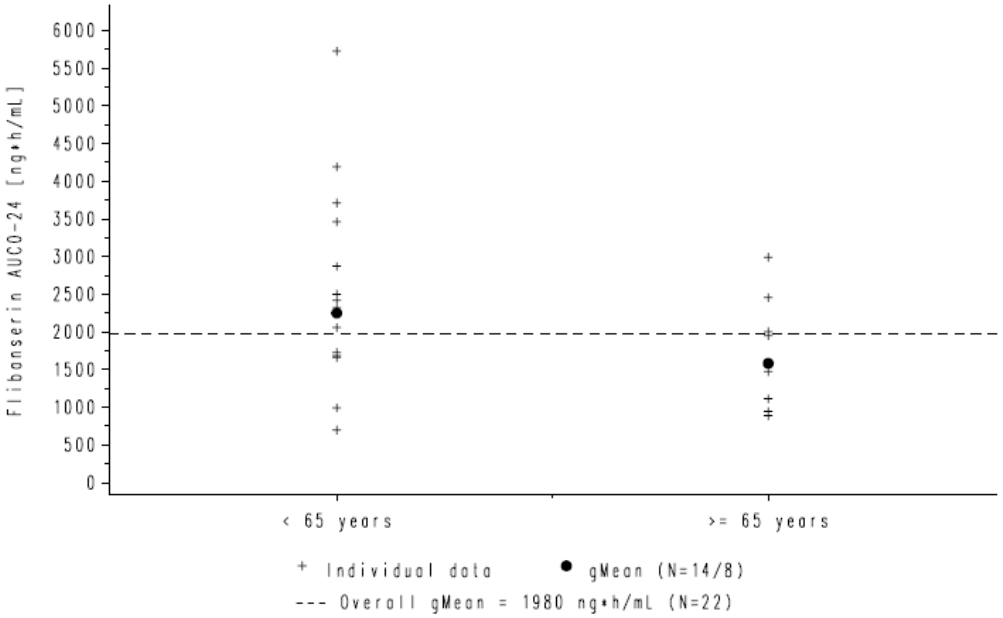
Geometric Mean PK Parameters of Flibanserin Following a Single 100 mg Dose of Flibanserin Tablet in Postmenopausal Women (sponsor's table 11.5.2.2.2:1, section 11.5.2.2).

Single dose	<65 years (N=14)		≥65 years (N=8)		All patients (N=22)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-24} [ng·h/mL]	2250	60.6	1580	47.6	1980	58.2
$AUC_{0-\infty}$ [ng·h/mL]	3010	76.8	1950	57.3	2570	73.0
$\%AUC_{tz-\infty}$ [%]	19.8	103	17.3	56.1	18.8	84.9
C_{max} [ng/mL]	314	65.8	272	39.4	298	56.4
t_{max}[a] [h]	1.5	0.500-6.00	1.00	0.75-4.00	1.5	0.500-6.00
$t_{½}$ [h]	11.5	55.3	10.6	34.0	11.2	47.5
MRT_{po} [h]	16.1	52.3	13.3	31.6	15.0	45.7
CL/F [mL/min]	554	76.8	856	57.3	649	73.0
V_z/F [L]	551	52.0	784	46.5	627	52.5

Geometric Mean PK Parameters of Flibanserin Following Multiple (Once Daily for 8 Days) Doses of 100 mg Dose of Flibanserin Tablet in Postmenopausal Women (sponsor's table 11.5.2.2.2:1, section 11.5.2.2).

Steady-state	<65 years (N=16)		≥65 years (N=8)		All patients (N=24)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	3480	60.8	2230	48.6	3000	60.9
$R_{A,AUC}$ [ ]	1.57	23.5	1.41	13.2	1.51	20.7
$C_{max,ss}$ [ng/mL]	437	59.4	350	64.2	406	60.7
$R_{A,Cmax}$ [ ]	1.46	45.9	1.29	30.2	1.39	40.4
$t_{max,ss}$[a] [h]	1.50	0.500-3.00	1.38	0.500-3.00	1.50	0.500-3.00
$t_{½,ss}$ [h]	15.0	45.1	13.6	25.4	14.5	39.1
$MRT_{po,ss}$ [h]	18.8	47.9	15.9	38.5	17.8	44.9
$CL/F_{,ss}$ [mL/min]	479	60.8	747	48.6	555	60.9
$V_z/F_{,ss}$ [L]	624	44.6	879	25.7	699	42.4

Individual and Geometric Mean AUC_{0-24} of Flibanserin Following Multiple Doses (Once Daily for 8 Days) of 100 mg Flibanserin Tablets in Younger and Elderly Healthy Postmenopausal Women with HSDD (sponsor's figure 15.6.5.4:1, section 15.6).



Safety Findings:
The most frequently reported AEs were dizziness (25%), somnolence (21%), nausea (17%), dyspepsia (13%), dry mouth (13%) and vomiting (13%), constipation (8%), headache (8%), and insomnia (8%).

Frequency [N (%)] of Patients With Adverse Events Occurring with Incidence Greater Than or Equal to 5% (sponsor's table 12.2.2.1:1, section 12.2.2).

MedDRA System organ class/ Preferred term	Screening	Flibanserin[a]	Post-treatment	Post-study	Total
Number of patients	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)
Total with adverse events	3 (12.5)	16 (66.7)	0 (0.0)	2 (8.3)	18 (75.0)
Psychiatric disorders					
Insomnia	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (8.3)
Nervous system disorders					
Dizziness	0 (0.0)	6 (25.0)	0 (0.0)	0 (0.0)	6 (25.0)
Somnolence	0 (0.0)	5 (20.8)	0 (0.0)	0 (0.0)	5 (20.8)
Headache	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (8.3)
Gastrointestinal disorders					
Nausea	0 (0.0)	4 (16.7)	0 (0.0)	0 (0.0)	4 (16.7)
Dry mouth	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	3 (12.5)
Dyspepsia	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	3 (12.5)
Vomiting	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	3 (12.5)
Constipation	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	2 (8.3)
Investigations					
Urine leukocyte esterase positive	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	2 (8.3)
White blood cell count increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	2 (8.3)

Note: Percentages are calculated using total number of patients per column as the denominator. MedDRA version used for reporting: 13.1
a. Includes all AEs occurring between first drug administration and 72 hours after last drug administration.
Source: Table 15.3.2: 2

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 022526 **Applicant: Sprout Pharmaceuticals** **Stamp Date: March 29, 2013**

Drug Name: Flibanserin **NDA Type: Resubmission/Class 2**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	In original NDA
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Additional DDI studies
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	In original NDA
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	In original NDA
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	In original NDA
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	In original NDA
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	In original NDA
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	In original NDA
15	Are the pediatric exclusivity studies adequately designed to			X	

	demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

There are no information requests or 74-Day Letter issues to convey to the Applicant from the Office of Clinical Pharmacology.

LaiMing Lee	April 23, 2013
Reviewing Clinical Pharmacologist	Date
Myong-Jin Kim	May 2, 2013
Team Leader/Supervisor	Date

Office of Clinical Pharmacology Filing Memo

NDA: 022526
Compound: Flibanserin
Sponsor: Sprout Pharmaceuticals

Submission Date: March 29, 2013
Filing Review Date: April 23, 2013
Reviewer: LaiMing Lee, PhD

Flibanserin is being developed by Sprout Pharmaceuticals for the treatment of hyposexual desire disorder (HSDD). Flibanserin is an oval, pink, film-coated tablet debossed on one side with "f100" and blank on the other side. The proposed dosing regimen is one 100 mg tablet taken once daily at bedtime with or without food.

Flibanserin was originally developed by Boehringer Ingelheim (BI) for the treatment of major depressive disorder but it failed to prove efficacy in Phase 2 studies. In Phase 2 depression studies, flibanserin was associated with nearly no sexual dysfunction and in one of these studies the multi-dimensional measure of sexual dysfunction, the Arizona Sexual Experiences Scale, showed that flibanserin was superior to placebo mainly on the "sex drive" item in women. BI decided to pursue the HSDD indication in premenopausal women based on the Phase 2 findings.

BI submitted the original NDA October 27, 2009 and received a Complete Response on August 27, 2010 due to lack of efficacy and safety concerns. The entry criteria for the Phase 3 trials submitted to the original NDA were very restrictive (i.e., presence of co-morbid conditions and concomitant medications) and thereby precluded a thorough assessment of efficacy in the target population. Flibanserin efficacy and safety findings were discussed at an Advisory Committee Meeting on June 18, 2010; the committee members voted against approval of flibanserin. Following the issue of a Complete Response, BI transferred ownership of the flibanserin NDA and associated INDs to Sprout Pharmaceuticals.

The following list from the Complete Response Letter describes the basis for not approving flibanserin:

EFFICACY

1. There is lack of substantial evidence that flibanserin is effective for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

Two randomized placebo-controlled trials demonstrated a statistically significant change from baseline in the number of satisfying sexual events (SSEs), one of two co-primary endpoints, for flibanserin relative to placebo. However, a statistically significant improvement for flibanserin relative to placebo was not demonstrated for the change from baseline in the second co-primary endpoint, the eDiary sexual desire item measured daily over 24 weeks. Flibanserin treatment was associated with reduced HSDD-related distress, evaluated by the Female Sexual Distress Scale-Revised (FSDS-R). While results on sexual desire as measured by the sexual desire domain of the Female Sexual Function Index (FSFI-SD) favored flibanserin, we do not believe that it is appropriate to disregard the negative results obtained with the pre-specified eDiary sexual desire item analyses in favor of the positive results obtained using another instrument.

In addition, the entry criteria for subjects enrolled in these controlled clinical trials were very restrictive, precluding a full clinical evaluation of efficacy in the target population of women who experience HSDD.

We recommend that you conduct an additional blinded, placebo-controlled clinical trial to assess the effects of flibanserin on SSEs and sexual desire (as co-primary endpoints), and HSDD-related distress (as a key secondary endpoint). If you use an instrument other than the eDiary employed in the trials

submitted in this NDA, 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's "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," December 2009.

You should provide evidence that the assessment schedule of the instrument that is used to measure sexual desire can adequately capture the subject's entire range of experiences over the assessment period (i.e., four weeks).

The trial should have less restrictive entry criteria compared to previously conducted HSDD clinical trials with respect to the presence of co-morbid conditions in enrolled subjects, and use of concomitant medications including dietary supplements. For example, women with mild forms of depression and anxiety should be included, as long as the HSDD is not a function of the underlying psychiatric diagnosis. Subjects taking commonly prescribed medications, including centrally acting drugs such as triptans, should also be enrolled.

We also recommend that you submit your trial protocol for a special protocol assessment prior to initiating this trial.

2. There is insufficient information to characterize the efficacy of the recommended dose of flibanserin in the presence of moderate CYP3A4 inducers.

Co-administration of flibanserin with a strong CYP3A4 inducer resulted in markedly reduced flibanserin plasma concentrations. We believe the magnitude of this effect is such that flibanserin efficacy in HSDD patients co-administered strong CYP3A4 inducers would be seriously compromised.

We recommend that you conduct a drug-drug interaction study to evaluate the effect of co administration of a moderate CYP3A4 inducer on the pharmacokinetic profile of flibanserin 100 mg.

SAFETY

1. There is insufficient information to characterize the safety profile of the recommended 100 mg dose of flibanserin in premenopausal women with HSDD who have co-morbid conditions or ingest concomitant medications including dietary supplements, or alcohol. To address this deficiency, we recommend that you:

   a. Enroll a broad population of premenopausal women with HSDD in ongoing or future placebo-controlled HSDD clinical trials of flibanserin. As stated above, we recommend that you enroll women with mild psychiatric conditions, assuming the HSDD is not a function of the underlying psychiatric diagnosis, and women taking commonly prescribed concomitant medications, including centrally acting drugs.

   b. Complete your ongoing 12-week, double-blind, placebo-controlled study to assess the safety of concomitant use of flibanserin 100 mg daily with selective serotonin or norepinephrine reuptake inhibitors. Special attention should be paid to the possibility of exacerbation of depression in subjects with a prior history of major depressive disorder.

   c. Conduct a drug-drug interaction study to determine the effect of simultaneous administration of flibanserin 100 mg with alcohol. This study should assess the tolerability and effects on pharmacodynamic endpoints, such as blood pressure and orthostatic vital signs, in flibanserin-treated subjects ingesting alcohol as compared to subjects on flibanserin alone.

d. Conduct a pharmacokinetic, pharmacodynamic, safety study in healthy premenopausal women ingesting supra-therapeutic doses of flibanserin to assess the effect of such exposure on orthostatic vital signs and the risk of syncope.

e. Conduct a drug-drug interaction study to evaluate the pharmacokinetic profile and safety of flibanserin 100 mg when co-administered with moderate CYP3A4 inhibitors.

f. Submit the final report of a meta-analysis of phase 1 pharmacokinetic and safety data in women who received oral contraceptives and various doses of flibanserin concomitantly. A determination of the need for a drug-drug interaction study to evaluate the pharmacokinetic profile and safety of flibanserin 100 mg when co-administered with weak CYP3A4 inhibitors will be made after FDA has completed its review of your meta-analysis.

2. There is insufficient information to assess the risk of accidental injury associated with the use of flibanserin and to assess the root cause of these events (e.g., drug-related somnolence, syncope, depression-related inattention, or other causes).

We recommend that the incidence of accidental injury (e.g., falls, automobile accidents, etc.) be assessed in flibanserin- and placebo-treated subjects enrolled in ongoing and future HSDD clinical trials of flibanserin.

3. Flibanserin is active in the CNS, has sedative properties, and there is evidence that it produces physical dependence. These properties are suggestive of a drug with abuse potential. However, in the absence of a human abuse potential study, it is not possible to draw definitive conclusions about the abuse potential of flibanserin.

New Clinical Studies

To address the deficiencies outlined in the Complete Response Letter, Sprout submitted in the current NDA fourteen new clinical studies. The studies include 1 pivotal 24-week safety and efficacy Phase 3 study (511.133), 3 supportive safety and efficacy Phase 3 studies, 3 long-term safety studies. Of the Phase 1 studies submitted, 5 are PK studies and 2 are PK/PD studies. The following PK studies are intended to address the effect of:

- Moderate CYP3A4 inhibitors (fluconazole & grapefruit juice) on flibanserin exposure (Study SPR-12-01)
- Moderate CYP3A4 inducer (etravirine) on flibanserin exposure (Study SPR-12-02)
- Alcohol on orthostasis and syncope (Study SPR-12-03)
- Supratherapeutic doses on safety and orthostasis (Study SPR-12-04)
- Flibanserin in recreational poly-drug users and potential for abuse (Study SPR-12-05)
- SD and MD administration of flibanserin in postmenopausal women to evaluate the effect of age (Study 511.146)
- MD of flibanserin on a SD of digoxin in male and female subjects (Study 511.158)

Type of Study	Study Identifier	Study Report Location	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Admin.	No. Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	SPR-12-01	Module 5.3.3.1	Effect of fluconazole on flibanserin and effect of grapefruit juice on flibanserin	Open, randomized, 2-way crossover	100 mg flibanserin, single oral dose, 400 mg fluconazole single oral loading dose, followed by 200 mg oral, fluconzazole for 5 days; single 8 ounce glass of grapefruit juice	26	Healthy female subjects	Single dose
PK	SPR-12-04	Module 5.3.3.1	Effect of standard and supratherapeutic doses of flibanserin on PK of healthy subjects	Open, randomized, 2-stage study with first phase a 3-way crossover; second phase parallel group, dose escalation	100, 150, 200 and 250 mg flibanserin, single oral dose, white film-coated tablet	20	Healthy female subjects	Two doses in phase 1, and single dose in phase 2
PK	511.158 U11-1029-01	Module 5.3.3.1	Effect multiple dose flibanserin on single-dose PK digoxin	Open, randomized, 2-way crossover	Flibanserin 100 mg once daily single dose 0.5 mg (2x0.25mg) digoxin on Day 5.	24	Healthy male and female subjects	Single dose

Type of Study	Study Identifier	Study Report Location	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Admin.	No. Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	511.146 U11-3112-01	Module 5.3.3.2	Single dose and steady state PK in post-menopausal women with HSDD; systemic exposure elderly compared to young.	Open-label, single period, multicenter	100 mg flibanserin, tablet, single oral dose, q.h.s.	40	Female patients with HSDD	Single dose
PK	SPR-12-02	Module 5.3.3.4	Effect of etravirine on flibanserin	Open, randomized, 2-way crossover	100 mg flibanserin, single oral dose, ; 200 mg etravirine oral bid;	30	Healthy female subjects	Single dose
PK/PD	SPR-12-03	Module 5.3.4.1	Effect of ethanol and flibanserin on PK/PD of healthy subjects	Open, randomized, 5-way crossover	100 mg flibanserin, oral dose, caspule 0.4 mg/kg and 0.8 mg/kg ethanol; matching placebo	25	Healthy male and female subjects	Three doses
PK/PD	SPR-12-05	Module 5.3.4.1	Evaluate abuse potential of flibanserin compared to zolpidem	Double-blind,, randomized, 6-way crossover	Placebo, 100, 200, 250 mg flibanserin oral dose; 15, 20, 30 mg zolpidem oral doses	36	Healthy recreational polydrug users male and female subjects	Three doses

Type of Study	Study Identifier	Study Report Location	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Admin.	No. Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	511.147 U11-3190-01	Module 5.3.5.1	Pivotal efficacy; safety and tolerability; clinically meaningful therapeutic response	Randomized, double-blind, placebo-controlled	100 mg flibanserin tablets q.h.s., oral 100 mg matching placebo tablet q.h.s.; oral	1736	Female patients with HSDD	24 weeks	Complete; full
Efficacy	511.130 U11-3281-01	Module 5.3.5.1	Efficacy, safety and tolerability	Double-blind, placebo controlled	100 mg flibanserin tablets q.h.s., oral 100 mg matching placebo tablet q.h.s.; oral	1997	Female postmenopausal patients with HSDD	24 weeks	Complete; full
Efficacy	511.114 U11-3247-01	Module 5.3.5.1	Safety, tolerability and withdrawal	Double-blind, placebo controlled, parallel group, multiple dose increasing	50 mg flibanserin plus placebo 14 days with up-titration to 100 mg (2x50 mg) or 100 mg (2x50 mg) flibanserin q.h.s., oral; 100 mg (2x50mg) matching placebo tablet	180	Female subjects on SSRI or SNRI with decreased desire and distress	12 weeks	Complete; full
Efficacy	511.156 U11-3244-01	Module 5.3.5.1	Efficacy, safety and tolerability	Double-blind, placebo controlled, parallel-group, multiple dose increasing	50 mg 14 days with up-titration to 100 mg flibanserin q.h.s., oral; 100 mg matching placebo tablet	1612	Female postmenopausal patients with HSDD	24 weeks	Complete; full

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/s/

LAI M LEE
05/02/2013

MYONG JIN KIM
05/02/2013

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/s/

LAI M LEE
08/29/2013

MYONG JIN KIM
08/29/2013

EDWARD D BASHAW
08/29/2013

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 22-526	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DRUP		
Applicant:	Sprout Pharmaceuticals Inc.	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	TBD	**Acting Supervisor:** Richard T. Lostritto, Ph.D.	
Generic Name:	Flibanserin	**Date Assigned:**	May 12, 2013
Indication:	Hypoactive sexual desire disorder (HSDD) in premenopausal women	**Date of Review:**	August 6, 2013
Formulation/strength	Immediate Release Film-Coated Tablet/100 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates:	Dates of Consult	PDUFA DATE
March 29, 2013 June 14, 2013	May 12, 2013 June 14, 2013	September 29, 2013

Type of Submission:	Resubmission (Response to August 27, 2010 Complete Response Letter)
Key review points	Acceptability of the dissolution documentation in support of a change to the film coat (b) (4) to (b) (4) Pink (b) (4)

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Background: Flibanserin is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Flibanserin is supplied as pink 100 mg immediate release film-coated tablets. The recommended daily dose is 100 mg once daily at bedtime.

Submission: A New Drug Application (NDA 22-526, Sequence 0000) was submitted by Boehringer Ingelheim Pharma GmbH & Co (BI) on October 27, 2009. A Complete Response (CR) letter was issued on August 27, 2010. The CR letter identified that additional data to establish the efficacy and safety of flibanserin were required to support a determination for approval. There were no Biopharmaceutics issues identified in the CR letter (See in DARRTS Biopharmaceutics Reviews dated June 2, 2010 and June 23, 2010).

In December 2011, Sprout Pharmaceuticals, Inc. (SPI) acquired worldwide rights from BI for the development of flibanserin, including IND (b) (4) and NDA 22-526 for the indication of HSDD in premenopausal women. The transfer of ownership was acknowledged by FDA on February 17, 2012.

Review: This Biopharmaceutics review focuses on the evaluation of the acceptability of the dissolution documentation in support of proposed changes to the composition of the film coat ((b) (4) Pink).

The following documents are referred to in this review:

- The Biopharmaceutics reviews of the Original submission in DARRTS by this Reviewer (see Dr. Houda Mahayni's review dated June 2, 2010, and June 23, 2010).
- The Applicant's submissions dated March 29, 2013 (proposed changing the composition of the (b) (4) Pink).
- Biopharmaceutics Information Request (IR) sent via e-mail dated May 31, 2013.
- The Applicant Response dated June 14, 2013 to Biopharmaceutics IR dated May 31, 2013.

Assessment:

The Acceptability of the Dissolution Documentation in Support of a change to the film coat (b) (4) to (b) (4) Pink (b) (4):

In the original NDA submission dated October 27, 2009, the Applicant used (b) (4) Pink (b) (4) as the film coat. In the Resubmission dated March 29, 2013, the Applicant implemented the use of (b) (4) Pink (b) (4) instead of (b) (4) Pink (b) (4).

In support of the change to the film coat, the Applicant submitted only the mean comparative dissolution profiles of the colorant change batch and the process validation batches. The Applicant did not provide the raw dissolution data used to construct the comparative dissolution profiles. Since the raw dissolution data used to construct the comparative dissolution profiles with f2 testing was needed in support of the change to the film coat, FDA conveyed to the Applicant via an E-mail dated May 31, 2013 the following comment:

Provide the raw dissolution data used to construct the comparative dissolution profiles with f2 testing for all tested lots under the two stability testing conditions.

The Applicant responded on June 14, 2013 to the Biopharmaceutics Information Request dated May 31, 2013. The Applicant pointed out that a typographical error was included in the previously submitted information (Section 3.2.P.8.3, submission dated March 29, 2013). The error is in mis-identification of the comparison batches as the primary stability batches when in fact they are process validation batches. The Applicant corrected this error by replacing the previously submitted document with a revised Section 3.2.P.8.3 that correctly identifies the process validation batches, as batches: #458479, #458480 and #458481. Also, the Applicant provided comparative dissolution profiles of the colorant change batch (batch #4001397) to the primary stability batches: batch #059056, #059057 and #059058.

Based on the dissolution data presented in the submissions dated May 12, 2013 and June 14, 2013, the change of the film coat (b) (4) to (b) (4) Pink (b) (4) is found acceptable.

II) RECOMMENDATION

The ONDQA-Biopharmaceutics team had reviewed the submissions dated: March 29, 2013 and June 14, 2013 for NDA 22-526 for Flibanserin tablets, 100 mg, and found the dissolution documentation acceptable to support the change to the film coat (b) (4) to (b) (4) Pink (b) (4).

From the Biopharmaceutics perspective, NDA 22-526 for Flibanserin Tablets is recommended for APPROVAL.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) BIOPHARMACEUTICS ASSESSMENT

Acceptability of the proposed dissolution documentation in support of the proposed changes to the composition of the film coat ((b) (4) Pink)

The Applicant did not provide the raw dissolution data used to construct the comparative dissolution profiles in Figure 1 below. Although the data through 3 months of testing met the dissolution acceptance criteria, the raw dissolution data used to construct the comparative dissolution profile with f2 testing need to be submitted for batches tested at both stability testing conditions.

FDA conveyed to the Applicant via an E-mail dated May 31, 2013 the following comment:

Provide the raw dissolution data used to construct the comparative dissolution profiles with f2 testing for all tested lots under the two stability testing conditions.

The Applicant sent the following two questions via e-mail dated May 31, 2013:

1. ***The data to be provided is for the batches included as part of our resubmission only (e.g., colorant change batches)?***
2. ***Should we provide this as a sequence to the NDA in addition to responding via e-mail?***

FDA responded on May 31, 2013 with the following response:

The answer is yes. For clarification, provide individual dissolution data for each batch (n=12) including mean, minimum, maximum, RSD used to generate the comparative dissolution profile on batches manufactured before and after the proposed change in colorant using the regulatory dissolution method and calculate the f2 similarity factor.

The Applicant responded on June 14, 2013 to the Biopharmaceutics Information Request dated May 31, 2013. The Applicant pointed out for our information that a typographical error was included in the previously submitted information in Section 3.2.P.8.3 which was submitted in the submission dated March 29, 2013. The Applicant stated that in that submission, the dissolution comparison was performed with the primary stability batches, but the dissolution comparison was performed using data from the process validation batches instead. The error is in mis-identification of the comparison batches as the primary stability batches. Therefore, there is no change needed to the profiles, data, or batch numbering that was originally provided in Section 3.2.P.8.3. The Applicant corrected this error by replacing the previously submitted document with a revised Section 3.2.P.8.3 that correctly identifies the process validation batches (#458479, #458480 and #458481). Also, the Applicant provided comparative dissolution profiles of the colorant change batch (batch #4001397) to the primary stability batches (#059056, #059057 and #059058).

The components and composition of Flibanserin tablet is shown in Table 1.

Table 1: Components and Composition of Flibanserin Tablets, 100 mg

Ingredient	mg per Tablet	Function	Reference to Standards
Flibanserin	100.000	Active ingredient	Company standard
Lactose monohydrate (b) (4)	(b) (4)	(b) (4)	NF/Ph. Eur./JP
Microcrystalline cellulose			NF/Ph. Eur./JP
Hypromellose (b) (4) (b) (4)			USP/Ph. Eur./JP
Croscarmellose sodium			NF/Ph. Eur./JP
Magnesium stearate			NF/Ph. Eur./JP
(b) (4)			USP/Ph. Eur./JP
(b) (4) Pink (b) (4)			Company standard
Total	**347.0**		(b) (4)

The current film coat is (b) (4) Pink (b) (4) which is used in the production of the primary stability batches. The Applicant implemented a change to the coating film (b) (4) to (b) (4) Pink (b) (4) A comparison of the qualitative and quantitative composition of and (b) (4) Pink (b) (4) is shown in Table 2.

Table 2: Comparison of Qualitative and Quantitative Composition of (b) (4) and (b) (4) Pink (b) (4)

Ingredient	(b) (4) mg per Tablet	(b) (4) mg per Tablet	Function
(b) (4)			

The differences between the two film coats (b) (4)

Therefore, the change is a Level 1 change per SUPAC-IR, as the total additive effect of all excipients changes is not more than (b) (4)%. Also, the amount of coating film per tablet and theoretical amount per batch (b) (4) the proposed change.

To qualify the use of the new (b) (4) Pink (b) (4), the Applicant manufactured one batch (Batch No. 4001397) (b) (4) accelerated and long-term storage conditions. The individual dissolution test results for each batch (n=6) from the 3 month test point is shown Tables 1 through 4 in the Appendix.

The Applicant provided the comparative dissolution profiles of the colorant change batch to the process validation batches and the primary stability batches. Figure 1 shows the dissolution profile of the colorant change batch to the process validation batches.

Figure 1: Dissolution Profiles of Batch 4001397, Process Validation Batches 458479, 458480, 458481

The Applicant calculated the f2 values as shown in Table 3 below. The f2 values are >50 which indicate that colorant batch (4001397) is similar to the process validation batches (458479, 458480, and 458481). The individual dissolution testing results for the colorant change batch (n=12) and each of the process validation batches (n=12) are provided in the Appendix (Table 5 to Table8).

Table 3: f2 comparison of the colorant batch and the process validation batches

f2 Comparison	f2 Value[1]
Lot 458479 vs. 4001397	86
Lot 458480 vs. 4001397	62
Lot 458481 vs. 4001397	70

[1] As per the USP at least 3 timepoints are required for the calculation of f2 values, and not more than one dissolution value should exceed (b) (4)%. These calculation criteria were not met for the validation batches 458479, 458480 and 458481: Out of the three time points that were used to calculate the f2 value, two time points were at least (b) (4)% or higher. However, these are the time points that were available for the comparison, and have been utilized in the absence of alternate statistical comparison tools in FDA guidance documents.

Also, the Applicant provided Figure 2 to show the dissolution profile comparison of the colorant change batch to the primary stability batches.

Figure 2: Dissolution Profiles of Batch 4001397, Primary Stability Batches 059056, 059057, 059058

The Applicant calculated the f2 values as shown in Table 4 below. The f2 values are >50 which indicate that colorant batch (4001397) is similar to the primary stability batches (059056, 059057, and 059058). The individual dissolution results for the colorant change batch (n=12) and each of the primary stability batches (n=12) are provided in the Appendix (Table 9 to Table 12).

Table 4: f2 comparison of the colorant batch and the primary stability batches

f2 Comparison	f2 Value[1]
Lot 059056 vs. 4001397	68
Lot 059057 vs. 4001397	71
Lot 059058 vs. 4001397	69

[1] As per the USP at least 3 timepoints are required for the calculation of f2 values, and not more than one dissolution value should exceed (b) (4)%. These calculation criteria were not met for the NDA batches 059056, 059057 and 059058: Out of the three time points that were used to calculate the f2 value, two time points were at least (b) (4)% or higher. However, these are the time points that were available for the comparison, and have been utilized in the absence of alternate statistical comparison tools in FDA guidance documents.

Also, the Applicant provided 3 months of stability data at long-term conditions and accelerated conditions using (b) (4)

The Applicant concluded that (b) (4) Pink (b) (4) is suitable for use to manufacture Flibanserin Tablets, 100 mg.

Reviewer's Assessment: ***Satisfactory***

The overall dissolution data support the proposed changes to the composition of the film coat ((b) (4) Pink). Also, this reviewer re-calculated the f2 factor and the results matched the Applicant results.

APPENDIX

Dissolution results [redacted] with colorant change from the 3-month stability test point are summarized below in Tables 1-4.

Table 1: Dissolution Results of Colorant Change Batches of Flibanserin Tablets, 100 mg Stored at 40° C/75% RH [redacted]

Tablet	Time – 30 (min)
1	[redacted]
2	
3	
4	
5	
6	
Average:	
Dissolution	
Maximum:	
Minimum:	
RSDActive <1:	
Initial Sample:	

Table 2: Dissolution Results Colorant Change Batches of Flibanserin Tablets, 100 mg Stored at 25° C/60% RH [redacted]

Tablet	Time – 30 (min)
1	[redacted]
2	
3	
4	
5	
6	
Average:	
Dissolution	
Maximum:	
Minimum:	
RSDActive <1:	
Initial Sample:	

Table 3: Dissolution Results Colorant Change Batches of Flibanserin Tablets, 100 mg Stored at 40° C/75% RH (b) (4) HDPE Bottles – Batch (b) (4)

Tablet	Time – 30 (min)
1	(b) (4)
2	
3	
4	
5	
6	
Average:	
Dissolution	
Maximum:	
Minimum:	
RSDActive <1:	
Initial Sample:	

Table 4: Dissolution Results Colorant Change Batches of Flibanserin Tablets, 100 mg Stored at 25° C/60% RH (b) (4) HDPE Bottles – Batch (b) (4)

Tablet	Time – 30 (min)
1	(b) (4)
2	
3	
4	
5	
6	
Average:	
Dissolution	
Maximum:	
Minimum:	
RSDActive <1:	
Initial Sample:	

Individual dissolution data for the colorant change batch and process validation batches

Table 5: Individual Dissolution Data: Colorant Change Batch 4001397

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Table 6: Individual Dissolution Data: Process Validation Batch 458479

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Table 7: Individual Dissolution Data: Process Validation Batch 458480

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Table 8: Individual Dissolution Data: Process Validation Batch 458481

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Individual dissolution data of the colorant batch and primary stability batches.

Table 9: Individual Dissolution Data: Colorant Change Batch 4001397

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Table 10: Individual Dissolution Data: Primary Stability Batch 059056

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Table 11: Individual Dissolution Data: Primary Stability Batch 059057

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

Table 12: Individual Dissolution Data: Primary Stability Batch 059058

Tablet/Profile Time (minutes)	10	20	30	45
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average:				
Minimum:				
Maximum:				
%RSD:				

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/s/

HOUDA MAHAYNI
08/07/2013

ANGELICA DORANTES
08/07/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 022526 **Applicant: Sprout Pharmaceuticals** **Stamp Date: March 29, 2013**

Drug Name: Flibanserin **NDA Type: Resubmission/Class 2**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	In original NDA
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Additional DDI studies
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	In original NDA
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	In original NDA
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	In original NDA
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	In original NDA
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	In original NDA
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	In original NDA
15	Are the pediatric exclusivity studies adequately designed to			X	

	demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

There are no information requests or 74-Day Letter issues to convey to the Applicant from the Office of Clinical Pharmacology.

LaiMing Lee	April 23, 2013
Reviewing Clinical Pharmacologist	Date
Myong-Jin Kim	May 2, 2013
Team Leader/Supervisor	Date

Office of Clinical Pharmacology Filing Memo

NDA: 022526
Compound: Flibanserin
Sponsor: Sprout Pharmaceuticals

Submission Date: March 29, 2013
Filing Review Date: April 23, 2013
Reviewer: LaiMing Lee, PhD

Flibanserin is being developed by Sprout Pharmaceuticals for the treatment of hyposexual desire disorder (HSDD). Flibanserin is an oval, pink, film-coated tablet debossed on one side with "f100" and blank on the other side. The proposed dosing regimen is one 100 mg tablet taken once daily at bedtime with or without food.

Flibanserin was originally developed by Boehringer Ingelheim (BI) for the treatment of major depressive disorder but it failed to prove efficacy in Phase 2 studies. In Phase 2 depression studies, flibanserin was associated with nearly no sexual dysfunction and in one of these studies the multi-dimensional measure of sexual dysfunction, the Arizona Sexual Experiences Scale, showed that flibanserin was superior to placebo mainly on the "sex drive" item in women. BI decided to pursue the HSDD indication in premenopausal women based on the Phase 2 findings.

BI submitted the original NDA October 27, 2009 and received a Complete Response on August 27, 2010 due to lack of efficacy and safety concerns. The entry criteria for the Phase 3 trials submitted to the original NDA were very restrictive (i.e., presence of co-morbid conditions and concomitant medications) and thereby precluded a thorough assessment of efficacy in the target population. Flibanserin efficacy and safety findings were discussed at an Advisory Committee Meeting on June 18, 2010; the committee members voted against approval of flibanserin. Following the issue of a Complete Response, BI transferred ownership of the flibanserin NDA and associated INDs to Sprout Pharmaceuticals.

The following list from the Complete Response Letter describes the basis for not approving flibanserin:

EFFICACY

1. There is lack of substantial evidence that flibanserin is effective for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

Two randomized placebo-controlled trials demonstrated a statistically significant change from baseline in the number of satisfying sexual events (SSEs), one of two co-primary endpoints, for flibanserin relative to placebo. However, a statistically significant improvement for flibanserin relative to placebo was not demonstrated for the change from baseline in the second co-primary endpoint, the eDiary sexual desire item measured daily over 24 weeks. Flibanserin treatment was associated with reduced HSDD-related distress, evaluated by the Female Sexual Distress Scale-Revised (FSDS-R). While results on sexual desire as measured by the sexual desire domain of the Female Sexual Function Index (FSFI-SD) favored flibanserin, we do not believe that it is appropriate to disregard the negative results obtained with the pre-specified eDiary sexual desire item analyses in favor of the positive results obtained using another instrument.

In addition, the entry criteria for subjects enrolled in these controlled clinical trials were very restrictive, precluding a full clinical evaluation of efficacy in the target population of women who experience HSDD.

We recommend that you conduct an additional blinded, placebo-controlled clinical trial to assess the effects of flibanserin on SSEs and sexual desire (as co-primary endpoints), and HSDD-related distress (as a key secondary endpoint). If you use an instrument other than the eDiary employed in the trials

submitted in this NDA, 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's "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," December 2009.

You should provide evidence that the assessment schedule of the instrument that is used to measure sexual desire can adequately capture the subject's entire range of experiences over the assessment period (i.e., four weeks).

The trial should have less restrictive entry criteria compared to previously conducted HSDD clinical trials with respect to the presence of co-morbid conditions in enrolled subjects, and use of concomitant medications including dietary supplements. For example, women with mild forms of depression and anxiety should be included, as long as the HSDD is not a function of the underlying psychiatric diagnosis. Subjects taking commonly prescribed medications, including centrally acting drugs such as triptans, should also be enrolled.

We also recommend that you submit your trial protocol for a special protocol assessment prior to initiating this trial.

2. There is insufficient information to characterize the efficacy of the recommended dose of flibanserin in the presence of moderate CYP3A4 inducers.

Co-administration of flibanserin with a strong CYP3A4 inducer resulted in markedly reduced flibanserin plasma concentrations. We believe the magnitude of this effect is such that flibanserin efficacy in HSDD patients co-administered strong CYP3A4 inducers would be seriously compromised.

We recommend that you conduct a drug-drug interaction study to evaluate the effect of co administration of a moderate CYP3A4 inducer on the pharmacokinetic profile of flibanserin 100 mg.

SAFETY

1. There is insufficient information to characterize the safety profile of the recommended 100 mg dose of flibanserin in premenopausal women with HSDD who have co-morbid conditions or ingest concomitant medications including dietary supplements, or alcohol. To address this deficiency, we recommend that you:

   a. Enroll a broad population of premenopausal women with HSDD in ongoing or future placebo-controlled HSDD clinical trials of flibanserin. As stated above, we recommend that you enroll women with mild psychiatric conditions, assuming the HSDD is not a function of the underlying psychiatric diagnosis, and women taking commonly prescribed concomitant medications, including centrally acting drugs.

   b. Complete your ongoing 12-week, double-blind, placebo-controlled study to assess the safety of concomitant use of flibanserin 100 mg daily with selective serotonin or norepinephrine reuptake inhibitors. Special attention should be paid to the possibility of exacerbation of depression in subjects with a prior history of major depressive disorder.

   c. Conduct a drug-drug interaction study to determine the effect of simultaneous administration of flibanserin 100 mg with alcohol. This study should assess the tolerability and effects on pharmacodynamic endpoints, such as blood pressure and orthostatic vital signs, in flibanserin-treated subjects ingesting alcohol as compared to subjects on flibanserin alone.

d. Conduct a pharmacokinetic, pharmacodynamic, safety study in healthy premenopausal women ingesting supra-therapeutic doses of flibanserin to assess the effect of such exposure on orthostatic vital signs and the risk of syncope.

e. Conduct a drug-drug interaction study to evaluate the pharmacokinetic profile and safety of flibanserin 100 mg when co-administered with moderate CYP3A4 inhibitors.

f. Submit the final report of a meta-analysis of phase 1 pharmacokinetic and safety data in women who received oral contraceptives and various doses of flibanserin concomitantly. A determination of the need for a drug-drug interaction study to evaluate the pharmacokinetic profile and safety of flibanserin 100 mg when co-administered with weak CYP3A4 inhibitors will be made after FDA has completed its review of your meta-analysis.

2. There is insufficient information to assess the risk of accidental injury associated with the use of flibanserin and to assess the root cause of these events (e.g., drug-related somnolence, syncope, depression-related inattention, or other causes).

We recommend that the incidence of accidental injury (e.g., falls, automobile accidents, etc.) be assessed in flibanserin- and placebo-treated subjects enrolled in ongoing and future HSDD clinical trials of flibanserin.

3. Flibanserin is active in the CNS, has sedative properties, and there is evidence that it produces physical dependence. These properties are suggestive of a drug with abuse potential. However, in the absence of a human abuse potential study, it is not possible to draw definitive conclusions about the abuse potential of flibanserin.

New Clinical Studies

To address the deficiencies outlined in the Complete Response Letter, Sprout submitted in the current NDA fourteen new clinical studies. The studies include 1 pivotal 24-week safety and efficacy Phase 3 study (511.133), 3 supportive safety and efficacy Phase 3 studies, 3 long-term safety studies. Of the Phase 1 studies submitted, 5 are PK studies and 2 are PK/PD studies. The following PK studies are intended to address the effect of:

- Moderate CYP3A4 inhibitors (fluconazole & grapefruit juice) on flibanserin exposure (Study SPR-12-01)
- Moderate CYP3A4 inducer (etravirine) on flibanserin exposure (Study SPR-12-02)
- Alcohol on orthostasis and syncope (Study SPR-12-03)
- Supratherapeutic doses on safety and orthostasis (Study SPR-12-04)
- Flibanserin in recreational poly-drug users and potential for abuse (Study SPR-12-05)
- SD and MD administration of flibanserin in postmenopausal women to evaluate the effect of age (Study 511.146)
- MD of flibanserin on a SD of digoxin in male and female subjects (Study 511.158)

Type of Study	Study Identifier	Study Report Location	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Admin.	No. Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	SPR-12-01	Module 5.3.3.1	Effect of fluconazole on flibanserin and effect of grapefruit juice on flibanserin	Open, randomized, 2-way crossover	100 mg flibanserin, single oral dose, 400 mg fluconazole single oral loading dose, followed by 200 mg oral, fluconzazole for 5 days; single 8 ounce glass of grapefruit juice	26	Healthy female subjects	Single dose
PK	SPR-12-04	Module 5.3.3.1	Effect of standard and supratherapeutic doses of flibanserin on PK of healthy subjects	Open, randomized, 2-stage study with first phase a 3-way crossover; second phase parallel group, dose escalation	100, 150, 200 and 250 mg flibanserin, single oral dose, white film-coated tablet	20	Healthy female subjects	Two doses in phase 1, and single dose in phase 2
PK	511.158 U11-1029-01	Module 5.3.3.1	Effect multiple dose flibanserin on single-dose PK digoxin	Open, randomized, 2-way crossover	Flibanserin 100 mg once daily single dose 0.5 mg (2x0.25mg) digoxin on Day 5.	24	Healthy male and female subjects	Single dose

Type of Study	Study Identifier	Study Report Location	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Admin.	No. Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	511.146 U11-3112-01	Module 5.3.3.2	Single dose and steady state PK in post-menopausal women with HSDD; systemic exposure elderly compared to young.	Open-label, single period, multicenter	100 mg flibanserin, tablet, single oral dose, q.h.s.	40	Female patients with HSDD	Single dose
PK	SPR-12-02	Module 5.3.3.4	Effect of etravirine on flibanserin	Open, randomized, 2-way crossover	100 mg flibanserin, single oral dose, ; 200 mg etravirine oral bid;	30	Healthy female subjects	Single dose
PK/PD	SPR-12-03	Module 5.3.4.1	Effect of ethanol and flibanserin on PK/PD of healthy subjects	Open, randomized, 5-way crossover	100 mg flibanserin, oral dose, caspule 0.4 mg/kg and 0.8 mg/kg ethanol; matching placebo	25	Healthy male and female subjects	Three doses
PK/PD	SPR-12-05	Module 5.3.4.1	Evaluate abuse potential of flibanserin compared to zolpidem	Double-blind,, randomized, 6-way crossover	Placebo, 100, 200, 250 mg flibanserin oral dose; 15, 20, 30 mg zolpidem oral doses	36	Healthy recreational polydrug users male and female subjects	Three doses

Type of Study	Study Identifier	Study Report Location	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Admin.	No. Enrolled Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	511.147 U11-3190-01	Module 5.3.5.1	Pivotal efficacy; safety and tolerability; clinically meaningful therapeutic response	Randomized, double-blind, placebo-controlled	100 mg flibanserin tablets q.h.s., oral 100 mg matching placebo tablet q.h.s.; oral	1736	Female patients with HSDD	24 weeks	Complete; full
Efficacy	511.130 U11-3281-01	Module 5.3.5.1	Efficacy, safety and tolerability	Double-blind, placebo controlled	100 mg flibanserin tablets q.h.s., oral 100 mg matching placebo tablet q.h.s.; oral	1997	Female postmenopausal patients with HSDD	24 weeks	Complete; full
Efficacy	511.114 U11-3247-01	Module 5.3.5.1	Safety, tolerability and withdrawal	Double-blind, placebo controlled, parallel group, multiple dose increasing	50 mg flibanserin plus placebo 14 days with up-titration to 100 mg (2x50 mg) or 100 mg (2x50 mg) flibanserin q.h.s., oral; 100 mg (2x50mg) matching placebo tablet	180	Female subjects on SSRI or SNRI with decreased desire and distress	12 weeks	Complete; full
Efficacy	511.156 U11-3244-01	Module 5.3.5.1	Efficacy, safety and tolerability	Double-blind, placebo controlled, parallel-group, multiple dose increasing	50 mg 14 days with up-titration to 100 mg flibanserin q.h.s., oral; 100 mg matching placebo tablet	1612	Female postmenopausal patients with HSDD	24 weeks	Complete; full

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/s/

LAI M LEE
05/02/2013

MYONG JIN KIM
05/02/2013

REVIEW OF CLINICAL PHARMACOLOGY

NDA	**022526**	***Submission Date(s)***	**October 27, 2009; March 26, 2010; May 14, 2010**
Brand Name		**Girosa**	
Generic Name		**Flibanserin**	
Reviewer		**LaiMing Lee, Ph.D.**	
Team Leader		**Myong-Jin Kim, Pharm.D.**	
OCP Division		**Division of Clinical Pharmacology 3**	
OND Division		**Division of Reproductive and Urologic Products**	
Sponsor		**Boehringer Ingelheim**	
Relevant IND		(b) (4)	
Submission Type; Code		**Original; 1S**	
Formulation; Strengths; Regimen		**Immediate Release Oral Tablet; 100 mg; 100 mg daily at bedtime**	
Proposed Indication		**Treatment of Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women**	

A Required Office Level OCP Briefing was held on June 11, 2010 and was attended by Lawrence Lesko, Shiew-Mei Huang, E. Dennis Bashaw, Hae-Young Ahn, Myong-Jin Kim, Lisa Soule, Dan Davis, Olivia Easley, Jogarao Gobburu, Darrell Abernathy, Mehul Mehta, John Lazor, Lei Zhang, Sandhya Apparaju, Hyunjin Kim, Gilbert Burckart, Seongeun Cho, Dilara Jappar, Nancy Hu, Kevin Krudys, Dionna Green, Ritesh Jain, Suresh Doddapaneni, Immo Zdrojewski, Elizabeth Shang, Ju-Ping Lai, and Jee Eun Lee.

Table of Contents

1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 022526 for flibanserin 100 mg tablets submitted to the Agency on October 27, 2009. We have found this NDA acceptable from a Clinical Pharmacology perspective.

1.2 Post-Marketing Commitment/Post-Marketing Requirement

If the NDA is approved, this reviewer recommends the sponsor evaluate the effect of weak and moderate CYP3A4 inhibitors on flibanserin concentrations as a post-marketing requirement (PMR). If the NDA receives a Complete Response (CR), the sponsor should be made aware that OCP is concerned about the effect of weak and moderate CYP3A4 inhibitors on flibanserin concentrations and that this issue should be addressed at the time of resubmission. Based on discussions held on August 24, 2010 in preparation of the Complete Response letter, the Review Team will be requesting additional studies in the resubmission of the NDA from the sponsor and will include drug-drug interaction studies with flibanserin and moderate CYP3A4 inducer, moderate CYP3A4 inhibitor and potentially weak CYP3A4 inhibitor, alcohol, and SSRIs/SNRIs.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Boehringer Ingelheim is seeking approval of flibanserin (BIMT 17 BS) oral tablets, 100 mg for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women ($\geq$ 18 years of age). The sponsor initially investigated flibanserin for treatment of depression. Flibanserin is a post-synaptic serotonin 5-HT_{1A} agonist and a 5-HT_{2A} antagonist. There is currently no FDA-approved pharmacologic therapy for HSDD. The proposed dose and dosing regimen is one - 100 mg oral tablet to be given daily at bedtime (qhs) with or without food. Flibanserin is extensively metabolized by CY3A4 and to a minor extent CYP2D6. Ketoconazole, a strong inhibitor of CYP3A4, has been shown to significantly increase flibanserin exposure. Hepatic impairment has also significantly increased systemic flibanserin exposure.

Clinical (efficacy and safety) and Clinical Pharmacology (hepatic impairment and CYP3A4 inhibition) findings from NDA 022526 were discussed at an Advisory Committee meeting on June 18, 2010.

The sponsor evaluate the single dose and steady state pharmacokinetics of 100 mg flibanserin in a phase I, open-label, parallel group, and within-groups sequential trial in premenopausal women with HSDD.

Single Dose Pharmacokinetics (PK) of Flibanserin (N=28)

	$AUC_{0\text{-inf}}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max}[1] (hr)	$t_{1/2}$ (hr)
flibanserin	1630 (54.6%)	336 (50.7%)	1.00 (0.50-3.00)	9.33 (27.8%)

geometric mean and gCV (%)
[1] median and range

Multiple Dose PK of Flibanserin (N=29)

	$AUC_{\tau,ss}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max}[1] (hr)	$t_{1/2}$ (hr)
flibanserin	2080 (46.6%)	469 (42.7%)	1.00 (0.50-3.00)	11.4 (24.3%)

geometric mean and gCV (%)
[1] median and range

Exposure (Dose)-Response Relationship

Efficacy Endpoints

For this NDA, the two co-primary endpoints used to demonstrate clinical efficacy for flibanserin in HSDD women were change from baseline in number of satisfying sexual events (SSEs) and change from baseline in eDiary desire scores.

Efficacy

Flibanserin is a centrally acting drug that was initially evaluated for the treatment of major depressive disorder (MDD). The sponsor evaluated PK with varying dose ranges in several phase 1 studies and proof-of-concept phase 2 studies. Based on an early single dose study, the sponsor concluded that 50 mg and 100 mg produced centrally-acting sedative effects, which were correlated closely to Tmax. Single doses of 150 mg of flibanserin were tolerated.

In two 12-week proof-of-concept studies for the treatment of HSDD, the sponsor evaluated the efficacy of flibanserin 50 mg bid with the option to up-titrate to 100 mg bid. There were positive findings in the primary endpoint Arizona Sexual Experiences Scale (ASEX) Sex Drive from baseline to the end of trial visit. Secondary endpoints such as Female Sexual Function Index (FSFI) and the (Changes in Sexual Functioning Questionnaire-F (CSFQ-F) were included in these trials, ASEX Desire Item was included as the primary endpoint because results on this questionnaire were available from previous flibanserin trials in MDD.

In one pivotal phase 3 trial, the sponsor evaluated 50 mg and 100 mg qhs; in another pivotal phase 3 trial, 25 mg twice daily (bid), 50 mg bid (uptitrated from 50 mg qhs), and 100 mg qhs (up-titrated from 50 mg qhs) were evaluated. Efficacy results with the 25 mg bid or 50 mg qhs doses were less positive than those for the 100 mg qhs dose. Based on tolerability, the 100 mg qhs dose was better than the 50 mg bid dose. The sponsor is therefore seeking approval of the 100 mg qhs dose for the HSDD indication.

At the proposed clinical dose of 100 mg qhs, the sponsor failed to demonstrate statistically significant difference in desire (one of the two co-primary endpoints), compared to placebo. The sponsor was able to demonstrate statistically significant difference in the other co-primary endpoint SSEs, compared with placebo.

Safety

The most common treatment-emergent adverse events (AEs) for subjects treated with flibanserin are fatigue, somnolence, dizziness, and nausea. In a phase 1 tolerability and PK study, the sponsor evaluated multiple increasing oral doses of flibanserin with bid or three times daily (tid) dosing regimen of up to 100 mg tid in healthy men and women. It was concluded that doses up to 100 mg tid was generally safe; however, a dose-dependent increase in AEs such as fatigue and dizziness was observed.

Intrinsic and Extrinsic Factors

The sponsor conducted the following studies to evaluate intrinsic and extrinsic factors that may affect the PK of flibanserin: renal impairment, hepatic impairment, CYP2D6 polymorphism, drug interaction with paroxetine, ethnicity (Japanese women), drug interaction with itraconazole and ketoconazole, drug interaction with rifampicin, drug interaction with bupropion, drug interaction with oral contraceptive containing ethinyl estradiol and levonorgestrel (EE/LNG), and effect of food effect.

Renal impairment

Mild-to-moderate renal impairment did not significantly impact the systemic exposure to flibanserin (AUC0-inf increased by 12%), compared to subjects with normal renal function. Severe renal impairment had a moderate impact on the systemic exposure to flibanserin (AUC0-inf increased by 21%), compared to subjects with normal renal function.

Cmax decreased by 4% in mild-to-moderate renal impairment patients, compared to subjects with normal renal function. This is not significant given the level of variability in the data. Cmax increased 31% in severe renal impairment patients, compared to subjects with normal renal function.

Hepatic impairment

Systemic exposure to flibanserin was significantly affected by hepatic impairment. The AUC0-inf of flibanserin was significantly higher (4.5-fold) in patients with mild hepatic impairment compared to subjects with normal hepatic function. The AUC0-inf of flibanserin was higher (2.6-fold) in patients with moderate hepatic impairment compared to subjects with normal hepatic function.

Patients with mild hepatic impairment had a slightly reduced Cmax (9.5%), but it was significantly lower (63% decrease) in patients with moderate hepatic impairment, compared to healthy subjects. Clearance decreased 78% and 62% in the mild and moderate hepatic impairment patients, respectively, compared to the healthy matched subjects.

QT Prolongation

The therapeutic dose (50 mg bid) used in the QT study produced subtherapeutic Cmax values. The supratherapeutic dose (100 mg tid) produced flibanserin mean Cmax values 1.2-fold higher than the mean flibanserin Cmax for the therapeutic dose (100 mg qd). The Cmax of metabolite M38 at the supratherapeutic dose was 77% of the value previously observed after the 100 mg qd dose; therefore, the supratherapeutic dose used in the study can be considered to provide therapeutic Cmax. There was no significant QT prolongation effect. Baseline-corrected QTc based on the individual correction method (QTcI) was 0.7 and 2.0 ms for the 50 mg bid and 100 mg tid group, respectively; both are below 10 ms, the threshold for regulatory concern.

However, interaction with potent inhibitors of CYP3A4, such as itraconazole and ketoconazole increase Cmax 1.69- to 1.8-fold. Hepatic impairment also increased flibanserin concentration. The results of the QT study do not preclude prolongation of the QT interval in patients with impaired liver function or patients receiving potent inhibitors of CYP3A4 receiving the 100 mg qd dose.

CYP2D6 polymorphism and effect of potent CYP2D6 inhibitor, paroxetine

In CYP2D6 poor metabolizers (PMs), the geometric mean AUCτ,ss increased by 18% and Cmax,ss decreased by 4.1%, compared to CYP2D6 extensive metabolizers (EMs).

In CYP2D6 EMs only, the geometric mean AUCτ,ss decreased by 2.5% and geometric mean Cmax,ss increased by 3.4% with co-administration of paroxetine; neither are considered significant.

In CYP2D6 intermediate metabolizers (IMs), the geometric mean AUCτ,ss decreased by 5.8% and Cmax increased by 8.9% with co-administration of paroxetine.

Overall, there were very small changes in flibanserin PK due to CYP2D6 polymorphism or co-administration of paroxetine. These findings are not surprising considering flibanserin is extensively metabolized by CYP3A4 and only to a minor extent by CYP2D6.

Race

To help the sponsor select an appropriate dosing regimen for future studies with flibanserin in Japan, a phase I PK study in Japanese women was conducted. The effect of race (i.e., between racial sub-groups) was not specifically evaluated by the sponsor. A cross study comparison between healthy Japanese women (Study 511.117) and Caucasian women with HSDD (Study 511.105) who are otherwise healthy is presented below.

In comparison to HSDD women of mainly Caucasian descent, AUCτ,ss and Cmax,ss were higher by 41.3% and 43.7%, respectively, in Japanese women. Tmax was the same in both groups, while $t_{1/2}$ was decreased by 1.72 hrs in Japanese women. The differences in steady state PK observed between Japanese and mainly Caucasian women contrast the findings with single dose flibanserin.

An underlying question is whether other intrinsic factors such as age, weight, and BMI affecting flibanserin PK. It is worthy to note that in comparing the above PK data, Caucasian women weighed significantly more and had a higher body mass index (BMI) than Japanese women. Weight and BMI can impact the volume of distribution and, ultimately, flibanserin exposure and is likely more apparent upon multiple dosing. Therefore, the differences in PK may not be attributed race, but rather to weight and BMI; both factors were not evaluated by the sponsor in the NDA.

When the mean flibanserin exposure in Japanese women was adjusted for weight (a factor of 0.764 (51.8/67.8) - weight of Japanese women divided by weight of Caucasian women), the AUCτ,ss in Japanese women was 2246 ng.hr/mL, which is comparable to 2080 ng.hr/mL in Caucasian women. The similarity in weight-adjusted AUCτ,ss suggests that weight, not race, is the driving factor contributing to the observed difference in flibanserin exposure between Japanese and Caucasian women.

Effect of strong CYP3A4 inhibitors, itraconazole and ketoconazole

Itraconazole 200 mg daily for 8 days co-administered with flibanserin 50 mg increased flibanserin AUC0-inf by 2.6-fold and Cmax by 1.7-fold. $t_{1/2}$ was extended by 4.2 hrs from 7.44 to 11.6 hrs in the presence of itraconazole.

Although itraconazole is a suitable drug to evaluate potential CYP3A4 inhibition, the 200 mg dose selected for this study is lower than the recommended 400 mg dose and therefore the degree of inhibition by itraconazole is not maximized. The results from this sub-optimally designed study did demonstrate that flibanserin exposure increased in the presence of itraconazole. As the results from the study cannot confirm the degree of interaction between flibanserin and a strong CYP3A4 inhibitor the sponsor conducted another CYP3A4 inhibition study using ketoconazole 400 mg daily, a strong CYP3A4 inhibitor.

Ketoconazole 400 mg daily for 5 days inhibited flibanserin 50 mg metabolism leading to a 4.6-fold increase in flibanserin AUC0-inf. Cmax increased 1.8-fold. Tmax increased slightly from 1.25 to 1.50 hr and $t_{1/2}$ was significantly prolonged by 7.4 hrs from 8.5 to 15.9 hrs. These results are more significant compared with a previous interaction study with itraconazole 200 mg daily for up to 8 days. Based on the observed relationship between dose and adverse events, it is likely that patients using a CYP3A4 inhibitor will likely experience an increase in adverse events compared with healthy subjects.

The sponsor did not evaluate the effect of weak or moderate CYP3A4 inhibitors on flibanserin PK. (b) (4) Phase 1 and 3 studies excluded use of CYP3A4 inhibitors, grapefruit juice, herbal medications and dietary supplements. It is important to address the effect of mild and moderate CYP3A4 inhibitors considering the long list (5 pages) of excluded medications in the pivotal Phase 3 studies and its likelihood of use in HSDD women.

Effect of rifampicin

The influence of rifampicin 600 mg for 10 days, a potent CYP3A4 inducer, on the PK of flibanserin 100 mg and relevant metabolites was evaluated. The geometric mean flibanserin exposure AUC0-inf was significantly lower when co-administered with rifampicin. Flibanserin AUC0-inf was reduced by 96% with rifampicin pre-treatment. Geometric mean flibanserin Cmax was also significantly lowered when co-administered with rifampicin. Cmax for flibanserin was reduced by 91%. Flibanserin metabolism is clearly influenced by the potent CYP3A4 inducer rifampicin.

(b) (4) This statement is weak in providing the level of detail to the user and prescriber regarding the extent of CYP3A4 induction. This reviewer recommends the sponsor state more explicitly the level of reduction in flibanserin exposure (~95%) when flibanserin is co-administered with a strong CYP3A4 inducer.

Effect of flibanserin on CYP3A4 probe, simvastatin

Flibanserin (50 mg bid for 4 days) co-administered with single dose simvastatin 40 mg increased simvastatin total exposure by 1.3-fold (90% CI: 1.08-1.61) and Cmax by 1.2-fold (90%CI: 0.95-1.39). Half-life of simvastatin was extended slightly from 2.16 to 2.60 hrs in the presence of flibanserin. It is possible that the degree of CYP3A4 inhibition by flibanserin may be higher in the proposed 100 mg qhs dosing regimen, compared with 50 mg bid due to higher exposure with 100 mg qhs.

Flibanserin co-administered with simvastatin increased simvastatin acid exposure by 1.5-fold and Cmax by 1.4-fold. Half-life of simvastatin acid was extended slightly from 3.55 to 4.31 hrs in the presence of flibanserin.

Effect of flibanserin on bupropion, a CYP2B6 substrate

Based on in vitro CYP metabolism studies, the sponsor decided to conduct an in vivo study, using bupropion as CYP2B6 substrate, to assess the extent of CYP2B6 inhibition by flibanserin.

There was essentially no difference in geometric mean exposure AUCss and Cmax for bupropion at steady-state when co-administered with flibanserin 100 mg. For bupropion,

the geometric mean ratio (90% CI) for AUCτ,ss and Cmax,ss was 102.7 (97.2-108.5%) and 102.5 (94.1-111.6%) with and without flibanserin 100 mg qd, respectively.

In Vitro Permeability, P-glycoprotein and Multi-Drug Resistance Associated Protein Transport of Flibanserin

The sponsor undertook a series of in vitro permeability and transporter studies to assess the impact of and potential for transporter mediated drug-drug interactions:

- The in vitro bi-directional transport experiment showed that the transport of flibanserin was concentration independent from 0.3 to 60 uM. Flibanserin showed high and comparable permeability for both transport directions, and thus classifying flibanserin as a highly permeable drug.

- To determine whether flibanserin is actively transported by P-gp or MRP, the apical-to-basal and basal-to-apical permeability of flibanserin were assessed in the absence and presence of P-gp inhibitors verapamil and cyclosporin A, and MRP inhibitor MK571. The concentration of flibanserin was 10 uM.

- To determine whether flibanserin is a P-gp inhibitor, the sponsor conduct an in vitro study with flibanserin and [^{3}H]-digoxin 1uM, a P-gp substrate. As positive controls, the sponsor evaluated the transport of digoxin in the presence of P-gp inhibitors verapamil 200 uM and cyclosporin A 12 uM.

Overall, in vitro drug-drug interaction studies showed that flibanserin was not a P-gp substrate. At a high flibanserin concentration (30 and 60 uM), the apical to basal transport of digoxin was increased slightly, though the basolateral to apical transport of digoxin was not affected. Flibanserin does not appear to be a P-gp inhibitor.

Effect of flibanserin on oral contraceptives

The target population for flibanserin is premenopausal women, who are likely to take oral contraceptives (OCs) or combination oral contraceptives (COCs). To rule out potential drug-drug interaction between flibanserin and OCs/COCs, the sponsor evaluated the PK of ethinyl estradiol (EE) and levonorgestrel (LNG) in the presence of flibanserin. There appeared to be a small increase in EE when the COC Microgynon® was co-administered with flibanserin. Overall, flibanserin, given daily, did not appear to affect EE and LNG exposure.

EE increased slightly when COC was co-administered with flibanserin. Following flibanserin administration, the geometric mean AUC0-inf and Cmax increased 8.3% and 5.7%, respectively.

LNG PK was essentially the same when COC was co-administered with flibanserin. AUC0-inf increased 1.2%. Cmax did not change. Half-life remained relatively unchanged: 26.0 and 26.3 hrs in the absence and presence of flibanserin, respectively.

Effect of food

The effect of different food types on the PK of flibanserin after a single 50 mg dose of flibanserin tablet was evaluated in an open-label, four-way, crossover study in 16 healthy subjects (Study 511.26). Compared to the fasted condition, the exposure of flibanserin was 17%, 41%, and 53% higher after administration of a light, medium, and high

fat/caloric breakfast, respectively. The total flibanserin exposure increased with increasing fat/calorie content.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Boehringer Ingelheim (BI) is seeking approval of flibanserin for the treatment of HSDD in premenopausal women (≥ 18 years of age). Flibanserin is a serotonin 5-HT_{1A} agonist and a 5-HT_{2A} antagonist. There is currently no FDA-approved pharmacologic therapy for HSDD. The proposed dose and dosing regimen is one - 100 mg oral tablet to be given daily at bedtime with or without food.

BI developed flibanserin originally to treat depression, based on anti-depressant-like effects in preclinical models. The sponsor stated that flibanserin failed to show efficacy on the primary endpoint in a Phase IIa depression clinical trial and virtually no sexual dysfunction was noted so a multi-dimensional measure, the ASEX, of sexual dysfunction was included in four Phase IIb depression studies. The sponsor again stated that flibanserin failed to show consistent efficacy as an antidepressant. The sponsor found that in one of the 4 studies, flibanserin was superior in women not only to the positive depression comparator, but also to placebo on the ASEX scale.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Flibanserin is a benzimidazolone derivative with the chemical name 2H-benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(tri-fluoromethyl)phenyl]-1-piperazinyl]ethyl]. The molecular formula is $C_{20}H_{21}F_3N_4O$ and the molecular weight is 390.41 g/mol. The free base is used to make the drug product. The drug substance does not contain any chiral centers and does not exhibit any optical isomerism. The drug substance exists (b) (4)

Flibanserin is a white to off-white powder, non-hygroscopic, and is poorly insoluble in neutral pH. In acidic solution (phosphate buffer at pH 8.0, 0.002 mg/ml; 0.01 N HCl), aqueous solubility is 3.3 mg/ml. In water, aqueous solubility is 0.008 mg/ml. (b) (4)

The formulations of the film-coated tablets used in pivotal Phase 3 trials and in majority of clinical pharmacology studies are the same (BIMT-17-BS-TAF-54-5B-1B (25 mg), BIMT-17-BS-TAF-54-1H 1B (50 mg), and BIMT-17-BS-TAF-54-4E-1B (100 mg)). With the exception of the film-coating suspension, the Phase 3 clinical formulation and to-be-marketed formulation (b) (4). Instead of preparing the film-coating suspension using (b) (4) excipients, the sponsor plans to use (b) (4)

The table below summarizes the components and composition of the to-be-marketed film-coated flibanserin tablets. The only dose strength the sponsor intends to market are the 100 mg tablets.

Ingredient	25 mg tablet mg per tablet	50 mg tablet mg per tablet	100 mg tablet mg per tablet
(b) (4)			(b) (4)
BIMT 17 BS	25.000	50.000	100.000
Lactose monohydrate		(b) (4	(b) (4)
Microcrystalline cellulose			
Hypromellose (b) (4			
Croscarmellose sodium			
Magnesium stearate			
(b) (4			
(b) (4) Pink (b) (4 (b) (4			
Total			347.000

* As applicable to Production Site BIRI
** Removed during processing, does not appear in the final product
*** Composition according to table 16

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The sponsor would like to market flibanserin for the treatment of HSDD, though it was initially evaluated for the treatment of depression. Flibanserin is a serotonin 5-HT_{1A} agonist and a 5-HT_{2A} antagonist with high affinity binding to 5-HT_{1A} and a 5-HT_{2A} receptors. Flibanserin also has moderate affinity for dopamine D4, 5-HT_{2B} and a 5-HT_{2C} receptors. The exact mechanism of action for treatment of HSDD is unknown. The sponsor believes the therapeutic benefit is derived from its effects on norepinephrine, serotonin, and dopamine activities in the central nervous system.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted two proof-of-concept clinical trials in women with HSDD in North America using dosages studied in prior depression trials. In these 12-week trials,

women were treated with flibanserin or placebo with the initial dosage of 50 mg bid. Up-titration to 100 mg bid was permitted at Week 8 if efficacy was unsatisfactory. The sponsor states that through proof-of-concept studies, flibanserin appeared to benefit premenopausal women with HSDD based on positive findings on several endpoints, including statistically significant differences on some endpoints. But they found more dropouts, due to AEs, from Week 8 to Week 12 associated with 100 mg flibanserin bid than with 50 mg flibanserin bid. Therefore, the sponsor chose 50 mg flibanserin bid and 100 mg flibanserin qd as the maximum dosages for further clinical evaluation. Based on prior results in depression studies, the sponsor expected the daily total dosage of 50 mg qd to produce improved tolerability compared to 50 mg bid, and with lower incidences of sedative effects compared to placebo.

In one of the pivotal phase 3 studies, the dosages were 50 mg qhs and 100 mg qhs. In the other pivotal phase 3 study, the dosages were 25 mg bid; 50 mg qhs for 14 days, then up-titrated to 50 mg bid; and 50 mg qhs, then up-titrated to 100 qhs.

The majority of clinical pharmacology studies were conducted with 50 mg flibanserin. The one crucial study to evaluate single dose and steady state pharmacokinetics in the intended population, HSDD women, included dosages evaluated in the pivotal phase 3 studies: 25 mg bid, 50 mg qd, 50 mg bid, and 100 mg qd. The proposed clinical dosing regimen (100 mg qhs) was never assessed in Phase 1 or 2 studies.

2.2.2 What are the clinical endpoints measured in clinical pharmacology and clinical studies?

The co-primary efficacy endpoints for the 24-week pivotal Phase 3 studies are change from baseline in SSEs and desire, both to be measured by subject responses in an electronic diary (eDiary). In the Phase 2 studies proof-of-concept studies, ASEX was the primary endpoint due to its use in prior depression trials. In clinical pharmacology studies, the endpoints for the majority of studies were PK parameters of flibanserin. In some cases such as drug-drug interactions, the endpoints in clinical pharmacology studies were PK parameters of the interacting drug.

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In a two-way crossover study in six healthy male subjects, the sponsor evaluated the metabolism of a single intravenous dose of 20 mg and a single oral solution dose of 50 mg ^{14}C-radiolabelled flibanserin (study 511.15). Flibanserin was well absorbed and extensively metabolized; only detected in trace amounts in urine and feces. After oral dosing of ^{14}C-radiolabelled flibanserin, 44.1% of the total ^{14}C-flibanserin related radioactivity was recovered in urine, and 50.9% in feces.

The metabolite profiles were established in all urine fractions of all volunteers collected through 48 hrs after intravenous and oral dosing. At least 35 metabolites were formed in humans. They are mainly formed by CYP3A4 and to a minor extent by CYP2D6 followed by sulphation and glucuronidation. Metabolites extending a mean cumulative 0-48 hr excretion of 2% of the dose were defined by the sponsor as major metabolites. BIML 7 ZW (M38) was identified as the major metabolite and accounts for approximately 10.29% of 25.14% of all major metabolites. Metabolites M2, M8, M26,

M30, are M34 all considered major metabolites as they reached mean 0-48 hr excretion levels between 2 to 4%. All metabolites are renally excreted.

The table below summarizes all major metabolites of flibanserin with a mean cumulative 0-48hr excretion of 2% or more (sponsor's table 3.1:2 Study 511.15).

metabolites	intravenous			oral		
	Mean	Min	Max	Mean	Min	Max
all major metabolites	21.60	17.13	23.46	25.14	17.27	32.60
detailed: M37/M38	11.61	10.42	13.68	10.29	8.29	12.80
M2	2.25	0.72	3.55	4.10	0.99	6.51
M8	2.55	0.86	3.47	3.20	0.96	6.21
M26	2.72	1.87	4.21	2.84	2.25	4.36
M30	2.48	1.72	3.26	2.58	1.79	3.45
M34	-	-	-	2.14	1.37	4.19

Mean (arithmetic, n=60), minimum and maximum metabolites (% of the dose) in human urine

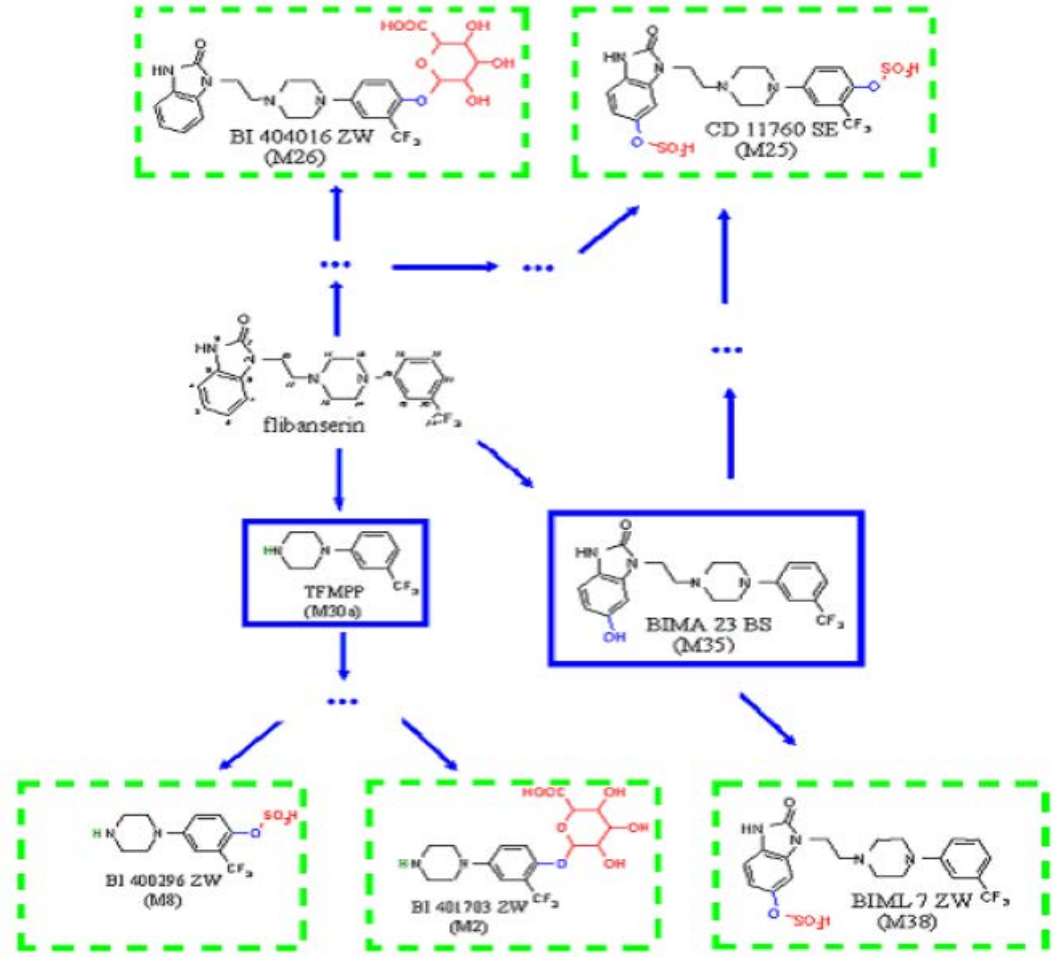
From the total set of identified metabolites, seven metabolites were investigated - five were conjugates and two were Phase I metabolites (TFMPP (M30a) and BIMA 23 BS (M35)). M35 is mainly formed by CYP3A4 metabolism and to a lesser extent by CYP2D6 and other enzymes, and is most likely representing the major elimination pathway. M30a is solely formed by CYP3A4 and further metabolized by mainly CYP2D6.

In a broad receptor screening, M35, M38, and M30a showed some affinity to serotonergic receptors, reaching approximately 15%, 60%, and 5% of molar exposure in plasma compared to flibanserin, respectively. Of these three, only M30a was shown to cross the blood brain barrier in rat (Study A050/06FU). Based on brain to plasma ratios of radioactivity, flibanserin and M30a showed a significant distribution into the brain of 3.71 and 2.81 nmol/kg, respectively. M35 and M38 showed almost no distribution into the brain. Compared to flibanserin, M30a has similar level of distribution in the rat brain; however, its presence in plasma is fairly low at 5%. For this review, the primary focus will be on reporting PK of flibanserin, the parent compound.

The following table is a summary of the radioactivity concentrations in blood, plasma, and brain and corresponding brain to plasma ratios of radioactivity at 4 hr after intravenous infusion of 10 µmol/kg ^{14}C-flibanserin (BIMT 17 BS), ^{14}C-M30a (TFMPP), ^{14}C-M35 (BIMA 23 BS) or ^{14}C-M38 (BIML 7 ZW). (sponsor's summary table from Study A050/06FU).

	mean	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
compound:	**BIMT 17 BS**		**TFMPP**		**BIMA 23 BS**		**BIML 7 ZW**	
sample	**[nmol/kg]**		**[nmol/kg]**		**[nmol/kg]**		**[nmol/kg]**	
BRAIN	7302	1627	6290	1490	149	18	42	12
PLASMA	1972	224	2940	957	2037	332	2040	592
BLOOD	2000	188	2890	905	1768	243	1269	377
BPR	**3.71**	**0.80**	**2.80**	**0.29**	**0.08**	**0.01**	**0.02**	**0.01**

The figure below is the metabolic pathways of flibanserin. **Blue solid** frames indicate Phase I metabolites. **Green dashed** frames indicated Phase II metabolites by sulphation and glucuronidation of hydroxylated flibanserin. (sponsor's figure 1.1.2:1 Module 2.7.2)



2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure (dose)-response relationships for efficacy?

The sponsor submitted data from two Phase 3 North American studies to support the proposed indication HSDD in premenopausal women that compared two doses of flibanserin - 50 mg qhs and 100 mg daily (as 50 mg bid or 100 mg qhs) - to placebo in premenopausal women with documented HSDD. Flibanserin 100 mg qhs led to a statistically significant increase from baseline in number of SSEs compared to placebo in each study 4.6 vs. 3.5 (p-value 0.005) in Study 511.71 and 4.4 vs. 3.7 (p-value 0.024) in Study 511.75. However, the co-primary endpoint of change from baseline in desire, as assessed by the eDiary desire score 21.2 vs. 18.1 (p-value 0.132) in Study 511.71 and 20.1 vs. 16.9 (p-value 0.346) in Study 511.75, did not demonstrate statistically significant improvement for flibanserin 100 mg qhs as compared to placebo. Other Phase 3 studies conducted outside of North America were not considered pivotal to demonstrating

clinical efficacy by the Medical Office Dan Davis because the patients in those studies are not representative of Americans who would be prescribed flibanserin, if approved by the Agency.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The most common treatment-emergent adverse events for subjects treated with flibanserin are dizziness, nausea, fatigue, and somnolence. Patients in the Phase 3 studies who received flibanserin once daily were given the drug at bedtime, not in the morning as in the PK study.

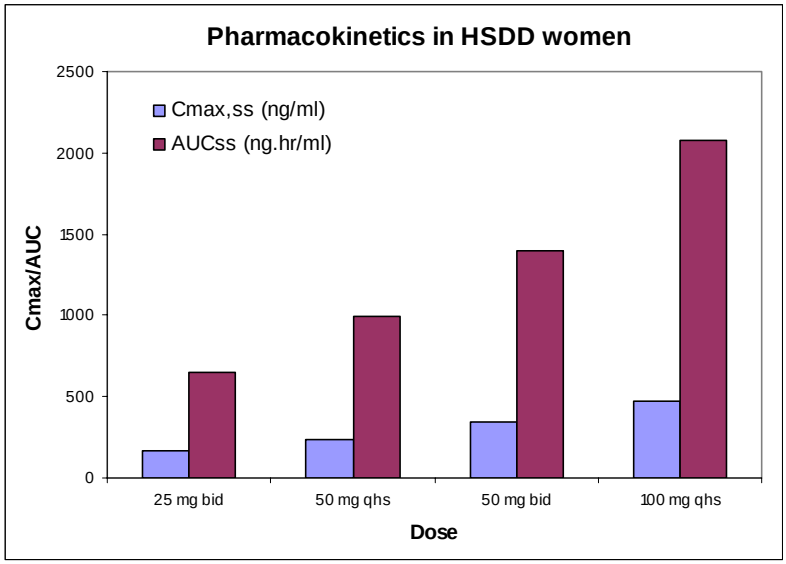
Single dose and steady state PK were evaluated in 61 HSDD women in an open-label, parallel, and within-groups sequential trial (Study 511.105). Flibanserin tablets were given to women in the morning under fasted condition.

The following table summarizes the steady state PK parameters of flibanserin from four different dosing regimens.

	Dosing Regimen			
SS PK parameter*	**25 mg bid** (N=33)	**50 mg qd** (N=30)	**50 mg bid** (N=32)	**100 mg qd** (N=28)
AUCτ,ss (ng hr/ml)[a]	653 (60.1)	991 (47.7)	1400 (46.9)	2080 (46.6)
Cmax,ss (ng/ml)[a]	168 (50.9)	234 (41.2)	346 (34.4)	469 (42.7)
Tmax (hr)[b]	1.00 (0.50-3.00)	1.00 (0.42-4.00)	0.75 (0.50-3.00)	1.00 (0.50-3.00)

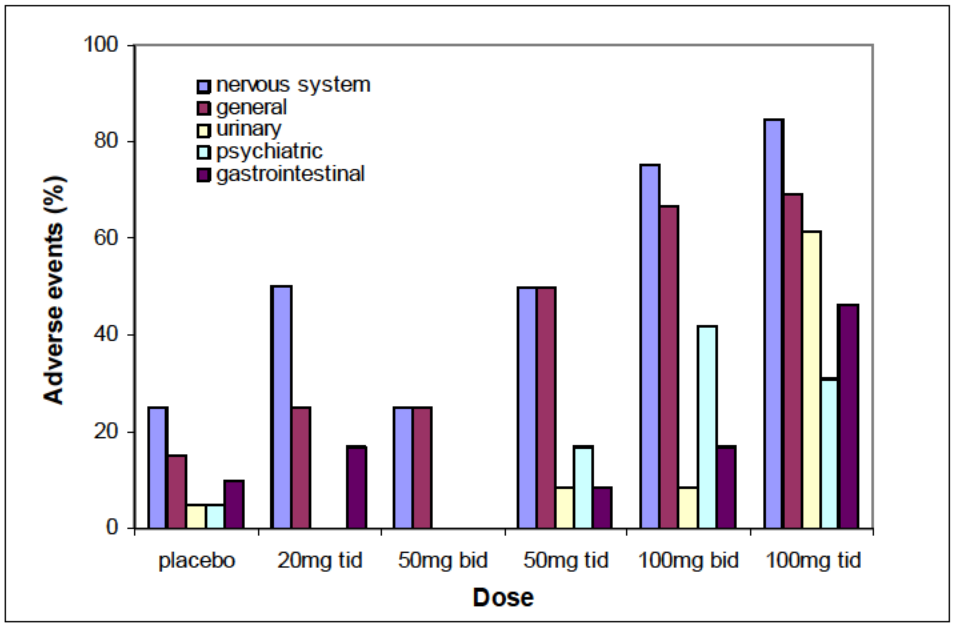
[a] geometric mean and gCV (%)
[b] median and range
HSDD women in the qd dosing regimen were given flibanserin in the morning.

An increase in steady state AUC and Cmax with increasing dose is illustrated in the following figure.



In Study 511.2 in male and female subjects, the sponsor evaluated the PK and clinical tolerability of six different dosing regimens. The most common treatment-emergent AEs for subjects treated with flibanserin were fatigue, somnolence, dizziness, and nausea. In the phase 1 tolerability and PK study, the sponsor evaluated multiple increasing oral doses of flibanserin with bid or tid dosing regimen of up to 100 mg tid in healthy men and women. It was concluded that doses up to 100 mg tid was generally safe; however, a dose-dependent increase in AEs such as fatigue and dizziness was observed. In comparison to the lower doses, insomnia and nausea were observed only in the two highest doses (100 mg bid and 100 tid) evaluated. The following figure is the AEs profile (grouped by body system) for flibanserin at five different dose groups studied in the phase 1 study. There appears to be greater incidences of AEs with increasing dose, particularly at the three highest doses.

The figure below is a dose-adverse events profile from 81 healthy subjects from the clinical tolerability and PK Study 511.2.



The following table is the AEs occurring in >1% and at least twice that of placebo in the randomized treatment groups in Phase 3 placebo-controlled HSDD Trials*

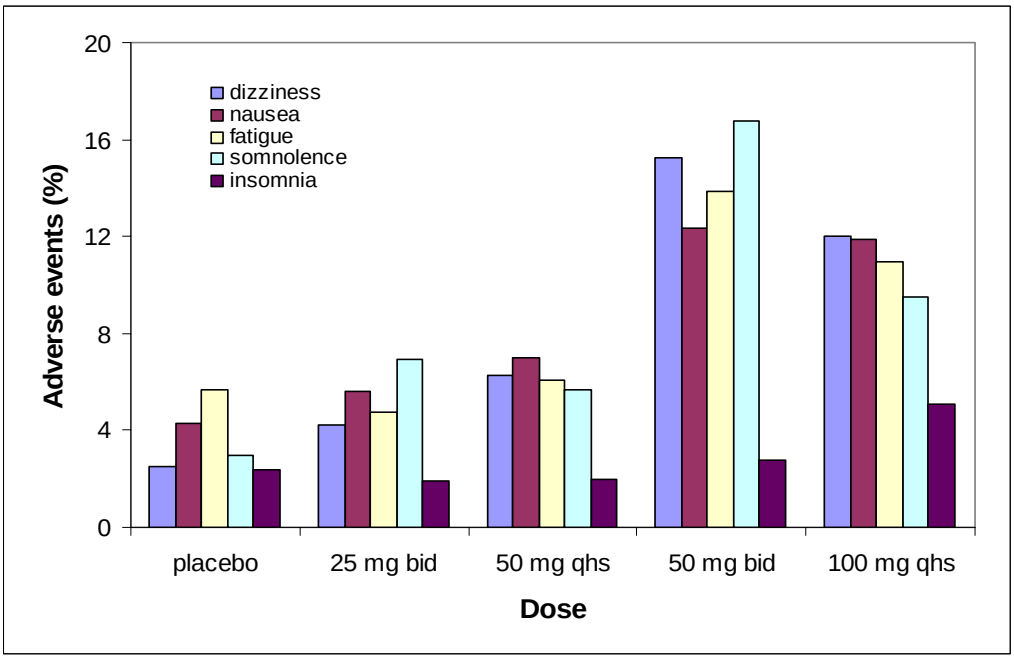
	Placebo	25 mg bid	50 mg qhs	50 mg bid	100 mg qhs
	N = 1360	N = 733	N = 969	N = 728	N = 1001
Any event	785 (57.7)	430 (58.7)	628 (64.8)	517 (71.0)	696 (69.5)
Subjects with severe AE's	71 (5.2)	32 (4.4)	69 (7.1)	44 (6.0)	83 (8.3)
Dizziness	34 (2.5)	31 (4.23)	61 (6.30)	111 (15.25)	120 (11.99)
Nausea	58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

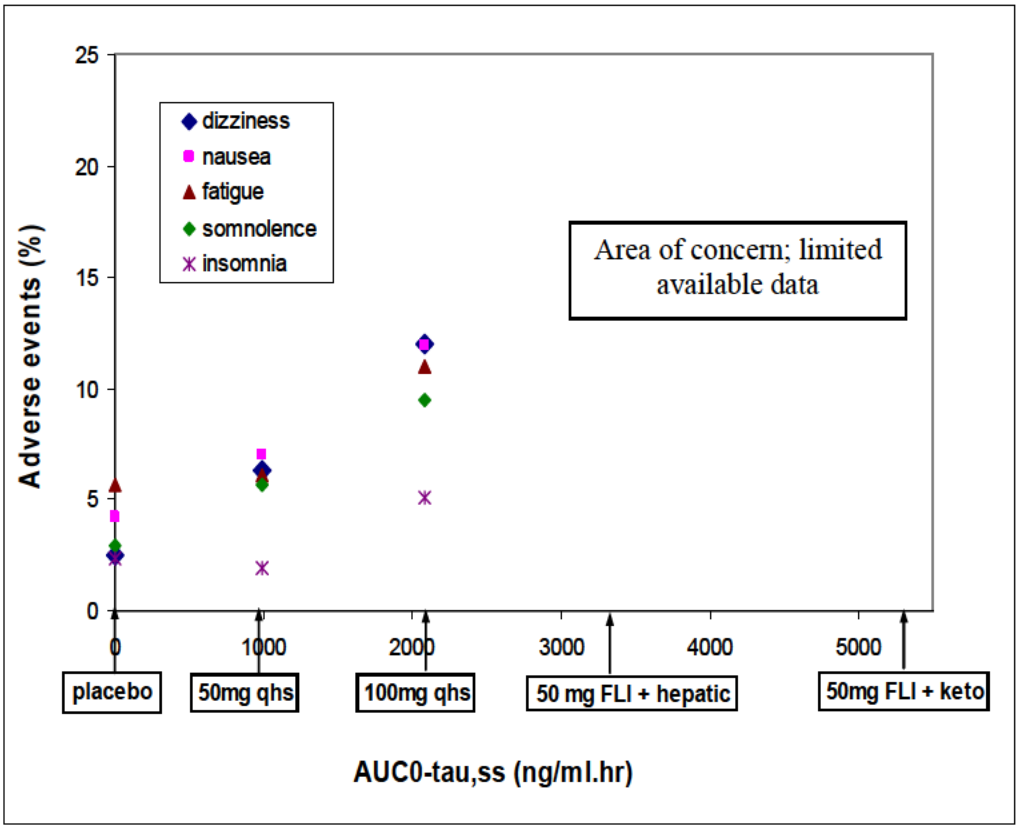
* Includes trials 511.70, 511.71, 511.75 and 511.77;

Source: Table 2.1.2.1.1, p 93, Integrated Summary of Safety

The figures below are a dose- and an exposure-adverse events profile for flibanserin. Adverse events data are from the above four phase 3 studies (511.70, 511.71, 511.75, and 511.77) and exposure data for each corresponding dose group are from PK study 511.105 in HSDD women; no PK data were collected during the Phase 3 studies. These Phase 3 studies were evaluated for safety by the Medical Officer Dr. Olivia Easley.

At the same total daily dose, giving flibanserin 100 mg qhs appears to lower the incidences of AEs such as dizziness, nausea, fatigue, and somnolence despite the higher systemic exposure of flibanserin, compared to 50 mg bid. This finding is not surprising considering the patients would be asleep after taking flibanserin and, therefore, not awake to experience nor report incidences of dizziness, nausea, fatigue, and somnolence. That is the rationale for the qhs dosing regimen proposed in this NDA. Despite reducing the incidences of AEs by giving flibanserin at bedtime, there is a clear and possibly linear relationship in the incidences of adverse events and flibanserin exposure, especially if comparison is made with the bid and qhs groups separately.





2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

Yes.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of the drug and its major metabolites?

From the total set of identified metabolites, seven metabolites (M30a, M8, M2, M35, M38, M26, M25) were further investigated – five were conjugates and two were phase I metabolites (M30a and M35). Based on an average of six volunteers, about 12% of the intravenous dose and 10% of the oral dose were excreted as metabolite M37/M38 into the urine during 0-48 hours. Metabolites M2, M8, M26, M30, and M34 (oral only) are also major metabolites that reached mean cumulative 0-48 hr excretion levels of 2 to 4 % of the dose after both oral and intravenous dose routes.

M35 is mainly formed by CYP3A4 , the major elimination pathway, and, to a lesser extent, by CYP2D6 and other enzymes. M30a is solely formed by CYP3A4 and further metabolized by mainly CYP2D6. The sum mean cumulative renal excretion of all seven major metabolites account for 21.6% of the intravenous dose and 25.1% of the oral dose. M38 is the conjugated moiety of M37/M38, while M37 is the non-deconjugatable part of M37/M38.

The following table summarizes the single dose geometric mean (%CV) PK parameters of flibanserin 100 mg and 3 major metabolites in HSDD women.

	$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max}[1] (hr)	$t_{1/2}$ (hr)
Flibanserin	1630 (54.6)	336 (50.7)	1.00 (0.50-3.00)	9.33 (27.8)
M35	228 (60.9)	31.3 (62.4)	0.75 (0.50-3.00)	10.1 (29.8%)
M38	1610 (75.6)	506 (86.3)	1.00 (0.50-3.00)	16.3 (86.1)
M30a	55.4 (56.3)	5.69 (56.2)	3.00 (1.00-6.00)	7.17 (32.5)

geometric mean and gCV (%)
[1] median and range

The following table summarizes the steady state geometric mean (%CV) PK parameters of flibanserin 100 mg in HSDD women.

	$AUC_{\tau,ss}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max}[1] (hr)	$t_{1/2}$ (hr)
Flibanserin	2080 (46.6)	469 (42.7)	1.00 (0.50-3.00)	11.4 (24.3)
M35	1760 (36.7)	641 (51.5)	1.00 (0.75-3.00)	12.6 (35.6)
M38	1760 (36.7)	641 (51.5)	1.00 (0.75-3.00)	12.6 (35.6)
M30a	57.2 (46.3)	6.39 (45.4)	2.00 (0.75-6.00)	9.49 (47.3)

geometric mean and gCV (%)
[1] median and range

2.2.5.3. What are the single dose and multiple dose PK parameters?

Single Dose Pharmacokinetics: The sponsor conducted a single dose PK study in HSDD women to evaluate the PK parameters of 100 mg qd flibanserin.

The following table summarizes single dose PK parameters of flibanserin.

	$AUC_{0\text{-}inf}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max}[1] (hr)	$t_{1/2}$ (hr)
flibanserin	1630 (54.6%)	336 (50.7%)	1.00 (0.50-3.00)	9.33 (27.8%)

geometric mean and gCV (%)
[1] median and range

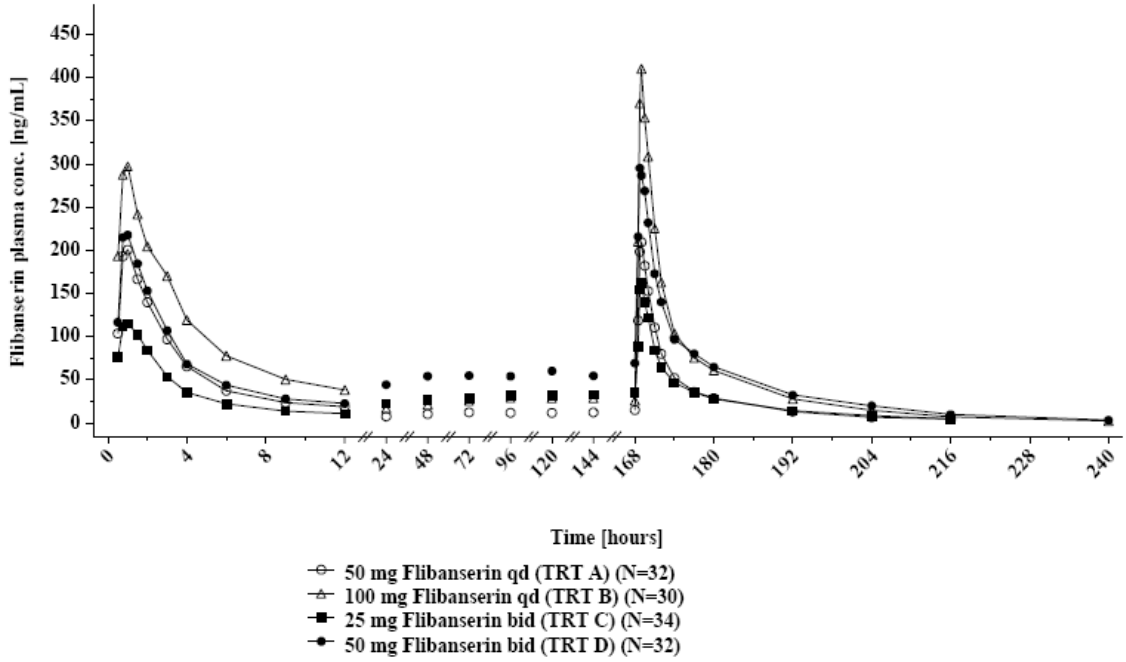
Multiple Dose Pharmacokinetics: The sponsor conducted a multiple dose PK study in HSDD women to evaluate the PK parameters of 100 mg qd flibanserin at steady state. Steady state was reached after 3 days.

The following table summarizes steady state PK parameters of flibanserin.

	$AUC_{\tau,ss}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max}[1] (hr)	$t_{1/2}$ (hr)
flibanserin	2080 (46.6%)	469 (42.7%)	1.00 (0.50-3.00)	11.4 (24.3%)

geometric mean and gCV (%)
[1] median and range

The following figure is the arithmetic mean drug concentraion-time profiles of flibanserin after oral administration (sponsor's figure 15.6.5.3:1).



Steady state was achieved after 3 days for flibanserin and metabolites in all dose groups. The flibanserin exposure increased generally in proportion with dose after single and multiple dosing and was slightly lower at steady state in the bid dose groups than in the qd dose groups. This was also reflected by the mean area under the AUC and Cmax accumulation ratios ranging from 1.20 to 1.44 and from 1.09 to 1.36, respectively, in the qd dose groups.

2.2.5.3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The sponsor did not evaluate PK of flibanserin 100 mg tablets in healthy women. Early in the development program the sponsor conducted PK studies in healthy male subjects. Prior to the NDA submission, DRUP requested sparse PK samples be taken from during the Phase 3 studies, the sponsor decided to assess PK for the doses studied in the pivotal Phase 3 trials (Study 511.105).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (race, BMI, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Renal impairment

The effect of mild-to-moderate renal impairment (7 patients) and severe renal impairment (9 patients) on the PK of flibanserin administered as a single oral dose of 50 mg in an open-label, single dose, parallel group comparison study was evaluated by the sponsor. Mild-to-moderate renal impairment did not significantly impact the systemic exposure to flibanserin (AUC0-inf increased by 12.0%), compared to subjects with normal renal function. Severe renal impairment had a moderate impact on the systemic exposure to flibanserin (AUC0-inf increased by 20.8%), compared to subjects with normal renal function.

Cmax decreased by 4.2% in mild-to-moderate renal impairment patients, compared to subjects with normal renal function. This is not significant given the level of variability in the data. Cmax increased 31.1% in severe renal impairment patients, compared to subjects with normal renal function.

The following table summarizes the PK parameters of flibanserin for mild-to-moderate and severe renal impairment patients, and matched healthy subjects.

PK parameter*	Mild-moderate renal impairment	Mild-moderate healthy matched	Severe renal impairment	Severe healthy matched
AUC0-inf (ng.hr/ml)	957 (69.3)	854 (45.7)	1220 (39.8)	1010 (41.9)
Cmax (ng/ml)	230 (53.6)	240 (35.3)	274 (41.8)	209 (64.2)
Tmax (hr)[1]	0.75 (0.53 – 1.50)	0.75 (0.50 – 0.75)	0.75 (0.27 – 1.00)	0.75 (0.48 – 2.00)
$t_{1/2}$ (hr)	9.85 (32.1)	10.1 (46.7)	10.9 (38.1)	11.2 (17.4)
CL/F (ml/min)	871 (69.3)	976 (45.7)	686 (39.8)	825 (41.9)

*geometric mean (%CV)
[1] tmax: median and range

The dose evaluated in this renal impairment study was 50 mg, while the proposed dose is 100 mg. A larger effect of renal impairment on flibanserin PK is possible at the higher dose. The proposed indication of flibanserin is for premenopausal women between the ages of 18 and 45 years.

(b) (4)

However, for the severe impairment group, an increase of 20.8% and 31.1% in AUC0-inf and Cmax, respectively, is not negligible considering the lower 50 mg dose evaluated in the study.

Hepatic impairment

The effects of mild (n=10 patients) and moderate (n=4 patients) hepatic impairments on the PK of flibanserin administered as a single oral dose of 50 mg were evaluated by the sponsor in an open-label, parallel group study. Systemic exposure to flibanserin was significantly affected by hepatic impairment. The AUC0-inf of flibanserin was significantly higher (4.5-fold) in patients with mild hepatic impairment compared to matched subjects. The AUC0-inf of flibanserin was higher (2.6-fold) in patients with moderate hepatic impairment compared to matched subjects.

Compared to their matching control group, patients with mild hepatic impairment had a slightly reduced Cmax (9.5%), but it was significantly lower (63% decrease) in patients with moderate hepatic impairment, compared to healthy controls. Clearance decreased 78% and 62% in the mild and moderate hepatic impairment patients, respectively, compared to the healthy matched subjects.

The following table summarizes the PK parameters of flibanserin for mild and moderate hepatic impairment patients, and matched healthy subjects.

PK parameter*	Mild hepatic impairment	Mild healthy matched	Moderate hepatic impairment	Moderate healthy matched
AUC0-inf (ng.hr/ml)	3310 (43.0)	730 (39.5)	2420 (65.1)	925 (52.9)
Cmax (ng/ml)	191 (53.9)	211 (38.9)	88.0 (62.8)	243 (65.9)
Tmax (hr)[1]	0.50 (0.25 – 4.00)	0.75 (0.48 – 1.50)	1.75 (0.50 – 3.00)	0.87 (0.75 – 1.00)
$t_{1/2}$ (hr)	25.6 (47.4)	10.6 (25.2)	26.1 (57.3)	9.91 (31.4)
CL/F (ml/min)	252 (43.0)	1140 (39.5)	345 (65.1)	900 (52.9)

*geometric mean (%CV)
[1] median and range

Due to the small number of patients with moderate hepatic impairment (n=4) enrolled in the study, this reviewer cautions on the limitations of using data generated from that group in making regulatory decisions. The sponsor did not enroll patients with severe hepatic impairment. As in the renal impairment study, the dose evaluated in this hepatic impairment study was 50 mg, while the proposed dose is 100 mg. A larger effect of hepatic impairment on flibanserin PK is possible at the higher dose.

In the proposed label, the sponsor does not recommend the use of flibanserin in hepatic impaired patients. (b) (4) For the targeted premenopausal population, this reviewer agrees with the sponsor in contraindicating the use of flibanserin in patients with hepatic impairment.

The mean steady state systemic exposures of flibanserin (AUCτ,ss) in HSDD women following once daily dosing of 50 mg and 100 mg dose are 991 and 2080 ng.hr/ml, respectively (Study 511.105). Under conditions where the metabolism of flibanserin is altered such hepatic impairment, the systemic exposures of a single 50 mg dose

flibanserin increased to 3310 ng.hr/hr. Based on the observed relationship between dose and adverse events, it is likely that patients with hepatic impairment will experience an increase in adverse events compared with subjects with normal hepatic function.

QT Prolongation

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

CYP2D6 polymorphism and effect of CYP2D6 inhibitor, paroxetine

The sponsor evaluated the effect of impaired CYP2D6 function on the PK of flibanserin 50 mg bid when given to CYP2D6 PMs or co-administered with an inhibitor of CYP2D6 in EMs in Study 511.87. EM and PM status of CYP2D6 were assessed by genotyping. EMs were defined as carriers of two functional alleles (*1,*2) and PMs were defined as carriers of two non-functional alleles (*3, *4, *5, *6, *7, and *8). Based on intra-individual comparison, no significant differences in flibanserin AUCτ,ss and Cmax,ss were noted in CYP2D6 EMs with or without co-administration of multiple doses paroxetine 20 mg. In EMs only, the geometric mean AUCτ,ss decreased by 2.5% and geometric mean Cmax,ss increased by 3.4% with co-administration of paroxetine; neither are considered significant.

Little differences in AUCτ,ss and Cmax,ss were seen between CYP2D6 PMs and EMs. In PMs the geometric mean AUCτ,ss was 18% higher and Cmax,ss was 4.1%, lower compared to the EMs without paroxetine.

In CYP2D6 IMs, no significant differences in flibanserin AUCτ,ss and Cmax,ss were observed with or without co-administration of paroxetine. In IMs, the geometric mean AUCss decreased by 5.8% and Cmax increased by 8.9% with co-administration of paroxetine. These changes are not considered significant.

Overall, there were small changes in flibanserin PK due to CYP2D6 polymorphism or co-administration of paroxetine in CYP2D6 EMs/IMs. These findings are not surprising considering flibanserin is extensively metabolized by CYP3A4 and only to a minor extent by CYP2D6.

For the M30a, AUCτ,ss and Cmax,ss geometric mean ratios were significantly increased by 500.4% and 382.0%, respectively (90% CIs: 394.51-634.72% and 309.15-471.93%), in EMs co-administrated with and without paroxetine. Based on inter-individual comparison between PMs and EMs, there was also a significant increase in AUCτ,ss and Cmax,ss ratios - 407.6% (90% CI: 296.15-560.94%) and 289.18% (90% CI: 218.85-382.11%), respectively. M30a is a phase 1 metabolite of flibanserin metabolism formed by CYP3A4, which is then further metabolized to M8 and M2 by CYP2D6. By exogenously blocking CYP2D6 metabolism through the co-administration of paroxetine or endogenously as evaluated in PMs, M30a have no metabolic pathway for its metabolism and thus its accumulation. Through receptor screening, M30a possesses some affinity to serotonergic receptors with approximately 5% molar exposure in plasma

compared to flibanserin. Therefore, exposure of M30a can be increased to a significant degree, but there is little clinical concern regarding this accumulation as this metabolite is inactive.

Age

The majority of studies were conducted in women with a mean age in the mid 30s. The target population is premenopausal women; therefore the sponsor did not evaluate the effect of age on flibanserin pharmacokinetics.

Gender

The proposed indication of flibanserin is for premenopausal women only.

Race

The sponsor evaluated flibanserin PK in a randomized, double-blind, placebo-controlled within dose groups, single rising, single center study in healthy Japanese women with a mean (range) age of 26.4 (20-34) years (Study 511.117). For single dose groups, following an overnight fast of at least 10 hours, the medication was administration with about 150 ml of water in the sitting position under supervision of the investigating physician or a designee. For multiple dose groups, the medication was administration about 2.5 hours after meal with about 150 ml of water in the sitting position under supervision of the investigating physician or a designee.

The table below is an outline of the trial design and plan (sponsor's table 9.1:1).

Dose group	A	B	C	D	E
Dose (mg)	25 mg	50 mg	1st week : 25 mg once daily (morning) 2nd week : 25 mg twice daily (morning, evening)	1st week : 50 mg once daily (morning) 2nd week : 50 mg twice daily (morning, evening)	1st week : 50 mg once daily (morning) 2nd week : 100 mg once daily (morning)
Duration	single	single	7 days + 7 days	7 days + 7 days	7 days + 7 days
No. of subjects	12	12	15	15	15
Subjects receiving drug	9	9	12	12	12
Subjects receiving placebo	3	3	3	3	3

Following single dose of 25 mg and 50 mg flibanserin, median Tmax was reached at 0.75 hr. The geometric mean $t_{1/2}$ values were 7 and 9 hrs following a single dose of 25 mg and 50 mg flibanserin, respectively. In healthy Japanese women, geometric mean AUC0-inf values were 607 and 988 ng.hr/ml following a single dose of 25 mg and 50 mg flibanserin, respectively. Geometric mean Cmax values were 199 and 273 ng/ml following a single dose of 25 mg and 50 mg flibanserin, respectively.

The following table summarizes the PK parameters of flibanserin following a single dose of 25 mg and 50 mg flibanserin.

SD PK parameter*	25 mg	50 mg
AUC0-inf (ng.hr/ml)	607 (52.4)	988 (34.4)
Cmax (ng/ml)	199 (20.8)	273 (33.9)
Tmax (hr)[1]	0.75 (0.50 – 4.00)	0.75 (0.50 – 3.00)
$t_{1/2}$ (hr)	7.27 (21.7)	8.98 (24.3)

*geometric mean (%CV)
[1] tmax: median and range

Following multiple doses of 25 mg qd, 50 mg qd, 100 mg qd, 25 mg bid, and 50 mg bid, flibanserin concentration rapidly increased and reached the median Tmax,ss between 0.750 to 1.25 hrs. The geometric mean $t_{1/2,ss}$ of flibanserin was in the range of 8.81 to 9.68 hrs. The pharmacokinetics of flibanserin after single dose are comparable to multiple dose characteristics. The accumulation ratio is in the range of 1.05 to 1.34, based on 25 mg qd and 50 mg qd doses. A dose proportional increase in Cmax,ss and AUCτ,ss is observed after multiple oral administrations.

The following table summarizes the steady state PK parameters of flibanserin following multiple dose of 25 mg qd, 50 mg qd, and 100 mg qd flibanserin.

SS PK parameter*	25 mg qd	50 mg qd	100 mg qd
AUCτ,ss (ng.hr/ml)	639 (38.7)	1320 (54.5)	2940 (66.9)
Cmax,ss (ng/ml)	165 (38.7)	365 (42.3)	674 (51.3)
Tmax,ss (hr)[1]	1.25 (0.50 – 6.00)	0.75 (0.50 – 3.00)	1.00 (0.50 – 3.00)
$t_{1/2,ss}$ (hr)	NC	NC	9.68 (41.6)

*geometric mean (%CV)
[1] tmax: median and range
NC: not calculated

The following table summarizes the steady state PK parameters of flibanserin following multiple dose of 25 mg bid and 50 mg bid flibanserin.

SS PK parameter*	25 mg bid	50 mg bid
AUCτ,ss (ng.hr/ml)	686 (34.8)	1540 (45.2)
Cmax,ss (ng/ml)	216 (24.8)	415 (39.2)
Tmax,ss (hr)[1]	1.25 (0.50 – 3.00)	0.88 (0.50 – 3.00)
$t_{1/2,ss}$ (hr)	9.26 (18.5)	8.81 (14.5)

*geometric mean (%CV)
[1] tmax: median and range

The sponsor did not enroll non-Asian subjects in this study. The majority of healthy subjects and patients enrolled in the clinical trials were Caucasian women. In an effort to

assess potential differences in flibanserin PK due to race, two cross-study comparisons were made between Japanese women and mainly Caucasian women.

The following table summarizes single dose PK parameters of flibanserin following a single 50 mg dose of flibanserin tablets in healthy Japanese women (Study 511.117) and in healthy Caucasian women enrolled in the ketoconazole study (Study 511.111), and their corresponding demographics.

SD PK parameter*	Healthy Japanese Women	Healthy Caucasian Women
AUC0-inf (ng.hr/ml)	988 (34.4)	1140 (43.5)
Cmax (ng/ml)	273 (33.9)	256 (27.4)
Tmax (hr)[1]	0.75 (0.50 – 3.00)	1.25 (0.75 – 2.00)
$t_{1/2}$ (hr)	8.98 (24.3)	8.54 (29.8)
Demographics		
Mean Age (range) (yrs)	26.4 (20 – 34)	34.1 (19 – 47)
Mean Weight (range) (kg)	51.84 (42.9 – 72.5)	62.3 (51 - 88)
Mean BMI (range) (kg/m^2)	20.25 (17.7 – 24.3)	22.83 (18.7 – 28.4)

*geometric mean (%CV)
[1] median and range

Though there is a small increase in exposure in Caucasian women, overall, there are no significant differences in flibanserin PK between healthy Japanese and Caucasian women following a single 50 mg dose of flibanserin.

The following table summarizes steady-state PK parameters of flibanserin following multiple doses of 100 mg qd in healthy Japanese women (Study 511.117) and in HSDD women (61 Caucasians & 6 African-Americans) (Study 511.105), and their corresponding demographics.

SS PK parameter*	Healthy Japanese Women	HSDD Caucasian & African-American Women
AUCτ,ss (ng.hr/ml)	2940 (66.9)	2080 (46.6)
Cmax,ss (ng/ml)	674 (51.3)	469 (42.7)
Tmax,ss (hr)[1]	1.00 (0.50 – 3.00)	1.00 (0.50 – 3.00)
$t_{1/2,ss}$ (hr)	9.68 (41.6)	11.4 (24.3)

Demographics		
Mean Age (range) (yrs)	26.4 (20 – 34)	34.4 (21 – 47)
Mean Weight (range) (kg)	51.8 (42.9 – 72.5)	67.8 (52 - 89)
Mean BMI (range) (kg/m^2)	20.25 (17.7 – 24.3)	25.05 (20.5 – 30.5)

*geometric mean (%CV)
[1] median and range

Because the sponsor did not evaluate the PK of 100 mg flibanserin tablets in healthy non-Asian women, it is not possible to directly compare flibanserin PK at 100 mg qd (or qhs) between healthy Asians and healthy non-Asians. The sponsor did evaluate 100 mg in HSDD women, who are otherwise in good health. In comparison to HSDD women of mainly Caucasian descent, AUCτ,ss and Cmax,ss is higher by 41.3% and 43.7%, respectively, in Japanese women. Tmax was the same in both groups, while $t_{1/2}$ is decreased by 1.72 hrs in Japanese women. The differences in steady state PK observed between Japanese and mainly Caucasian women contrast the findings with single dose flibanserin.

An underlying question is whether other intrinsic factors such as age, weight, and BMI affect flibanserin PK. It is worthy to note that in comparing the above PK data, non-Asian women weighed significantly more and had a higher BMI than Japanese women. Usually as weight increases, the volume of distribution increases leading to a decrease in concentration and Cmax. In comparing the two groups of women, it can be noted that the weight is higher in the Caucasian women, while the AUC and Cmax are both lower. Therefore, the differences in PK may not be attributed race, but rather to weight and/or BMI; both factors were not evaluated directly by the sponsor in the NDA.

When the mean flibanserin exposure in Japanese women was adjusted for weight (a factor of 0.764 (51.8/67.8) - weight of Japanese women divided by weight of Caucasian women), the AUCτ,ss in Japanese women was 2246 ng.hr/mL, which is comparable to 2080 ng.hr/mL in Caucasian women. The similarity in weight-adjusted AUCτ,ss suggests that weight, not race, is the factor contributing to the observed difference in flibanserin exposure between Japanese and Caucasian women.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (CYP3A4 inhibitors, CYP3A4 inducer) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Effect of itraconazole (a strong CYP3A4 inhibitor)
The sponsor evaluated the influence of multiple doses itraconazole at steady state on the pharmacokinetics of a single dose flibanserin (Study 511.37). This was a randomized, open label, two-way crossover study in male and female subjects to investigate the influence of CYP3A4 inhibitor itraconazole (oral 200 mg qd for 8 days) on the pharmacokinetics of a single tablet administration of 50 mg flibanserin with water.

Itraconazole co-administered with flibanserin increased flibanserin AUC0-inf by 2.6-fold and Cmax by 1.7-fold. $t_{1/2}$ was extended by 4.2 hrs from 7.44 to 11.6 hrs in the presence of itraconazole.

The following table summarizes PK parameters of flibanserin 50 mg single dose with and without itraconazole 200 mg co-administration.

	Flibanserin	
SD PK parameter*	With co-administration of itraconazole	Without co-administration of itraconazole
AUC0-inf (ng.hr/ml)	2810 (76.3)	1090 (57.5)
Cmax (ng/ml)	341 (32.5)	201 (49.8)
Tmax (hr)[1]	1.25 (1.00 – 4.00)	1.25 (0.50 – 3.00)
$t_{1/2}$ (hr)	11.6 (46.5)	7.4 (27.0)

*geometric mean (%CV)
[1] median and range

To assess whether and to what degree flibanserin would be affected by a CYP3A4 inhibitor, the sponsor selected 200 mg itraconazole. Although itraconazole is a suitable drug to evaluate potential CYP3A4 inhibition, the 200 mg dose selected for this study is lower than the recommended 400 mg dose and therefore the degree of inhibition by itraconazole is not maximized. Nonetheless, the results from this study show that flibanserin exposure increases in the presence of a strong CYP3A4 inhibitor and a significant drug interaction between itraconazole and flibanserin was demonstrated. Due to dose dependent increases in adverse events, it is likely to observe more adverse events when flibanserin is co-administered with a strong CYP3A4 inhibitor. The sponsor conducted another CYP3A4 inhibition study using ketoconazole 400 mg daily, a strong CYP3A4 inhibitor.

Effect of ketoconazole (a strong CYP3A4 inhibitor)

The sponsor evaluated the influence of multiple doses of the strong CYP3A4 inhibitor ketoconazole on the PK of flibanserin and metabolites after a single oral dose of 50 mg flibanserin (Study 511.111). This study was an open-label, randomized, two-period, crossover study. Flibanserin was administered with 240 ml of water in the morning about 1 hr after ketoconazole and light breakfast.

Ketoconazole 400 mg daily for 5 days inhibited flibanserin metabolism leading to a 4.6-fold increase in flibanserin AUC0-inf. Cmax increased 1.8-fold. Tmax increased slightly from 1.25 to 1.50 hr and $t_{1/2}$ was significantly prolonged from 8.5 to 15.9 hrs.

The following table summarizes PK parameters of flibanserin with and without co-administration of ketoconazole.

	Flibanserin	
SD PK parameter*	With co-administration of ketoconazole	Without co-administration of ketoconazole
AUC0-inf (ng.hr/ml)	5260 (56.5)	1140 (43.5)
Cmax (ng/ml)	472 (24.6)	256 (27.4)
Tmax (hr)[1]	1.50 (0.75 – 4.00)	1.25 (0.75 – 2.00)
$t_{1/2}$ (hr)	15.9 (41.7)	8.5 (29.8)

*geometric mean (%CV)
[1] median and range

Due to the high degree of inhibition of flibanserin metabolism in the presence of a strong CYP3A4 inhibitor ketoconazole and the likely incidence of increased adverse events with increase flibanserin exposure, the unresolved question is whether and to what degree flibanserin metabolism will be inhibited by mild and moderate CYP3A4 enzymes.

In the 2006 Draft Guidance to Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling, there is a decision tree (Appendix B) on page 27 encouraging sponsors to conduct in vivo studies with other inhibitors/inducers when in vivo studies with the most potent inhibitors/inducers show a significant interaction. Despite this available guidance, the sponsor did not evaluate the effect of mild or moderate CYP3A4 inhibitors on flibanserin PK. In the proposed label, the sponsor recommends (b) (4) It is important to address the effect of mild and moderate CYP3A4 inhibitors on flibanserin considering the long list (5 pages) of excluded medications in the pivotal Phase 3 studies and its likelihood of use in HSDD women. To fully understand the extent of CYP3A4 inhibition on flibanserin PK and to adequately label flibanserin so patients and prescribers are aware of potential drug interactions with all classes of CYP3A4 inhibitors, the sponsor will be requested to conduct drug interaction studies between flibanserin and weak and moderate CYP3A4 inhibitors as a post-marketing requirement, if the NDA is approved.

Effect of rifampicin (a strong CYP3A inducer)

The sponsor evaluated the influence of rifampicin, a strong CYP3A4 inducer, on the PK of flibanserin and relevant metabolites in an open-label, single center, randomized, two-period cross-over study in healthy females (Study 511.86). Rifampicin 600 mg daily was given in the evening for 7 days followed by a morning dose of flibanserin 100 mg on Day 8, and then rifampicin 600 mg was given for 2 additional evenings. In the group receiving no rifampicin, flibanserin 100 mg was given in the morning of study Day 1. Flibanserin and rifampicin were administered with 240 ml of water.

The geometric mean flibanserin exposure AUC0-inf was significantly lower when co-administered with rifampicin. Flibanserin AUC0-inf was reduced by 96% with rifampicin pre-treatment. Geometric mean flibanserin Cmax was also significantly lowered when co-administered with rifampicin. Cmax for flibanserin was reduced by

91%. Flibanserin metabolism is clearly influenced by the strong CYP3A4 inducer rifampicin.

The following table summarizes single dose PK parameters of flibanserin 100 mg with and without co-administration of rifampicin 600 mg for 10 days.

	Flibanserin	
SD PK parameter*	With co-administration of rifampicin	Without co-administration of rifampicin
AUC0-inf (ng.hr/ml)	93.5 (54.8)	2080 (45.0)
Cmax (ng/ml)	37.1 (57.1)	377 (46.4)
Tmax (hr)[1]	0.75 (0.50 – 1.50)	0.75 (0.50 – 2.00)
$t_{1/2}$ (hr)	5.05 (101)	10.7 (34.8)

*geometric mean (%CV)
[1] median and range

(b) (4)

This statement is weak in providing the level of detail to the user and prescriber regarding the extent of CYP3A4 induction. The label should state more explicitly the level of reduction in flibanserin exposure (~95%) when flibanserin is co-administered with a strong CYP3A4 inducer. Such statement can be a contraindication to use CYP3A4 inducers in patients taking flibanserin.

2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

The sponsor evaluated the metabolism of [14C]-flibanserin in human liver microsomes. The major metabolites produced by liver microsomes were M35 > M30a> M32 and M36. Recombinant human CYP3A4, CYP2D6, CYP2A6, and CYP2C were able to metabolize flibanserin, but metabolism by human liver microsomes were only correlated with CYP3A4 activity. To a lower extent, CYP2D6 also contributed to flibanserin metabolism in microsomes. Flibanserin inhibited CYP3A4 and CYP2B6 with Ki values of 7.5 and 6.4 uM, respectively. Based on these in vitro data, in vivo studies were conducted with CYP3A4 inhibitors itraconazole and ketoconazole, CYP3A4 inducer rifampicin, CYP3A4 probe simvastatin, and CYP2B6 substrate buproprion.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Is flibanserin a substrate of CYP2D6: effect of impaired CYP2D6 function and paroxetine?
See findings and discussion in section 2.3.1.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The sponsor has shown in vitro that flibanserin moderately inhibits CYP3A4 and CYP2B6 with Ki values of 7.5 µM and 6.4 µM, respectively. The sponsor decided to conduct two in vivo studies: (1) using simvastatin as CYP3A4 substrate to assess the extent of CYP3A4 inhibition by flibanserin and (2) using bupropion as CYP2B6 substrate to assess the extent of CYP2B6 inhibition by flibanserin.

Is flibanserin a CYP3A4 inhibitor: effect of simvastatin?
The sponsor evaluated 50 mg flibanserin bid for 4 days as a possible CYP3A4 inhibitor on the single dose PK of oral administration of 40 mg simvastatin in healthy female and male subjects (Study 511.37). This was an open-label, randomized, crossover study.

Flibanserin co-administered with simvastatin increased simvastatin exposure by 1.3-fold and Cmax by 1.2-fold. Half-life of simvastatin was extended slightly from 2.16 to 2.60 hrs in the presence of flibanserin.

The following table summarizes PK parameters of simvastatin with and without pre-treatment with flibanserin.

	simvastatin 40 mg SD + 50 mg flibanserin bid	simvastatin 40 mg SD
SD PK parameter*	simvastatin	
AUC0-inf (ng.hr/ml)	47.4 (36.1)	36.1 (38.1)
Cmax (ng/ml)	19.0 (49.5)	16.6 (44.1)
Tmax (hr)[1]	1.00 (0.50 – 4.00)	1.00 (1.00 – 2.00)
$t_{1/2}$ (hr)	2.60 (41.7)	2.16 (24.6)

*geometric mean (%CV)
[1] median and range

Flibanserin co-administered with simvastatin increased simvastatin acid exposure by 1.5-fold and Cmax by 1.4-fold. $t_{1/2}$ of simvastatin acid was extended slightly from 3.55 to 4.31 hrs in the presence of flibanserin.

The following table summarizes PK parameters of simvastatin acid with and without pre-treatment with flibanserin.

	simvastatin 40 mg SD + 50 mg flibanserin bid	simvastatin 40 mg SD
SD PK parameter*	simvastatin acid	
AUC0-inf (ng.hr/ml)	22.6 (57.9)	15.4 (71.2)
Cmax (ng/ml)	3.56 (42.7)	2.61 (54.6)
Tmax (hr)[1]	1.25 (0.50 – 6.00)	1.75 (1.00 – 8.00)
$t_{1/2}$ (hr)	4.31 (39.0)	3.55 (39.2)

*geometric mean (%CV)
[1] median and range

The sponsor states that flibanserin showed only a minor interaction with simvastatin, a sensitive CYP3A4 substrate, and that flibanserin's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance. (b) (4) The proposed clinical dose being sought for the treatment of HSDD is 100 qhs. In an ascending multiple doses phase I study 511.105 in HSDD women, the steady-state exposure of flibanserin was 2080 and 1400 ng.hr/ml for 100 mg qhs and 50 mg bid, respectively. It is possible that the degree of CYP3A4 inhibition by flibanserin will be higher in the proposed 100 mg qhs dosing regimen, compared with 50 mg bid due to higher exposure with 100 mg qhs.

In the proposed label, the sponsor states (b) (4) Without data from a study evaluating simvastatin and flibanserin 100 mg, it is not possible to conclude that flibanserin does not inhibit CYP3A4 activity.

Is flibanserin a CYP2B6 inhibitor: effect on bupropion?

The sponsor states that based on in vitro results, there was a possibility that flibanserin inhibits the metabolism of bupropion by CYP2B6, despite Ki for CYP2B6 that is comparable to CYP3A4 inhibition where the in vivo simvastatin (a sensitive CYP3A4 substrate) inhibition was not clinically significant. The sponsor conducted an in vivo study, using bupropion as CYP2B6 substrate, to assess the extent of CYP2B6 inhibition by flibanserin (Study 511.88).

This was an open-label, randomized, two-period crossover study in Caucasian women. Flibanserin 50 mg bid was given for 2 days followed by 100 mg qd for 13 days. Bupropion 150 mg bid was given for 8 days beginning on Day 6 of flibanserin treatment. Subjects received the study drugs together with 240 ml tap water in the morning at about 8 am after an overnight fast of at least 10 hours. The intake of the evening dose was together with 240 ml tap water at about 8 pm.

There was essentially no difference in geometric mean exposure AUCss and Cmax for bupropion at steady-state when co-administered with flibanserin. For bupropion, the geometric mean ratio (90% CI) for AUCτ,ss and Cmax,ss was 102.7 (97.2-108.5%) and 102.5 (94.1-111.6%) with and without flibanserin 100 mg qd, respectively.

The following table summarizes PK parameters of bupropion with and without pre-treatment with flibanserin.

	bupropion 150 mg bid + flibanserin 100 mg qd	Bupropion 150 mg bid
SS PK parameter*	bupropion	
AUCτ,ss (ng.hr/ml)	540 (28.5)	525 (31.2)
Cmax,ss (ng/ml)	73.3 (30.9)	71.0 (32.9)
Tmax,ss (hr)[1]	3.00 (1.13 – 4.00)	3.00 (1.00 – 4.00)
$t_{1/2,ss}$ (hr)	24.3 (23.9)	25.0 (28.6)

*geometric mean (%CV)
[1] median and range

The geometric mean hydroxybupropion exposure AUCss and geometric mean hydroxybupropion Cmax at steady-state was lower when co-administered with flibanserin. Hydroxybupropion Tmax (median and range) was reached 4.00 hrs (2.00-10.00 hrs) and 4.00 (1.00-8.00 hrs) after the last dose for both groups, respectively. T1/2,ss were similar at 21.9 and 24.2 hrs for hydroxybupropion with and without pre-treatment with flibanserin, respectively.

The following table summarizes PK parameters of hydroxybupropion with and without pre-treatment with flibanserin.

	bupropion 150 mg bid + flibanserin 100 mg qd	Bupropion 150 mg bid
SS PK parameter*	hydroxybupropion	
AUCτ,ss (ng.hr/ml)	8760 (50.3)	9660 (39.8)
Cmax,ss (ng/ml)	822 (50.0)	928 (39.7)
Tmax,ss (hr)[1]	4.00 (2.00 – 10.00)	4.00 (1.00 – 8.00)
$t_{1/2,ss}$ (hr)	21.9 (28.8)	24.2 (39.6)

*geometric mean (%CV)
[1] median and range

In the proposed label, the sponsor states that flibanserin does not inhibit CYP2B6 and (b) (4) the metabolism of drugs metabolized by this enzyme.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The target population for flibanserin is premenopausal women, who are likely to take OCs or COCs. To rule out potential drug-drug interaction between flibanserin and OCs/COCs, the sponsor evaluated the pharmacokinetics of EE and LNG in the presence of flibanserin (Study 511.93). Healthy premenopausal women were given a single oral dose of 30 µg EE/150 µg LNG after 14 days of receiving flibanserin 100 mg daily. In subjects without flibanserin, they were given a single dose of 30 µg EE/150 µg LNG.

EE increased slightly when COC was co-administered with flibanserin. Following flibanserin administration, the geometric mean AUC0-inf and Cmax increased 8.3% and 5.7%, respectively. The half-life remained relatively constant: 13.0 and 13.6 hrs in the presence and absence of flibanserin, respectively.

The following table summarizes PK parameters of EE with and without flibanserin.

	30 µg EE/150 µg LNG + flibanserin 100 mg qd for 14 days	30 µg EE/150 µg LNG
SD PK parameter*	EE	
AUC0-inf (ng.hr/ml)	708 (30.6)	654 (34.3)
Cmax (ng/ml)	68.3 (38.5)	64.6 (27.3)
Tmax (hr)[1]	1.50 (1.00 – 2.00)	1.50 (1.00 – 3.00)
$t_{1/2}$ (hr)	13.0 (21.4)	13.6 (39.0)

*geometric mean (%CV)
[1] median and range

LNG PK was essentially the same when COC was co-administered with flibanserin. AUC0-inf increased 1.2%. Cmax change of 0.02 ng/ml is negligible. The half-life remained relatively constant: 26.3 and 26.0 hrs in the presence and absence of flibanserin, respectively.

The following table summarizes PK parameters of LNG with and without flibanserin.

	30 µg EE/150 µg LNG + flibanserin 100 mg qd for 14 days	30 µg EE/150 µg LNG
SD PK parameter*	LNG	
AUC0-inf (ng.hr/ml)	49.2 (44.9)	48.6 (42.2)
Cmax (ng/ml)	4.73 (35.2)	4.75 (36.1)
Tmax (hr)[1]	1.00 (0.50 – 2.00)	1.00 (0.50 – 1.50)
$t_{1/2}$ (hr)	26.3 (33.3)	26.0 (39.0)

*geometric mean (%CV)
[1] median and range

There appears to be a small increase in EE when the combination oral contraceptive Microgynon® was co-administered with flibanserin. Overall, flibanserin given daily does not appear to affect EE and LNG exposure.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Due to the high degree of inhibition of flibanserin metabolism in the presence of a strong CYP3A4 inhibitor ketoconazole and the likely incidence of increased adverse events with increase flibanserin exposure, the unresolved question is whether and to what degree flibanserin metabolism will be affected by weak and moderate CYP3A4 inhibitors. The sponsor did not evaluate the effect of weak and moderate CYP3A4 inhibitors on flibanserin pharmacokinetics. In a decision tree in the 2006 Draft Guidance to Industry Drug Interactions Studies, sponsors are encouraged to study other inhibitors/inducers when in vivo studies with the most potent inhibitors/inducers show a significant interaction. In a face-to-face pre-Advisory Committee meeting with the sponsor on April 26, 2010, the sponsor was made aware of our concern that there were no drug interaction data between flibanserin and weak and moderate CYP3A4 inhibitors. As a follow-up to that meeting, the sponsor submitted a preliminary risk management proposal (dated May 26, 2010) stating that they plan to conduct a drug-drug interaction study between flibanserin and to provide for review a meta-analysis of subjects on flibanserin and taking oral contraceptives (a weak CYP3A4 inhibitor).

In a face-to-face post-Advisory Committee meeting on July 22, 2010, the sponsor agreed to conduct a DDI study with flibanserin 100 mg and moderate CYP3A4 inhibitor. The sponsor also agreed to submit the meta-analysis report on flibanserin and oral contraceptives. Based on the results from the DDI study with moderate CYP3A4 inhibitor and report with oral contraceptives, a detemination will be made whether the sponsor will need to conduct a DDI study with flibanserin 100 mg and weak CYP3A4 inhibitor.

2.5 General Biopharmaceutics

Flibanserin was rapidly absorbed (Tmax 0.5-1.0 hr) after oral administration and has an absolute bioavailability of 33%. Excretion of ^{14}C-flibanserin was recovered in urine (~40%) and feces (~50%) after intravenous and oral administration. Flibanserin is 98% protein bound.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The sponsor evaluated the effect of different food types on the PK of flibanserin after a single 50 mg dose of flibanserin tablet in an open-label, four-way, crossover study in 16 healthy subjects (Study 511.26). Compared to the fasted condition, the exposure of flibanserin was 17%, 41%, and 53% higher after administration of a light, medium, and high fat/caloric breakfast, respectively. The total flibanserin exposure increased with increasing fat/calorie content.

The Cmax was essentially the same between the light breakfast and fasted groups, with slight decrease of 3.9% in the light breakfast group. This is not meaningful considering the level of variability in the data. In the medium and high fat/caloric breakfast groups, Cmax increased slightly by 12 and 14%, respectively, compared with the fasted condition.

Tmax was prolonged slightly from 0.8 hr under fasted condition up to 2 hrs under high fat/caloric meal.

The following table summarizes PK parameters of flibanserin after administration of food with varying fat/caloric content:

	Meal Type			
PK parameter*	Fasted	Light Fat	Medium fat	High Fat
AUC0-inf (ng.hr/ml)	821 (52.0)	959 (50.1)	1160 (46.6)	1260 (49.1)
Cmax (ng/ml)	207 (34.7)	199 (33.1)	232 (43.9)	236 (38.7)
Tmax (hr)	0.77 (36.7)	1.78 (67.8)	1.19 (65.0)	2.03 (74.1)
$t_{1/2}$ (hr)	7.55 (37.1)	7.79 (33.2)	7.52 (27.0)	7.93 (30.5)

*Arithmetic mean (%CV)

Under the worst case scenario with high fat/caloric breakfast, the exposure increased by 53%. Cmax was influenced less by food, while Tmax was prolonged slightly. The recommendation dose for flibanserin in HSDD women is 100 mg at bedtime. It is possible that the exposure can increase more than 53% when patients are taking the recommended 100 mg dose, compared to 50 mg as evaluated in this study.

There was no mention by the sponsor with regard to the administration of food in the pivotal phase 3 studies 511.71 and 511.75. The protocols for these studies indicate that flibanserin tablets were given with 150 ml of fluid. The sponsor proposes in the label that flibanserin be given at bedtime (b) (4). Even though there is an increase in exposure of up to 53% in the high fat/caloric breakfast group, it is unlikely patients taking this medication will consume a high fat/caloric meal prior to bedtime. Additionally, the dosing instruction for the phase 3 studies included 150 ml of fluid, not water. It is possible that patients consumed fluids (e.g. fruit juices) with varying levels of calories. Under the proposed dosing regimen at bedtime, this reviewer finds the sponsor's dosing recommendation (b) (4) acceptable.

The sponsor conducted two additional studies to evaluate the effect of food on extended release formulation. In study 511.110, the sponsor evaluated the relative bioavailability and sedative effects of three modified release formulations (b) (4), compared to immediate release tablets. The relative bioavailability between immediate release tablet and nine extended release formulations (b) (4) was evaluated in study 511.115. The to-be-marketed and phase 3 clinical trials formulation is an immediate tablet; therefore, the studies evaluating the effect of food on extended release formulations were briefly reviewed.

2.6. Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations and were they validated?

The sponsor used LC-MS/MS for the majority of PK studies and validated the method for the determination of flibanserin (BIMT 17 BS) and two metabolites (TFMPP and BIMA 23 BS) in human plasma. The method was validated for precision, accuracy, specificity, and recovery; the results are acceptable. The sponsor met the Agency's recommended acceptance criteria of $\leq$20% for precision (CV%) and within $\pm$20% for accuracy at the lower limit of quantitation and $\leq$15% or within $\pm$15% at all concentrations. There were 10 calibration standards with concentrations of 0.5, 1, 2.5, 5, 10, 25, 50, 100, 250, and 500 ng/mL.

The following table is a summary of the validation results (sponsor's table 1.1, study QA598).

Analyte	BIMT 17 BS		BIMA 23 BS		TFMPP	
Calibration range [ng/mL]	0.500 ng/mL (LLOQ) – 500 ng/mL (ULOQ)					
Required sample volume [µL]	100					
r^2 (mean) of the standard curves	0.99529		0.99863		0.99363	
Recovery Analyte (%)	72.9 – 83.0		75.8 – 83.2		34.4 – 35.8	
Recovery IS (%)	83.4		78.7		32.6	
QC level [ng/mL]	0.500	400	0.500	400	0.500	400
Number of replicates (n)	18	21	18	21	18	21
Precision (cv %) of QC samples	12.50	3.32	9.91	2.98	6.99	3.44
Accuracy (% bias) of QC samples	-8.93	-8.24	4.03	3.49	9.66	4.63

3. Labeling

The sponsor will receive a complete response; no labeling discussion will take place.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAI M LEE
08/25/2010

EDWARD D BASHAW
08/26/2010

3. Appendix

Individual Study Synopsis

Table of Contents

Study c-10165-040-0404

Title: Investigation of the passive and active (P-glycoprotein mediated) transport of flibanserin in vitro by means of permeability measurements across confluent Caco-2 cell monolayers.

Objectives: To classify the in vitro permeability of flibanserin and to assess whether flibanserin is a substrate and/or inhibitor for the efflux transporters P-glycoprotein (P-gp) and multidrug resistance associated protein (MRP).

Methods: Caco-2 cells were obtained by [redacted]. The maintenance culture cells were maintained at 37°C, 5% CO_2, and 90% relative humidity in 175 cm^2 culture flasks in supplemented Dulbecco's Modified Eagle Medium (DMEM). The cells were passaged once a week using trypsin/EDTA solution with about 1 x 10^6 cells per flask. The culture medium was changed three times a week. For transport experiments, Caco-2 cells were seeded at a density of 60,000 cells/cm^2 on transwell filter inserts. The inserts were placed into 12-well flat bottom cluster plates. The inserts (apical compartment) and the outer wells (basal compartment) were filled with 0.5 mL and 1.5 mL of DMEM culture medium, respectively. The cells were cultured at 37°C, 5% CO_2, and 90% relative humidity in DMEM culture medium to confluency for 14 to 30 days. Confluency and tightness of the cell monolayer was routinely checked by measuring the transepithelial electrical resistance using an Evom voltmeter.

Transport experiments: Each transport experiment consisted of triplicate incubations using different filter inserts for the incubation. About 0.5 hr before the start of the experiment, the culture medium on both sides of the monolayer was replaces by transport buffer and the cells were equilibrated in the transport buffer at 37°C. For the apical-to-basal (absorptive) or basal-to-apical (secretory) transport experiment, the transport buffer on the apical (0.5 mL) and basal (1.5 mL) side of the cell monolayer (donor compartment) was replaced by transport solution containing the radiolabelled drug with or without inhibitor. The opposite chamber (receiver compartment) was filled with bovine serum albumin (BSA) transport buffer supplemented with or without inhibitor. The cells were preincubated for 30-45 minutes. The transport experiment was started (time t=0) with the first samples taken from the receiver compartment. The cells were incubated for 90 minutes. Samples (100 uL) were taken at t=0 and 90 minutes from the donor compartment representing the start and end concentration in the donor compartment, respectively. Samples (300 uL) were taken at t=0, 30, 60, and 90 minutes from the receiver compartment; aliquots drawn from the receiver compartment were replaces with fresh pre-warmed BSA-transport buffer with or without inhibitor. The samples were measured for radioactivity by liquid scintillation counting. For experiments assessing the inhibition of P-gp-mediated transport, the transporter substrate was added to the donor compartment and the inhibitor was added at identical concentration to both sides of the monolayer.

Apparent permeability coefficient calculation:
The apparent permeability coefficient (Papp) was calculated from the initial concentration in the donor compartment and the transport rate using the following equation:

$$Papp\ (cm/s) = \frac{1}{A.C_{t0}} \cdot \frac{V_R.\Delta C_R}{\Delta t}$$

Papp: apparent permeability coefficient (cm/s)
C_{t0}: substance concentration in the donor compartment at time t=0 (dpm/mL)
A: area of the filter (cm2)

V_R: volume in the receiver compartment (mL)
$\Delta C_R/\Delta t$: change in substance concentration over time in the receiver compartment (dpm/(mL.s)

The transport rate $V_R.dC_R/dt$ was calculated from the linear part of the drug concentration versus time curve in the receiver compartment.

Individual permeability coefficients were calculated for each of the triplicate incubations performed per transport experiment and averaged to the reported apparent permeability coefficient (Papp) with the calculated standard deviation (sd) and coefficient of variation (cv) to describe the individual incubations within a transport experiment.

Efflux ratio:
The basal-to-apical to apical-to-basal transport was calculated with the following equation:

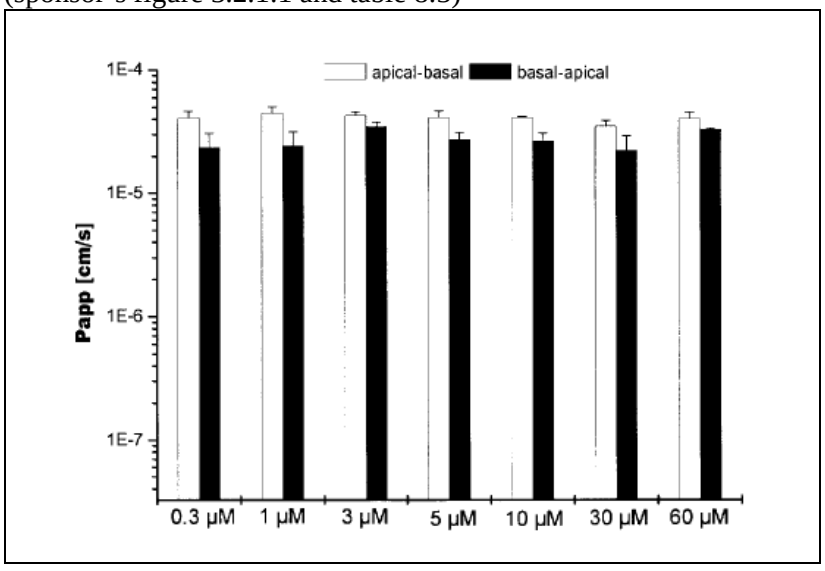
$$= \frac{\text{Papp, b-a}}{\text{Papp, a-b}}$$

Uptake ratio:
The apical-to-basal to basal-to-apical transport was calculated with the following equation:

$$= \frac{\text{Papp, a-b}}{\text{Papp, b-a}}$$

Results: The sponsor evaluated the passive and active P-glycoprotein or multidrug resistance associated protein transport of flibanserin in vitro by assessing the permeability across Caco-2 monolayers. The apical-to-basal and basal-to-apical permeability of flibanserin were measured in Caco-2 cell monolayers.

The following figure and table are the apical-to-basal and basal-to-apical apparent permeability coefficients (Papp) of flibanserin as a function of concentration in the donor compartment. (sponsor's figure 3.2.1:1 and table 8:3)

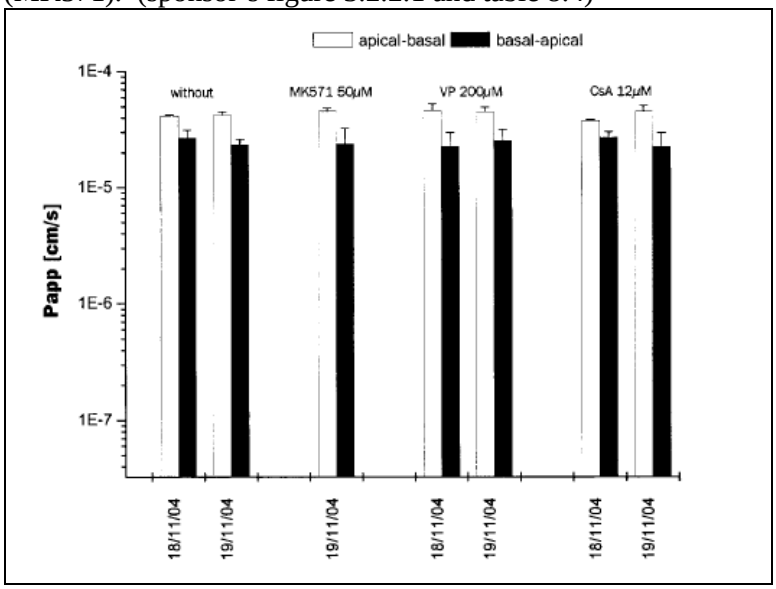


apical-basal					basal-apical				efflux	uptake
calculated conc. [µM]	measured conc. [µM]	Papp [cm/s] (n = 3) mean	sd	cv[%]	measured conc. [µM]	Papp [cm/s] (n = 3) mean	sd	cv[%]	ratio	ratio
0.3	0.24	4.10E-05	5.48E-06	13.4	0.34	2.35E-05	7.46E-06	31.7	0.57	1.74
1.0	0.69	4.51E-05	5.48E-06	12.1	0.97	2.44E-05	7.39E-06	30.3	0.54	1.85
3.0	2.23	4.32E-05	2.92E-06	6.8	2.94	3.52E-05	2.88E-06	8.2	0.82	1.23
5.0	3.66	4.16E-05	5.43E-06	13.1	4.92	2.76E-05	3.79E-06	13.7	0.66	1.51
10.0	7.48	4.15E-05	1.10E-06	2.6	10.48	2.67E-05	4.36E-06	16.3	0.64	1.55
30.0	18.23	3.56E-05	3.61E-06	10.1	28.18	2.26E-05	6.98E-06	30.9	0.64	1.57
60.0	31.96	4.07E-05	5.49E-06	13.5	48.17	3.35E-05	9.12E-07	2.7	0.82	1.22
	mean	**3.81E-05**				**2.81E-05**			**0.74**	**1.39**
	SD	**2.57E-06**				**5.44E-06**			**0.09**	**0.18**
	CV(%)	**6.7**				**19.4**			**12.7**	**12.8**
	N	**7**				**7**			**7**	**7**

The in vitro bi-directional transport experiment showed that the transport of flibanserin was concentration independent from 0.3 to 60 uM. The apical-to-basal permeability coefficient was relatively constant within the concentration range studied with an average of 3.81 x 10^{-5} cm/s (6.7% CV). Though the variability was a little higher, the basal-to-apical permeability coefficient was also relatively constant with an average of 2.81 x 10^{-5} cm/s (19.4% CV). The apical-to-basal permeability was slightly higher at all concentrations compared to the basal-to-apical permeability; the resulting average uptake and efflux ratio was 1.39 (12.8% CV) and 0.74 (12.7% CV), respectively. Flibanserin showed high and comparable permeability for both transport directions, and thus classifying flibanserin as a highly permeable drug.

To determine whether flibanserin is actively transported by P-gp or MRP, the apical-to-basal and basal-to-apical permeability of flibanserin were assessed in the absence and presence of P-gp inhibitors verapamil and cyclosporin A, and MRP inhibitor MK571. The concentration of flibanserin was 10 uM.

The following figure and table are the apparent permeability coefficients for the inhibition of the apical-to-basal and basal-to-apical transport of flibanserin in the absence (without) and presence of P-gp inhibitors verapamil (VP) and cyclosporin A (CsA), and MRP inhibitor MK571 (MK571). (sponsor's figure 3.2.2:1 and table 8:4)



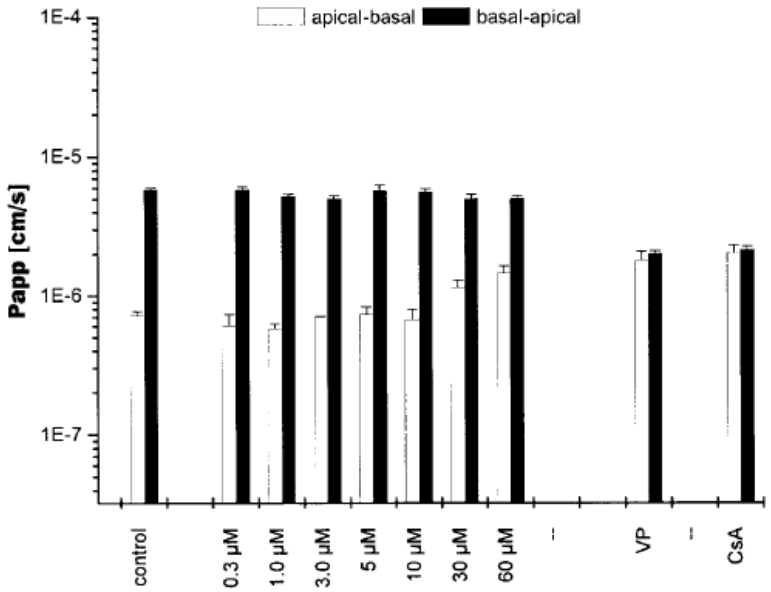
Note: the x-axis represents dates the experiments were conducted.

Date	Inhibitor	apical-basal				basal-apical				Efflux ratio	Uptake ratio
		conc. [µM]	Papp [cm/s] (n = 3) mean	sd	cv[%]	conc. [µM]	Papp [cm/s] (n = 3) mean	sd	cv[%]		
18.11.04	without	7.48	4.15E-05	1.10E-06	2.6	10.48	2.67E-05	4.36E-06	16.3	0.64	1.55
19.11.04	without	6.93	4.23E-05	2.93E-06	6.9	9.93	2.33E-05	2.65E-06	11.4	0.55	1.81
	mean		4.19E-05				2.50E-05			0.60	1.68
	SD		4.17E-07				1.70E-06			0.04	0.11
	CV(%)		1.0				6.8			6.4	6.4
19.11.04	MK571 25µM	7.10	4.56E-05	2.99E-06	6.6	10.68	2.39E-05	8.69E-06	36.3	0.52	1.91
18.11.04	VP 200 µM	7.54	4.61E-05	6.41E-06	13.9	10.84	2.25E-05	7.06E-06	31.4	0.49	2.05
19.11.04	VP 200 µM	7.16	4.51E-05	4.13E-06	9.2	10.41	2.54E-05	6.40E-06	25.3	0.56	1.78
	mean		**4.56E-05**				**2.39E-05**			**0.53**	**1.91**
	SD		**4.98E-07**				**1.43E-06**			**0.04**	**0.14**
	CV(%)		**1.1**				**6.0**			**7.1**	**7.1**
18.11.04	CsA 12 µM	8.12	3.78E-05	8.25E-07	2.2	11.02	2.70E-05	3.21E-06	11.9	0.71	1.40
19.11.04	CsA 12 µM	7.65	4.54E-05	5.26E-06	11.6	10.93	2.23E-05	7.39E-06	33.0	0.49	2.03
	mean		**4.16E-05**				**2.47E-05**			**0.60**	**1.72**
	SD		**3.76E-06**				**2.32E-06**			**0.11**	**0.31**
	CV(%)		**9.0**				**9.4**			**18.3**	**18.3**

In the absence of inhibitor (without), the mean efflux ratio was 0.60. There appears to be no active transport of flibanserin 10 uM by the P-gp inhibitors verapamil 200 uM (efflux ratio: 0.53) and cyclosporin A 12 uM (efflux ratio: 0.60), or MRP inhibitor MK571 50 uM (efflux ratio: 0.52). Even in the presence of known P-gp inhibitors verapamil and cyclosporin A, and MRP inhibitor MK571, efflux of flibanserin remained relatively constant with a mean efflux ratio of 0.53, 0.60, and 0.52, respectively. This suggests that flibanserin is not a substrate for P-gp or MRP. Not only is flibanserin transport unaffected by P-gp or MRP inhibitors, a low mean efflux ratio of less than 2 also suggests that P-gp and MRP do not impact the apparent permeability of flibanserin.

To determine whether flibanserin is a P-gp inhibitor, the sponsor conduct an in vitro study with flibanserin and [3H]-digoxin 1uM, a P-gp substrate. As positive controls, the sponsor evaluated the transport of digoxin in the presence of P-gp inhibitors verapamil 200 uM and cyclosporin A 12 uM.

The following figure and table are the apparent permeability coefficients for the inhibition of apical-to-basal and basal-to-apical transport of [3H]-digoxin in the absence (control) and presence of flibanserin and the P-gp inhibitors verapamil (VP) and cyclosporin A (CsA). (sponsor's figure 3.3:1 and table 8:5)



Inhibitor	apical-basal				basal-apical				Efflux ratio
	digoxin conc.	Papp [cm/s] (n = 3)			digoxin conc	Papp [cm/s] (n = 3)			
	[µM]	mean	sd	cv[%]	[µM]	mean	sd	cv[%]	
none	0.80	7.23E-07	4.99E-08	6.9	0.85	5.90E-06	1.82E-07	3.1	8.15
BIMT 17 BS 0.3 µM	0.87	6.10E-07	1.27E-07	20.8	0.92	5.83E-06	3.35E-07	5.7	9.54
BIMT 17 BS 1 µM	0.90	5.81E-07	4.93E-08	8.5	0.89	5.27E-06	1.65E-07	3.1	9.08
BIMT 17 BS 3 µM	0.87	7.03E-07	1.19E-08	1.7	0.91	5.04E-06	2.77E-07	5.5	7.17
BIMT 17 BS 5 µM	0.98	7.40E-07	9.55E-08	12.9	0.95	5.74E-06	5.61E-07	9.8	7.76
BIMT 17 BS 10 µM	0.95	6.76E-07	1.29E-07	19.0	1.04	5.68E-06	2.55E-07	4.5	8.39
BIMT 17 BS 30 µM	1.03	1.16E-06	1.46E-07	12.6	1.06	5.04E-06	3.60E-07	7.1	4.34
BIMT 17 BS 60 µM	1.08	1.46E-06	1.85E-07	12.6	1.09	5.04E-06	2.84E-07	5.6	3.44
VP 200 µM	1.07	1.82E-06	2.75E-07	15.1	1.05	2.02E-06	1.05E-07	5.2	1.11
CsA 12 µM	0.98	2.06E-06	2.61E-07	12.7	1.02	2.15E-06	1.31E-07	6.1	1.05

Based on an efflux ratio of 8.15, the transport of digoxin alone was clearly favored from basal to apical side. In contrast, in the presence of P-gp inhibitors verapamil and cyclosporin A, digoxin transport in both directions was the same and the efflux ratios were near unity at 1.11 and 1.05, respectively. At flibanserin concentrations from 0.3 to 10 uM, the permeabilities and efflux ratios were relatively constant and there appears to be no P-gp inhibitory effect from flibanserin. The efflux ratios ranged from 7.17 to 9.54, which are similar to digoxin without an inhibitor. At flibanserin concentrations of 30 and 60 uM , the efflux ratio decreases to 4.34 and 3.44, respectively, suggesting there may be some P-gp inhibitory effect from flibanserin. The degree of inhibition by flibanserin is not similar to well known inhibitors such as verapamil and cyclosporin A.

Overall, in vitro drug-drug interaction studies showed that flibanserin was not a P-gp substrate. At a high flibanserin concentration (30 and 60 uM), the apical to basal transport of digoxin was increased slightly, though the basolateral to apical transport of digoxin was not affected. Flibanserin does not appear to be a P-gp inhibitor.

Study 511.15

Title: A two-way crossover study investigating the pharmacokinetics and metabolism of flibanserin after administration of a single intravenous dose of 20 mg and a single oral dose of 50 mg [^{14}C]-radiolabelled flibanserin to six healthy male volunteers.

Objective: To primary object of the study was to evaluate the absorption, metabolism and excretion of [^{14}C]-flibanserin. The secondary objectives were to assess safety and tolerability.

Methods: This was a single dose, open-label, two-way crossover study. A total of eight healthy male subjects were enrolled and treated in the trial; 6 subjects completed the study while 2 subjects were withdrawn from the study because they did not receive the correct oral dose (25 mg [^{14}C]-flibanserin instead of 50 mg). The median age was 57.5 years; range was 51-62 years. Median (range) height and weight were 183.5 (175-192) cm and 76.05 (72.2-86.4) kg, respectively. Each volunteer was infused with 40.66 gm (38.72 mL) of [^{14}C]-radiolabelled flibanserin solution corresponding to 110.186 x 10^6 dpm of radioactivity and 20 mg flibanserin. Each volunteer received an oral dose of 50.0 gm (47.62 mL) of oral drinking solution, which corresponds 108.477 x 10^6 dpm of radioactivity and 50.0 mg of flibanserin.

Pharmacokinetic Sampling:
Blood samples were collected according to the following schedule:
Treatment A (intravenous infusion): predose, 10, 20, 30, 35, and 45 minutes and 1, 2, 4, 6, 8, 12, 24, 32, 48, 72, 96 and 120 hours after start of infusion.
Treatment B (oral solution): predose, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, 32, 48, 72, 96 and 120 hours after administration.

Urine samples were collected predose (-12-0), 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hrs after each administration.

Feces were collected predose, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hrs after each administration.

Results: Following oral administration of 50 mg [^{14}C]-flibanserin, the geometric mean Cmax (range) of radioactivity in plasma was 983 (861-1080) ng eq/mL and the terminal geometric mean plasma half-life of radioactivity (%CV) was 66.4 (11.2) hrs. The geometric mean (%CV) AUC0-inf for radioactivity was 10,207 ng eq.hr/mL (13.3) (sponsor's tables 9.4.2.1:1, 9.4.2.1:2 & 9.4.2.1:4)

C_{max}	intravenous infusion (n = 6)		oral administration (n = 6)	
	blood [ng eq/mL]	plasma [ng eq/mL]	blood [ng eq/mL]	plasma [ng eq/mL]
gmean	299	466	574	983
range	224-368	362-612	527-631	861-1080
gCV	19.6	22.4	7.5	9.5
Source data: Appendix 15.9.3.4, TABLE:	15.9.3.4: 9	15.9.3.4: 11	15.9.3.4: 10	15.9.3.4: 12

$t_{½}$		intravenous infusion (n = 6)	oral administration (n = 6)
		plasma	plasma
gmean	[h]	62.3	66.4
gCV	(%)	20.1	11.2
Source data: Appendix 15.9.3.4, TABLE:		15.9.3.4: 11	15.9.3.4: 12

Following oral administration of 50 mg [^{14}C]-flibanserin, the geometric mean Cmax (range) of flibanserin in plasma was 246.1 (152.3-432.5) ng/mL and the terminal geometric mean plasma half-life of flibanserin (%CV) was 6.78 (5.6-8.0) hrs. The geometric mean (range) AUC0-inf of flibanserin was 754.1 ng.hr/mL (578.6-1174). The absolute bioavailability described as AUC0-inf/dose was 33.2% with a 90% CI ranging from 26.8 to 41.0%. (sponsor's tables 9.4.2.2:1, 9.4.2.2:2 & 9.4.2.2:5)

C_{max}		intravenous infusion of 20 mg drug substance (n = 6) plasma	oral administration of 50 mg drug substance (n = 6) plasma
gmean	[ng/mL]	387.1	246.1
min. – max.	[ng/mL]	282.9 - 477.2	152.3 - 432.5
gCV	(%)	23.5	40.8

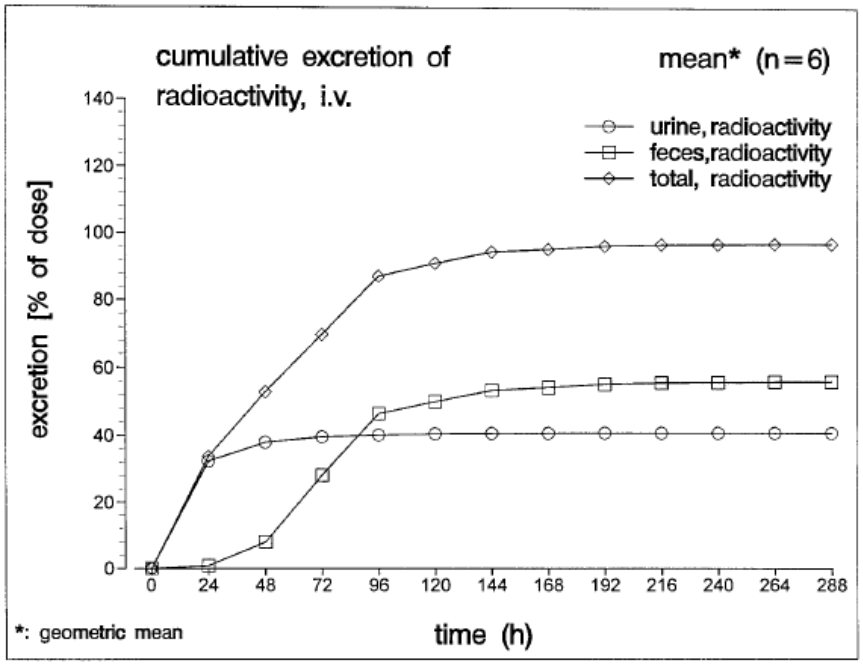
$t_{½}$		intravenous infusion (n = 6)	oral administration (n = 6)
		plasma	plasma
gmean	[h]	7.235	6.776
min. – max.	[h]	5.818 - 8.567	5.619 - 7.960
gCV	(%)	16.0	14.2

route	$AUC_{0-\infty}$		plasma
i.v.	gmean	[ng·h/mL]	909.8
(20 mg)	min. – max.	[ng·h/mL]	740.1 - 1206
(n = 6)	gCV	(%)	20.7
p.o.	gmean	[ng·h/mL]	754.1
(50 mg)	min. – max.	[ng·h/mL]	578.6 - 1174
(n = 6)	gCV	(%)	25.0
	$F_{0-\infty}$		plasma
p.o./i.v.*	gmean	(% of dose)	33.2
(n = 6)	min. – max.	(% of dose)	24.5 - 38.9
	gCV		18.8

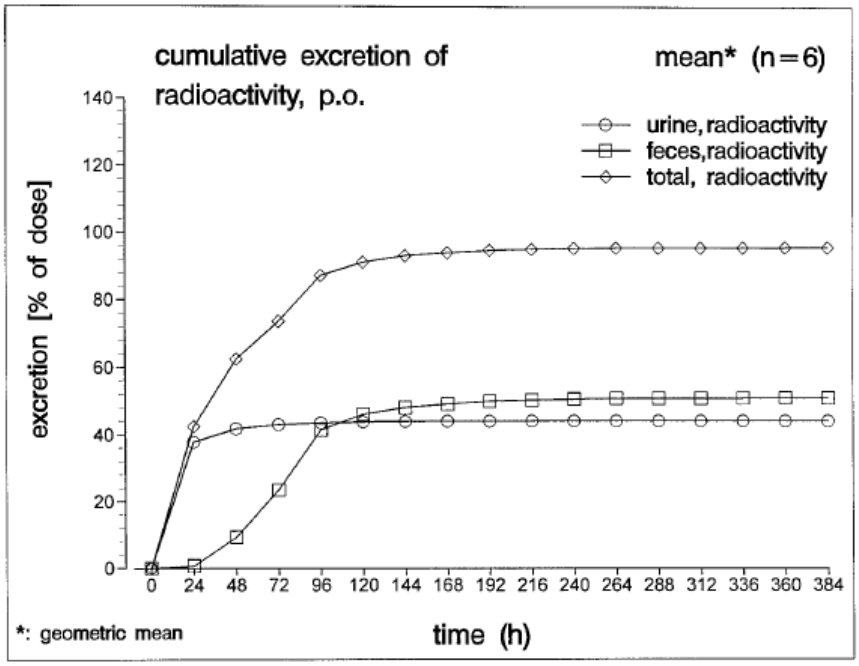
The geometric mean volume of distribution after oral administration (Vz/f) was 648.2 L with a range of 454.4 to 901.8 L (sponsor's table 15.9.3.4:29).

50 mg [^{14}C] Flibanserin solution oral						analyte: BIMT 17 BS			
parameter	**unit**	**n**	**mean**	**CV (%)**	**median**	**min**	**max**	**gmean**	**gCV (%)**
C_{max}	[ng/mL]	6	262.6	40.0	241.9	152.3	432.5	246.1	40.8
t_{max}	[h]	6	0.5833	35.0	0.5	0.5	1.0	0.5612	28.9
$t_{½}$	[h]	6	6.832	13.7	7.108	5.619	7.960	6.776	14.2
λ_z	[1/h]	6	0.1032	14.4	0.09763	0.08708	0.1233	0.1023	14.2
AUC_{0-24h}	[ng·h/mL]	6	737.7	26.6	697.3	562.3	1106	718.8	24.5
AUC_{0-tn}	[ng·h/mL]	6	743.7	28.2	697.3	562.3	1142	722.6	25.7
$AUC_{0-\infty}$	[ng·h/mL]	6	774.7	27.2	732.8	578.6	1174	754.1	25.0
$AUC_{tn-\infty}$	(%)	6	4.15	38.9	3.88	2.70	6.76	3.91	39.0
MRT_{tot}	[h]	6	5.969	12.5	5.933	5.068	6.811	5.930	12.6
CL_{tot}/f	[mL/min]	6	1131	22.2	1139	709.8	1440	1105	25.0
V_z/f	[L]	6	664.0	23.6	697.1	454.6	901.8	648.2	24.7

The following figure is the geometric mean cumulative excretion of [^{14}C]-radioactivity in urine, feces, and total after intravenous infusion of 20 mg [^{14}C]-flibanserin. (sponsor's figure 9.4.2.4:1)



The following figure is the geometric mean cumulative excretion of [^{14}C]-radioactivity in urine, feces, and total after oral administration of 50 mg [^{14}C]-flibanserin. (sponsor's figure 9.4.2.4:2)



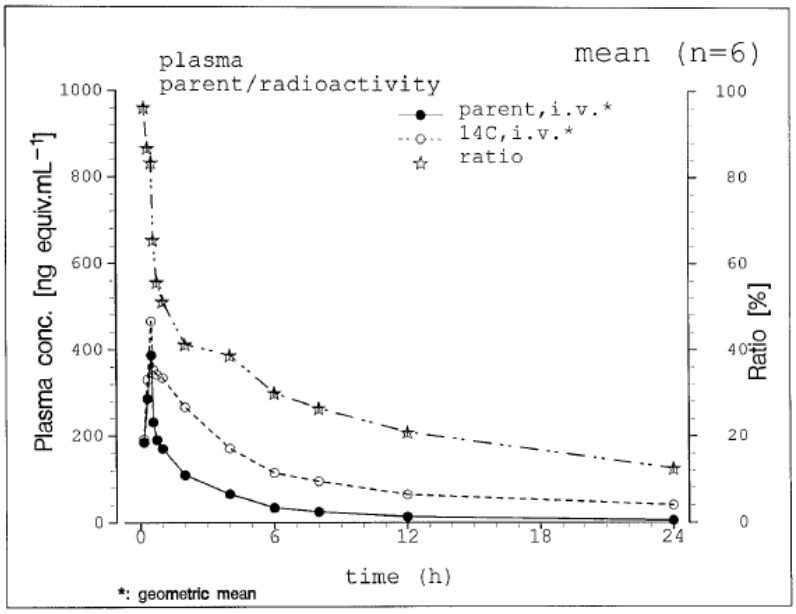
The following table is the excretion and mass balance of radioactivity after intravenous infusion of 20 mg or oral administration of 50 mg [^{14}C]-flibanserin. (sponsor's table 9.4.2.4:1)

excretion and mass balance		**radioactivity**		
		renal	**faecal**	**total**
route	fractional excretion	$Ae_{(urine,\ 0\text{-}192h)}$ * $Ae_{(urine,\ 0\text{-}264h)}$ ** (% of dose)	$Ae_{(faeces,\ 0\text{-}288h)}$ * $Ae_{(faeces,\ 0\text{-}384h)}$ ** (% of dose)	$Ae_{(total,\ 0\text{-}288h)}$ * $Ae_{(total,\ 0\text{-}384h)}$ ** (% of dose)
i.v. (n = 6)	gmean	40.7	56.0	97.0
	min. – max.	35.5 - 47.7	47.7 – 63.1	88.8 – 102
p.o. (n =6)	gmean	44.1	50.9	95.5
	min. – max.	36.6 - 54.0	44.7 – 59.5	93.2 - 98.7
Source data: Appendix 15.9.3.4, TABLE:		15.9.3.4: 19	15.9.3.4: 24	15.9.3.4: 26

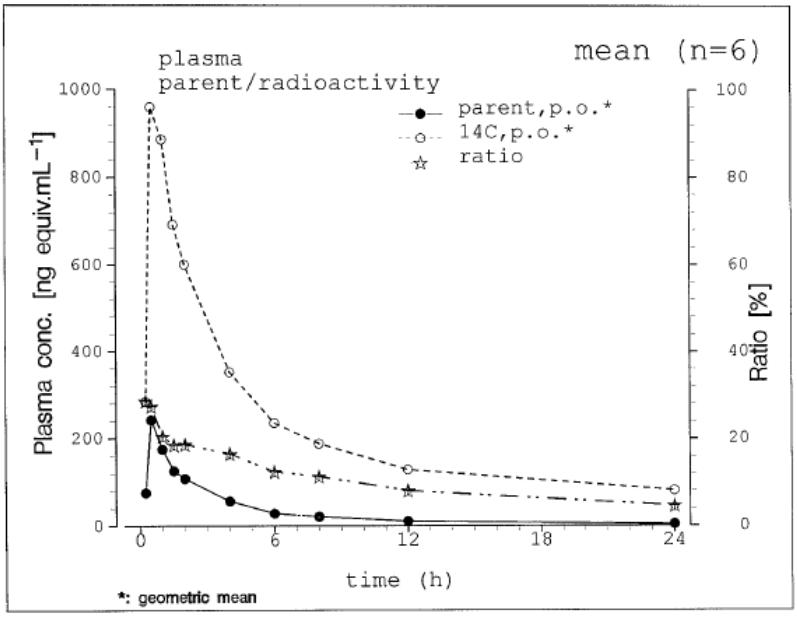
*: i.v.
**: p.o.

After intravenous infusion of [^{14}C]-flibanserin , 40.7% and 56.0% of the total flibanserin-related radioactivity was recovered in urine and feces, respectively. After oral dosing of [^{14}C]-flibanserin, 44.1% and 50.9% of the total flibanserin-related radioactivity was recovered in urine and feces, respectively. The mass balance including renal and fecal excretion of radioactivity showed that the mean total recovery of radioactivity was 97.0% after intravenous infusion and 95.5% after oral administration. Nearly complete radioactive dose was recovered after 288 and 384 hrs for the intravenous and oral dose, respectively.

The following figure is the geometric mean plasma concentration versus time curves for flibanserin (ng/mL), [^{14}C]-radioactivity (ng equiv/mL), and their ratio (%) after intravenous infusion of 20 mg [^{14}C]-flibanserin. (sponsor's table 9.4.1.8:1)



The following figure is the geometric mean plasma concentration versus time curves for flibanserin (ng/mL), [^{14}C]-radioactivity (ng equiv/mL), and their ratio (%) after oral administration of 50 mg [^{14}C]-flibanserin. (sponsor's table 9.4.1.8:2)



The following table is the mean pharmacokinetic parameters in blood after intravenous infusion of 20 mg [^{14}C]-flibanserin. (sponsor's table 15.9.3.4:9)

mean pharmacokinetic parameters in blood: radioactivity intravenous infusion									
parameter	**unit**	**N**	**artihm. mean**	**CV (%)**	**median**	**min**	**max**	**geom. mean**	**gCV (%)**
C_{max}	[ng eq/mL]	6	304	18.7	309	224	368	299	19.6
t_{max}	[h]	6			0.5	0.5	0.5		
AUC_{0-tn}	[ng eq·h/mL]	6	1368	33.2	1389	829	1805	1302	36.1

The following table is the mean pharmacokinetic parameters in blood after oral administration of 50 mg [^{14}C]-flibanserin. (sponsor's table 15.9.3.4:10)

mean pharmacokinetic parameters in blood: radioactivity oral administration									
parameter	**unit**	**N**	**artihm. mean**	**CV (%)**	**median**	**min**	**max**	**geom. mean**	**gCV (%)**
C_{max}	[ng eq/mL]	6	575	7.5	566	527	631	574	7.5
t_{max}	[h]	6			0.5	0.5	1.0		
AUC_{0-tn}	[ng eq.h/mL]	6	2540	32.8	2393	1601	4015	2436	32.0

Metabolite profiles in human urine fractions:
From the total set of identified metabolites, seven metabolites (M30a, M8, M2, M35, M38, M26, M25) were further investigated – five were conjugates and two were phase I metabolites (M30a and M35). Based on an average of six volunteers, about 12% of the intravenous dose and 10% of the oral dose were excreted as metabolite M37/M38 into the urine during 0-48 hours. Metabolites M2, M8, M26, M30, and M34 (oral only) are also major metabolites that reached mean cumulative 0-48 hr excretion levels of 2 to 4 % of the dose after both oral and intravenous dose routes.

M35 is mainly formed by CYP3A4 , the major elimination pathway, and, to a lesser extent, by CYP2D6 and other enzymes. M30a is solely formed by CYP3A4 and further metabolized by mainly CYP2D6. The sum mean cumulative renal excretion of all seven major metabolites account for 21.6% of the intravenous dose and 25.1% of the oral dose. M38 is the conjugated moiety of M37/M38, while M37 is the non-deconjugatable part of M37/M38.

The following table is arithmetic mean, minimum and maximum cumulative 0-48 hr excretion of metabolites (% of dose) in human urine. (sponsor's table 11:2)

mean (arithmetic, N=6) cumulative 0-48 h excretion of metabolites into human urine [% of the dose]						
metabolites	intravenous			oral		
	Mean	Min	Max	Mean	Min	Max
all major metabolites showing each 0-48 h excretion of ≥ 2 %	21.60	17.13	23.46	25.14	17.27	32.60
detailed: M37/M38	11.61	10.42	13.68	10.29	8.29	12.80
M2	2.25	0.72	3.55	4.10	0.99	6.51
M8	2.55	0.86	3.47	3.20	0.96	6.21
M26	2.72	1.87	4.21	2.84	2.25	4.36
M30	2.48	1.72	3.26	2.58	1.79	3.45
M34	-	-	-	2.14	1.37	4.19
all metabolites showing each 0-48 h excretion of > 1 to < 2 %	5.28 (M3, M21, M25, M34)	4.60	6.61	7.66 (M2a, M3, M5, M19, M25, M31b)	4.57	13.52
all metabolites showing each 0-48 h excretion of > 0.5 to < 1 %	4.98 (M1, M2a, M5, M19, M20, M31b, M31c)	3.43	7.27	3.86 (M1, M20, M21, M30a, M31, M31c)	2.38	5.66
all metabolites showing each 0-48 h excretion of < 0.5 %	6.21	4.92	7.72	5.44	4.70	7.73
total 0-48 h excretion of radioactivity	38.1	32.3	43.5	42.1	34.0	49.7
source data: Appendix 15.9.3.5	Table 15.9.3.5: 29			Table 15.9.3.5: 30		

Study 511.1

Title: A single increasing dose-tolerance study in healthy volunteers after oral administration on flibanserin BIMT 17BS (0.1 to 150 mg).

Objective: The objective of the study was to investigate the safety, tolerability, and PK of increasing oral doses of flibanserin in healthy male subjects.

Methods: This was a placebo-controlled, randomized, single increasing dose study. Twenty-four healthy white male subjects were randomized into three groups of 8 subjects receiving flibanserin capsules three times at increasing dose levels, on separate trial days that were at least 21 days apart. The median age was 30 years and ranged from 24-47 years. At each of 9 dose levels (0.1 to 150 mg), six subjects received active treatment and two subjects received placebo. Single increasing oral doses of 0.1 (1x0.1mg), 0.5 (5x0.1 mg), 2 (2x1mg), 5 (5x1mg), 10 (1x10mg), 20 (2x10mg), 50 (1x50mg), 100 (2x50mg), 150 (3x50mg) mg of flibanserin were evaluate in this study. The subjects were started with a single dose of 0.1 mg and was given the next higher dose based on the tolerability of the preceding dose level. Flibanserin was administered with 150 ml water between 9 and 10 am, approximately 1 hour after a light meal. The batch number for the 0.1, 1, 10, and 50 mg capsules is F4291, F4292, F4293, and F4294, respectively.

Pharmacokinetic Sampling: Approximately 10 mL of blood was taken from a forearm vein for pharmacokinetic determination. For doses 0.1 to 20 mg, the blood sampling time points were 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8, and 24 hrs after flibanserin administration. For doses 50 to 150 mg, the blood sampling time points were 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 hrs after flibanserin administration. Urine was collected pre-dose and in intervals of 0-6 hrs and 6-24 hrs after flibanserin administration. Bladder was voided completely at the end of each time interval with the total volumes determined and two 20 ml aliquots of each sample interval frozen at approximately -20C until analysis.

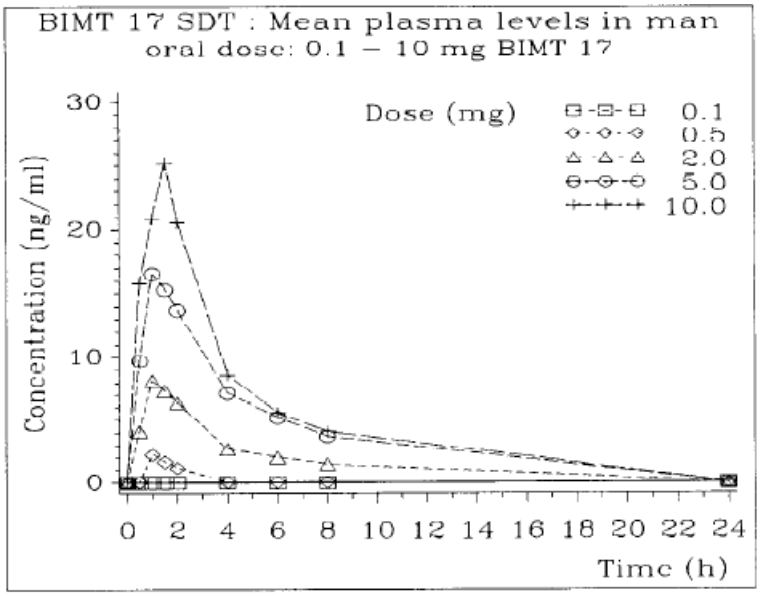
Results:
Based on these study results in healthy men, maximum flibanserin concentrations (Tmax) were reached at between 0.7 and 1.1 hrs (mean Tmax is 0.87 hr). Single dose half-life ($t_{1/2}$) at the higher doses, including the proposed clinical dose of 100 mg, is approximately 6 hrs (5.6 to 6.1 hrs). At 100 mg, the AUC0-inf and Cmax is 1185 ng.hr/ml and 334.9 ng/ml, respectively.

There were no time points between 8 and 24 hrs at the lower doses (0.1 to 20 mg), so there was significant extrapolation to obtain AUC0-24.

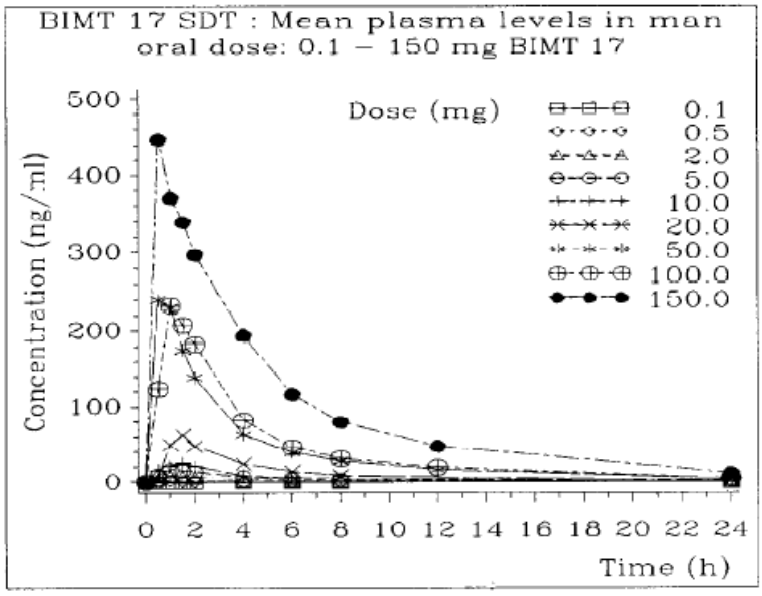
The following table is the geometric mean pharmacokinetic parameters of single dose flibanserin in healthy male volunteers (sponsor's table 15.9.3.3:5).

mean kinetic parameters	C_{max} (ng/ml)	t_{max} (h)	$AUC_{(0-6)}$ (ng·h/ml)	$AUC_{(0-24)}$ (ng·h/ml)	$AUC_{(0-inf)}$ (ng·h/ml)	$MRT_{(0-24)}$ (h)	$MRT_{(0-inf)}$ (h)	$t_{0.5}$ (term.) (h)	CL/F (l/h)
Dose (mg)									
0.1	*1.4	*0.9	ND	ND	ND	ND	ND	ND	ND
0.5	2.6	1.0	4.4	ND	ND	ND	ND	ND	ND
2	10.5	1.0	27.0	43.2	ND	4.6	ND	ND	ND
5	20.4	0.8	60.6	109.4	ND	5.8	ND	ND	ND
10	36.9	0.8	86.0	132.4	ND	4.5	ND	ND	ND
20	68.5	1.1	193.9	300.3	ND	4.7	ND	ND	ND
50	291.9	0.8	676.0	961.0	1005.0	4.7	5.9	6.1	49.8
100	334.9	0.7	798.4	1136.1	1185.0	4.7	5.8	5.8	84.4
150	510.4	0.7	1493.7	2309.1	2412.1	5.4	6.6	5.6	62.2

The following figure is the geometric mean concentration-time profile of single dose 0.1-10 mg flibanserin in healthy male volunteers (sponsor's figure 15.9.3.3:2).



The following figure is the geometric mean concentration-time profile of single dose 0.1-150 mg flibanserin in healthy male volunteers (sponsor's figure 15.9.3.3:2).



The following table is the summary of the dose relationship based on the general regression model $y=ax^b$ where y=AUC or Cmax and x=dose (sponsor's table 15.9.3.3:10). The sponsor claims dose proportionality from 0.1 to 150 mg, which appears to be supported by Cmax data with b close to unity at 0.8689 at all doses. However, AUC0-6 was not determined at the lowest dose (0.1 mg) and AUC0-24 was not determined for the two lowest doses (0.1 and 0.5 mg). Therefore dose proportionality based on AUC0-24 is applicable to doses 2 to 150 mg, not 0.1 to 150 mg as claimed by the sponsor.

Group	$AUC_{(0-24)}$		$AUC_{(0-6)}$		C_{max}	
	a	b	a	b	a	b
0.1 / 5 / 50	23.9673	0.9436	11.2228	1.0476	7.7162	0.8621
0.5 / 10 / 100	15.4321	0.9335	8.7445	0.9830	4.7297	0.9179
2 / 20 / 150	21.5767	0.9196	13.4699	0.9277	5.3139	0.8971
Common	21.8843	0.9039	10.6617	0.9872	6.1375	0.8689

Renal Excretion: At doses of 5 to 20 mg, very minute amounts (0 to 0.006%) of flibanserin were detected in the urine samples. At higher doses of 50 to 150 mg, small amounts (0 to 0.008%) of flibanserin were detected in the urine during the entire 0 to 24 hr time interval.

Renal excretion		Interval			Interval			cumul.
		predose	0 - 6h	6 - 24h	predose	0 - 6h	6 - 24h	
		(ng/ml)	(ng/ml)	(ng/ml)	% of dose	% of dose	% of dose	% of dose
Dose (mg)	Volunteer No							
5	1	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	2	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	3	0.00	0.00	0.00	NS	0.0000	0.0000	0.000
	5	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	6	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	7	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
10	9	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	10	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	11	0.00	1.42*	0.00	0.0000	0.0032	0.0000	0.003
	13	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	14	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	15	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
20	17	0.00	1.13*	0.00	0.0000	0.0058	0.0000	0.006
	18	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	20	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	21	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	22	0.00	1.37*	0.00	0.0000	0.0027	0.0000	0.003
	23	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000

Renal excretion		Interval			Interval			
		predose (ng/ml)	0 - 6h (ng/ml)	6 - 24h (ng/ml)	predose % of dose	0 - 6h % of dose	6 - 24h % of dose	cumul. % of dose
Dose (mg)	Volunteer No							
50	1	0.00	2.60	0.00	0.0000	0.0057	0.0000	0.006
	2	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.000
	3	0.00	1.69*	0.00	0.0000	0.0023	0.0000	0.002
	5	0.00	3.66	0.00	0.0000	0.0083	0.0000	0.008
	6	0.00	1.25*	0.00	0.0000	0.0009	0.0000	0.001
	7	0.00	3.30	0.00	0.0000	0.0054	0.0000	0.005
100	9	0.00	2.03	0.00	0.0000	0.0007	0.0000	0.001
	10	0.00	5.81	0.00	0.0000	0.0053	0.0000	0.005
	11	0.00	7.86	0.00	0.0000	0.0022	0.0000	0.002
	13	0.00	6.08	0.00	0.0000	0.0041	0.0000	0.004
	14	0.00	5.51	0.00	0.0000	0.0011	0.0000	0.001
	15	(9.34)	1.78*	0.00	0.0010	0.0018	0.0000	0.002
150	17	0.00	5.04	1.21*	0.0000	0.0035	0.0014	0.005
	18	0.00	1.97*	0.00	0.0000	0.0014	0.0000	0.001
	20	0.00	2.81	0.00	0.0000	0.0022	0.0000	0.002
	21	0.00	4.89	0.00	0.0000	0.0029	0.0000	0.003
	22	0.00	21.83	1.62*	0.0000	0.0041	0.0014	0.006
	23	0.00	10.19	1.35*	0.0000	0.0069	0.0015	0.008

Study 511.2

Title: A study to evaluate the clinical tolerability and pharmacokinetics of BIMT 17 BS after multiple increasing oral dosages of 20 mg tid, 50 mg bid, 50 mg tid, 100 mg bid, and 100 mg tid over 15 days in healthy men and women.

Objective: To evaluate the safety and tolerability including CNS effects and pharmacokinetics

Methods: A single center, randomized, placebo-controlled, rising multiple dose (60-300 mg/day), double-blind study. Five arms with 12 subjects (6 males and 6 females) on flibanserin and 4 subjects (2 males and 2 females) on placebo, from 21 to 50 years of age. Eighty-one healthy Caucasian subjects completed the study (41 males and 40 females), mean age between 32.75 and 37.70 years. The dosages evaluated were 20 mg tid (2x10 mg capsules), 50 mg bid (1x50 mg capsules), 50 tid (1x50 mg capsules), 100 mg bid (2x50 mg capsules), and 100 mg tid (2x50 mg capsules). Subjects received flibanserin at each dose level for 14 days. On Days 1-13, flibanserin was given according to the bid or tid scheduling; on Day 14, flibanserin was given once. The decision to proceed to the next higher dose level depended on the safety and tolerability of the preceding dose group. The batch number for the 10 and 50 mg capsules is F4293 and F4294, respectively. Flibanserin was given 1 hr after a light breakfast with 150 ml of water.

Pharmacokinetic Sampling: On Day 1, blood samples were taken pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post-morning dose (tid dosing regimen did not include 12 hrs time point). On Days 2-13, blood samples were taken before each morning flibanserin dose. On Day 14, blood samples were taken pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs post-dose. Urine was collected pre-dose and for 0-8, 8-16, and 16-24 hrs intervals after tid dosing and 0-12 and 12-24 hrs intervals after bid dosing on Day 1 and Day 14.

Results:
After a single dose of flibanserin on Day 1, Tmax was between 1.5 and 1.75 hrs. The geometric mean AUC0-inf values were 249 ng.hr/ml (20 mg tid), 654 ng.hr/ml (50 mg bid), 728 ng.hr/ml (50 mg tid), 1525 ng.hr/ml (100 bid) and 1272 ng.hr/ml (100 mg tid). The geometric mean Cmax values were 80 ng/ml (20 mg tid), 172 ng/ml (50 mg bid), 212 ng/ml (50 mg tid), 367 ng/ml (100 bid) and 417 ng/ml (100 mg tid).

After multiple doses of flibanserin on Day 14, Tmax was between 1.5 and 2.0 hrs. The geometric mean AUCss values were 463 ng.hr/ml (20 mg tid), 1085 ng.hr/ml (50 mg bid), 1482 ng.hr/ml (50 mg tid), 2594 ng.hr/ml (100 bid) and 3148 ng.hr/ml (100 mg tid). The geometric mean Cmax,ss values were 111 ng/ml (20 mg tid), 222 ng/ml (50 mg bid), 336 ng/ml (50 mg tid), 541 ng/ml (100 bid) and 729 ng/ml (100 mg tid). The terminal half-life ($t_{1/2}$) ranged 5.8 to 9.1 hrs. Comparing Day 14 to Day 1, there was an accumulation of flibanserin. R_A(AUC) was 1.7 for the bid dosing regimen and ranged from 1.9 to 2.5 for the tid dosing regimen.

Compared to single dose PK in males from Study 511.1, Tmax on Day 1 in this study was longer by 0.5 to 0.75 hr. Cmax was similar, but slightly higher in this study.

The following table is a summary of geometric mean pharmacokinetic parameters of flibanserin in healthy male and female subjects following a single (Day 1) and multiple doses (Day 14) of flibanserin (sponsor's table 9.4.3:1).

Day	Parameter	Unit	20 mg t.i.d.	50 mg b.i.d.	50 mg t.i.d.	100 mg b.i.d.	100 mg t.i.d.
1	T_{max}	[h]	1.75	1.75	1.75	1.5	1.5
	C_{max}	[ng/ml]	80	172	212	367	417
	$AUC_{0-\infty}$	[ng/ml·h]	249	654	728	1525	1272
14	$T_{max,ss}$	[h]	1.5	1.5	2.0	1.5	1.5
	$C_{max,ss}$	[ng/ml]	111	222	336	541	729
	$C_{min,ss}$	[ng/ml]	26	32	85	80	192
	AUC_{ss}	[ng/ml·h]	463	1085	1482	2594	3148
	MRT_{ss}	[h]	8.1	8.9	9.5	9.0	11.0
	$t_{1/2}$	[h]	5.8	7.1	7.4	7.2	9.1
	%PTF	[%]	141	208	133	212	134
14 / 1	$R_A(AUC)$	-	1.9	1.7	2.0	1.7	2.5

Tmax are median values.

The figure below is a summary of exposure (AUCss on Day 14) vs adverse events (by system disorders) profile from eighty-one subjects from this Phase 1 clinical tolerability and pharmacokinetic study. Six different dosing regimens were evaluated. Though the sponsor states that oral doses up to 100 mg tid were safe, there appears to be a dose-dependent increase in adverse events. The data used to generate this figure was obtained in the table below (sponsor's table 10.2.1:1).

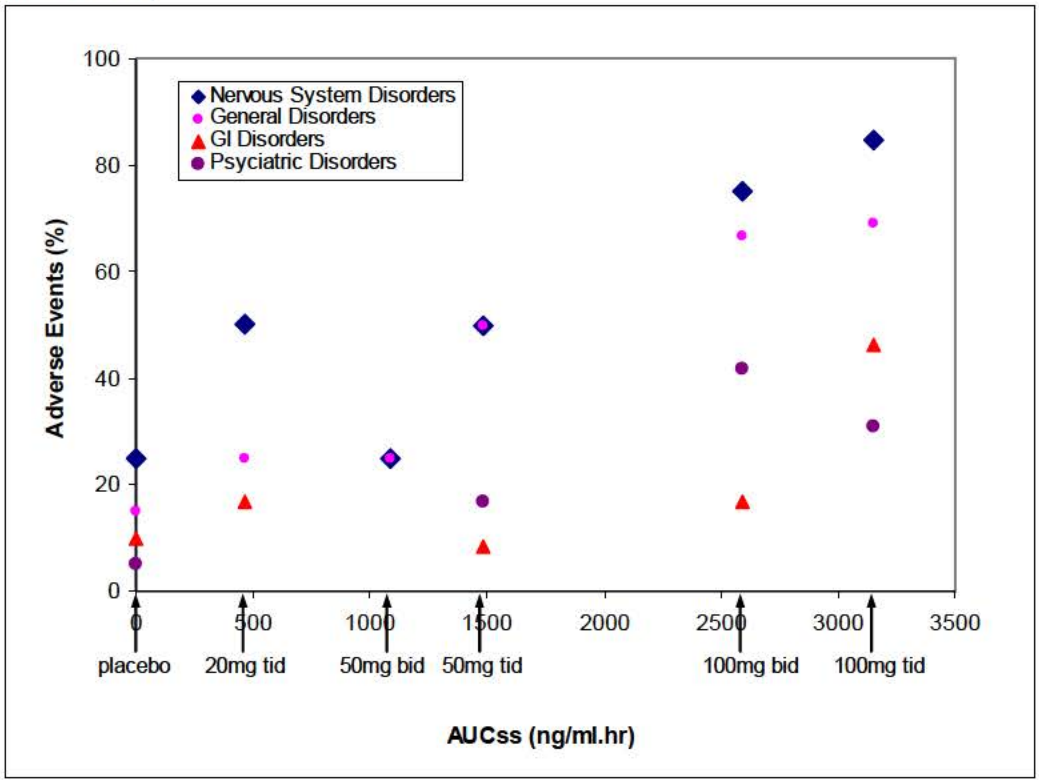


TABLE 10.2.1: 1: Treatment Emerged Adverse Events (WHO Preferred Terms) (Multiple Occurrences of a Symptom are Counted Once)

		Treatment												
		Placebo		20 mg t.i.d.		50 mg b.i.d.		50 mg t.i.d.		100 mg b.i.d.		100 mg t.i.d.		Tot.
Body System	Preferred Term	N	%	N	%	N	%	N	%	N	%	N	%	N
CENTR & PERIPH. NERVOUS SYSTEM DISORDERS	HEADACHE	4	20.0	7	58.3	2	16.7	5	41.7	5	41.7	7	53.9	30
	DIZZINESS	1	5.0	3	25.0	1	8.3	3	25.0	6	50.0	7	53.9	21
	PARAESTHESIA									2	16.7			2
	APHASIA											1	7.7	1
	TREMOR											1	7.7	1
	COORDINATION ABNORMAL	1	5.0											1
	MYASTHENIA GRAVIS-LIKE SYNDROME											2	15.4	2
Body System Total *)		**5**	**25.0**	**7**	**50.3**	**3**	**25.0**	**6**	**50.0**	**9**	**75.0**	**11**	**84.6**	**41**
BODY AS A WHOLE - GENERAL DISORDERS	FATIGUE	2	10.0	3	25.0	3	25.0	6	50.0	8	66.7	8	61.5	30
	BACK PAIN	1	5.0					1	8.3			1	7.7	3
	CHEST PAIN											2	15.4	2
	ASTHENIA							1	8.3					1
Body System Total *)		**3**	**15.0**	**3**	**25.0**	**3**	**25.0**	**6**	**50.0**	**8**	**66.7**	**9**	**69.2**	**32**
URINARY SYSTEM DISORDERS	POLYURIA	1	5.0							1	8.3	7	53.9	9
	DYSURIA											1	7.7	1
	URINARY INCONTINENCE							1	8.3					1
Body System Total *)		**1**	**5.0**					**1**	**8.3**	**1**	**8.3**	**8**	**61.5**	**11**
PSYCHIATRIC DISORDERS	PARONIRIA	1	5.0					2	16.7	1	8.3	1	7.7	5
	INSOMNIA									2	16.7	3	23.1	5
	SOMNOLENCE									2	16.7	1	7.7	3
	IMPOTENCE											1	7.7	1
	EMOTIONAL LABILITY							1	8.3					1
	CONCENTRATION IMPAIRED							1	8.3	2	16.7	1	7.7	4
Body System Total *)		**1**	**5.0**					**2**	**16.7**	**5**	**41.7**	**4**	**30.8**	**12**
GASTRO-INTESTINAL SYSTEM DISORDERS	NAUSEA							1	8.3	1	8.3	3	23.1	5
	ABDOMINAL PAIN	1	5.0	1	8.3					1	8.3			3
	FLATULENCE	1	5.0							1	8.3	1	7.7	3
	CONSTIPATION									1	8.3	2	15.4	3
	DIARRHOEA	1	5.0	1	8.3									2
	HICCUP											2	15.4	2
Body System Total *)		**2**	**10.0**	**2**	**16.7**			**1**	**8.3**	**2**	**16.7**	**6**	**46.2**	**13**
HEART RATE AND RHYTHM DISORDERS	PALPITATION	1	5.0	1	8.3									2
Body System Total *)		1	5.0	1	8.3									2

		Treatment												
		Placebo		20 mg t.i.d.		50 mg b.i.d.		50 mg t.i.d.		100 mg b.i.d.		100 mg t.i.d.		Tot.
Body System	Preferred Term	N	%	N	%	N	%	N	%	N	%	N	%	N
METABOLIC AND NUTRITIONAL DISORDERS	THIRST							2	16.7					2
Body System Total *)								2	16.7					2
VISION DISORDERS	VISION ABNORMAL									2	16.7			2
	CHROMATOPSIA									1	8.3			1
Body System Total *)										2	16.7			2
SKIN AND APPENDAGES DISORDERS	ALOPECIA									1	8.3			1
	ACNE											1	7.7	1
	PRURITUS											1	7.7	1
	SKIN DRY											1	7.7	1
Body System Total *)										1	8.3	2	15.4	3
AUTONOMIC NERVOUS SYSTEM DISORDERS	MOUTH DRY									1	8.3			1
	ANOREXIA											1	7.7	1
	SWEATING INCREASED							2	16.7	1	8.3			3
	APPETITE INCREASED							1	8.3					1
Body System Total *)								3	25.0	1	8.3	1	7.7	5
SPECIAL SENSES OTHER, DISORD.	PAROSMIA									1	8.3			1
Body System Total *)										1	8.3			1
REPRODUCTIVE DISORDERS, FEMALE	DYSMENORRHOEA									1	8.3			1
	MENSTRUAL DISORDER	1	5.0							2	16.7	1	7.7	4
Body System Total *)		1	5.0							2	16.7	1	7.7	4
Total Sum of Adverse Events:		**16**		**16**		**6**		**27**		**43**		**57**		**165**

*) Number and percentage of subjects with any adverse event in the respective body system.

The figure below is the Ingelheim Symptom Check List (SCL 9Li) sum score presenting the adverse events following 14 days of flibanserin treatment grouped by treatment regimen. **The number of subjects who reported dizziness increased with dosage from 3 of 12 for the 20 mg tid, 3 of 12 for 50 mg tid, 6 of 12 for 100 mg bid, and 7 of 13 for 100 mg tid groups, compared with 1 of 20 for the placebo group. There are greater incidences of adverse events with increasing dose.**

TABLE 4.3.4.2 Symptom Check List (SCL 91 I) - Number of Subjects with Increase of Complaints at Day 14
(Compared to pre Medication at Day 14)

Complaints at Day 14	No. of Subjects with Complaints						
	Treatment						
	Placebo	20 mg tid	50 mg bid	50 mg tid	100 mg bid	100 mg tid	Total
Item							
FATIGUE	4	1	3	5		2	15
TIREDNESS	2	3	3	4	1		13
LACK OF ENERGY	3	1	3	2		4	13
INNER RESTLESSNESS	1	2	2	4		3	12
EXCESSIVE NEED FOR SLEEP	2	2	2	4	2		12
WORRIES AT WORK OR AT HOME	1	1	3	2	1	2	10
FEELING OF WEAKNESS	1	2	1	3		2	9
IRRITABILITY	1	2	1	4	1		9
BROODING	1	2	2	1	3		9
DIZZINESS	1		2	3	3		9
DRYNESS OF THE MOUTH	2	2	3	1		1	9
EROTIC IDEAS, PHANTASY OR THOUGHTS	2	1	3		1	2	9
INSOMNIA	2	1	1	1	2	1	8
SEVERE THIRST	1		2		3	2	8
FLATULANCE, WIND	1	1	4	1	1		8
PHYSICAL SUPERACTIVITY		1	1	4	1	1	8
DRY LIPS	1		3	2	1		7
HEADACHE, FEELING OF PRESSURE IN HEAD		1		2	1	3	7
DIFFICULTIES WITH BALANCE		1	2	2		2	7
STOMACH PAIN (INCL. (HYPO-)GASTRIC PAIN)		2	2	1	1	1	7
LACK OF CONCENTRATION		1	2	2	2		7
FEELING OF ANXIETY	1		2	2		1	6
INNER TENSION	1		3	1		1	6
FORGETFULNESS	2	2	1	1			6
TENDENCY TO MOVE MOUTH, LIPS OR TONGUE	1	1	3	1			6
INDIFFERENCE OR LACK OF INTEREST	2	1		2		1	6
FEELING OF PRESSSURE/FULLNESS (ABDOMEN)		1	2	1	1	1	6
CONSTIPATION		1	1	2	1	1	6
GLOOMY THOUGHTS		1	3	1	1		6
OVERSENSITIVITY TO COLD			2	2		2	6
COUGH			1	3	2		6

Complaints at Day 14	No. of Subjects with Complaints						
	Treatment						
	Placebo	20 mg tid	50 mg bid	50 mg tid	100 mg bid	100 mg tid	Total
Item							
FEELING OF NUMBNESS IN THE HANDS/FEET			2	3	1		6
FEELING OF HEAVINESS/TIREDNESS IN LEGS	2		1	1		1	5
PAIN IN THE JOINTS OR LIMBS	1		1	1		2	5
HEARING DISORDERS	2		2			1	5
SENSITIVITY TO WEATHER	2			1	2		5
INCERTAIN FEELING OF BEING UNWELL	1	1	1	1	1		5
COLD FEET		1	1	2		1	5
URGE TO YAWN		2	1			2	5
EASILY EXHAUSTED	1	1	1	1			4
FEEL COLD	1		1	1		1	4
EXCESSIVE HUNGER	1		1	1	1		4
FEVER, RAISED TEMPERATURE	2		1	1			4
RHINITIS (COLD)	2		1			1	4
TENDENCY TO MAKE STEREOTYPE MOVEMENTS		1	1	1		1	4
HEARTBURN OR ACID ERUCTATION			1	2		1	4
TREMBLING			2	2			4
SENSITIVITY TO LIGHT			2	1		1	4
FEELING OF BEING "HIGH", AS IF DRUNK			1	1		2	4
SHORTNESS OF BREATH	1	1			1		3
RESTLESSNESS IN LEGS	1					2	3
OVERSENSITIVITY TO HEAT	1			1		1	3
WEIGHT LOSS	1		1	1			3
ATTACKS OF BREATHLESSNESS	1		1	1			3
TENDENCY TO WEEP	1		1	1			3
VOMITING, NAUSEA	2		1				3
SENSITIVITY TO PAIN	1			1	1		3
PAIN IN THE NECK OR SHOULDER		1		1		1	3
PALPITATION, RACING OF THE HEART		1		1		1	3
BODY ODOUR		1		1	1		3
SEVERE SWEATING			1	2			3
LOSS OF APPETIE			1	1	1		3

Study 511.105

Title: A Phase I, open-label, parallel, and within-groups sequential trial to evaluate the single dose and steady state pharmacokinetics of flibanserin in premenopausal women with hypoactive sexual desire disorder

Objective: The primary objective of the study was to investigate the PK of flibanserin and metabolites in women with HSDD after single and repeated doses, including dose proportionality, attainment of steady state, and accumulation.

Methods: This was an open-label, 4-week study of 2 parallel groups with 2 sequential treatments within the groups. Sixty-seven HSDD patients (61 Whites and 6 Blacks) were randomized to a qd or a bid dosing regimen, both with daily doses of 50 mg flibanserin for 8 days followed by 100 mg flibanserin for 8 days after a wash-out period. The mean (range) age was 34.4 (21 to 47) years. The mean (range) weight was 67.8 (52 to 89) kg and the mean (range) BMI was 25.05 (20.5 to 30.5) kg/m^2. Of the sixty-one patients who completed the study, 29 patients received once daily flibanserin, and 32 patients received twice daily flibanserin.

Once daily dosing: On the days when the patients were in the clinic for intensive PK investigations (Days 1, 8, 15, and 22), the following rules applied: following an overnight fast, the medication was administered in the morning with about 240 ml of water in the sitting/standing position under supervision of the investigating physician or a designee. Patients were kept under close medical surveillance for 2 hrs following drug administration and were not allowed to lie down during the 2 hrs following drug administration except for medical examination. They were also not allowed to sleep. Water was not allowed 1 hr before and after drug administration, except for 240 ml given during drug administration. At other times, water was allowed ad libitum.

Twice daily dosing: Same as once daily dosing. In addition, standardized meals were served at 2, 5, and 10 hrs following drug administration. On Days 1 and 15, an evening dose of the flibanserin was given 12 hrs after the morning dose. During the morning of Days 8 and 22, the last dose of each treatment was administered.

The single dose and steady state PK of flibanserin, BIMA 23 BS (M35), BIML 7 ZW (M38), TFMPP (M30a), BI 404016 ZW (M26), BI 401703 ZW(M2), and BI 400296 ZW (M8) were determined for each dosing scheme.

Treatment	Substance	Formulation, regimen	Number of units (tablets)	Unit strength (mg)	Total daily dose (mg)
Low dose	flibanserin	Tablet, qd	8	50	50
High dose	flibanserin	Tablet, qd	8	100	100
Low dose	flibanserin	Tablet, bid	15	25	50
High dose	flibanserin	Tablet, bid	15	50	100

The study was divided into 4 segments: (1) lower dosage, (2) first washout, (3) higher dosage, and (4) second washout. During the segments of dosing (Days 1-8 and 15-22), patients received either once daily or twice daily treatments of flibanserin.

Dose segments	Once daily dose
Days 1 – 8	50 mg flibanserin qd

Days 9 – 14	Washout period
Days 15 – 22	100 mg flibanserin qd
Days 23 - 28	Washout period

Dose segments	Twice daily dose
Days 1 – 8	25 mg flibanserin bid
Days 9 – 14	Washout period
Days 15 – 22	50 mg flibanserin bid
Days 23 - 28	Washout period

Pharmacokinetic Sampling: Blood samples were taken for the determination of flibanserin and metabolites concentrations according to the following schedule:
• pre-dose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, and 12 hrs following the first flibanserin administration on Days 1 and 15;
• pre-dose to the morning doses on Days 2 to 7 as well as on Days 16 to 21;
• pre-dose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hrs following flibanserin administration on Days 8 and 22.

Results: Flibanserin plasma concentrations reached median Tmax at 45 to 60 min post dose after single and multiple dosing and decreased biexponentially thereafter with a mean terminal $t_{1/2}$ ranging from 10.1 to 11.9 hrs at steady state.

Following a single 100 mg dose of flibanserin in HSDD women, geometric mean AUC0-inf (%CV) is 1630 ng.hr/ml (54.6%). Median Tmax (range) is 1.00 hr (0.50-3.00 hrs). Geometric mean terminal $t_{1/2}$ (%CV) is 9.33 (27.8%) hrs and geometric mean Cmax (%CV) is 336 (50.7%)

Following multiple doses (8 days) of 100 mg qd flibanserin in HSDD women, geometric mean AUC0-inf (%CV) is 2080 ng.hr/ml (46.6%). Median Tmax (range) is 1.00 hr (0.50-3.00 hrs). Geometric mean terminal $t_{1/2}$ (%CV) is 11.4 (24.3%) hrs and geometric mean Cmax,ss (%CV) is 469 (42.7%).

The plasma concentrations of the metabolites BIMA 23 BS (M35), BIML 7 ZW (M38), and BI 404016 ZW (M26) roughly followed the plasma concentrations of the parent drug; maximum concentrations of TFMPP (M30a) and its subsequent metabolites BI 400296 ZW (M8) and BI 401703 ZW (M2) were reached 2 to 3 hours after the flibanserin peak. The terminal half-lives of all metabolites at steady state were slightly longer than flibanserin $t_{1/2}$ and ranged from 9.32 to 17.4 hrs among the dose groups. Steady state was achieved after 3 days for flibanserin and metabolites in all dose groups. The flibanserin exposure increased generally in proportion with dose after single and multiple dosing and was slightly lower at steady state in the bid dose groups than in the qd dose groups. This was also reflected by the mean area under the AUC and Cmax accumulation ratios ranging from 1.20 to 1.44 and from 1.09 to 1.36, respectively, in the qd dose groups, and ranging from 1.70 to 1.82 and from 1.26 to 1.37, respectively, in the bid dose groups. The exposure to flibanserin metabolites also increased roughly in proportion with dose. At steady state, the relative exposure of the metabolites compared to flibanserin was approximately 14%, 5%, and 2.5% for BIMA 23 BS (M35), TFMPP (M30a), and BI 404016 ZW (M26), respectively, and ranged from 54% to 70%, from 28% to 42%, and from 29% to 48% for BIML 7 ZW (M38), BI 400296 ZW (M8), and BI 401703 ZW (M2), respectively.

The results of the primary analysis on dose proportionality on the natural scale, that included dose correction, are given in the table below.

Table 11.5.2.3: 1 Summary results of dose proportionality analyses for flibanserin (comparison included correction by dose)

		N	gMean of ratios (natural scale)	95% Confidence interval (natural scale)	
				from	to
Flibanserin 100 q.d. vs. Flibanserin 50 q.d.					
AUC_{0-12}	[ng·h/mL]	58	0.948	0.877	1.025
C_{max}	[ng/mL]	58	0.833	0.718	0.968
$AUC_{\tau,ss}$	[ng·h/mL]	59	1.045	0.953	1.146
$C_{max,ss}$	[ng/mL]	59	1.013	0.876	1.171
Flibanserin 50 b.i.d. vs. Flibanserin 25 b.i.d.					
AUC_{0-12}	[ng·h/mL]	65	0.972	0.905	1.045
C_{max}	[ng/mL]	65	0.940	0.829	1.066
$AUC_{\tau,ss}$	[ng·h/mL]	64	1.045	0.970	1.126
$C_{max,ss}$	[ng/mL]	64	1.018	0.889	1.166
Flibanserin 50 b.i.d. vs. Flibanserin 50 q.d.					
AUC_{0-12}	[ng·h/mL]	62	1.087	0.888	1.332
C_{max}	[ng/mL]	62	1.152	0.946	1.404
$AUC_{\tau,ss}$	[ng·h/mL]	61	1.417	1.125	1.784
$C_{max,ss}$	[ng/mL]	61	1.478	1.225	1.783

Table 11.5.2.2.1: 1 Comparison of key pharmacokinetic parameters of flibanserin after single dose by dose group

Single dose	50 mg q.d. (N=30)		100 mg q.d. (N=28)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=32)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-12} [ng·h/mL]	685	36.4	1150	52.4	391	50.5	745	45.9
$AUC_{0-12,norm}$ [ng·h/mL/mg]	13.7	36.4	11.5	52.4	15.7	50.5	14.9	45.9
AUC_{0-24} [ng·h/mL]	817	39:4	1420	54.7	---	---	---	---
$AUC_{0-24,norm}$ [ng·h/mL/mg]	16.3	39:4	14.2	54.7	---	---	---	---
AUC_{0-tz} [ng·h/mL]	816	39.3	1420	54.6	391	50.5	744	45.8
$AUC_{0-\infty}$ [ng·h/mL]	904	43.5	1630	54.6	474	53.2	919	52.0
$AUC_{0-\infty,norm}$ [ng·h/mL/mg]	18.1	43.5	16.3	54.6	19.0	53.2	18.4	52.0
$\%AUC_{tz-\infty}$ [%]	8.34	56.5	11.0	59.8	16.4	36.8	17.3	42.5
C_{max} [ng/mL]	217	40.8	336	50.7	136	41.9	250	40.0
$C_{max,norm}$ [ng/mL/mg]	4.33	40.8	3.36	50.7	5.45	41.9	4.99	40.0
t_{max}[1] [h]	0.875	0.500-3.00	1.00	0.500-3.00	0.750	0.500-3.00	1.00	0.500-3.00
$t_{½}$ [h]	8.45[2]	23.3[2]	9.33	27.8	5.93[3]	24.8[3]	6.06	27.0
MRT_{po} [h]	8.46	29.2	10.0	35.4	6.47	24.6	6.79	30.2
CL/F [mL/min]	922	43.5	1020	54.6	878	53.2	907	52.0
V_z/F [L]	676	33.2	827	62.6	457	58.2	476	43.7

Source Data: Section 15, Table 6.3: 1, Table 6.2.1: 1 and Table 6.2.1: 15

[1] median and range

[2] N=31; [3] N=34

Table 11.5.2.2.1: 2 Comparison of key pharmacokinetic parameters of flibanserin at steady state by dose group

Steady state	50 mg q.d. (N=30)		100 mg q.d. (N=29)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=31)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	991	47.7	2080	46.6	653	60.1	1400	46.9
$AUC_{\tau,ss,norm}$ [ng·h/mL/mg]	19.8	47.7	20.8	46.6	26.1	60.1	28.1	46.9
$R_{A,AUC}$ [ ]	1.20[2]	19.3[2]	1.44[3]	63.5[3]	1.70[4]	26.4[4]	1.84	21.4
$C_{max,ss}$ [ng/mL]	234	41.2	469	42.7	168	50.9	346	34.4
$C_{max,ss,norm}$ [ng/mL/mg]	4.68	41.2	4.69	42.7	6.72	50.9	6.91	34.4
$R_{A,Cmax}$ [ ]	1.09[2]	23.5[2]	1.36[3]	58.0[3]	1.28[4]	40.1[4]	1.37	31.4
$t_{max,ss}$[1] [h]	1.00	0.417-4.00	1.00	0.500-3.00	1.00	0.500-3.00	0.750	0.500-3.00
$t_{½,ss}$ [h]	10.1	23.3	11.4	24.3	11.9	25.5	11.6	21.4
$MRT_{po,ss}$ [h]	9.44	34.5	11.3	27.8	11.1	30.2	12.1	29.5
$CL/F_{,ss}$ [mL/min]	841	47.7	803	46.6	638	60.1	593	46.9
$V_z/F_{,ss}$ [L]	734	33.9	795	53.9	655	46.8	594	38.4

Source data: Section 15 Table 6.3.1: 1

[1] median and range

[2] N=28; [3] N=27; [4] N=32

The following are geometric mean plasma concentration-time profiles of flibanserin after multiple oral doses of flibanserin to HSDD patients

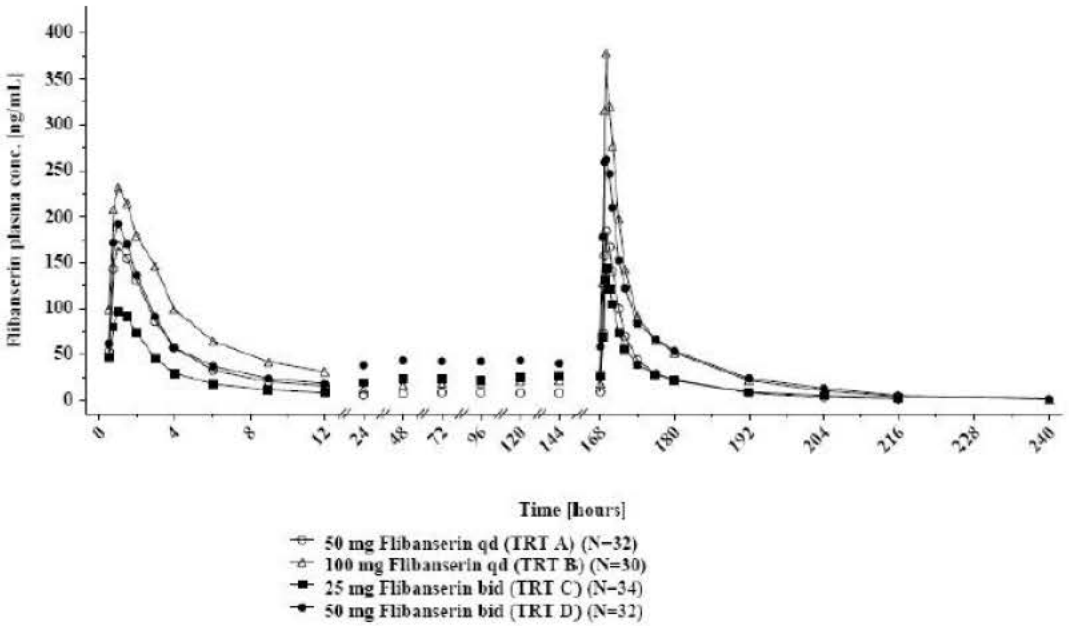


Table 11.5.2.2.2: 1 Comparison of key pharmacokinetic parameters of BIMA 23 BS after single dose by dose group

Single dose	50 mg q.d. (N=30)		100 mg q.d. (N=28)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=32)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-12} [ng·h/mL]	85.3	34.4	142	57.2	47.3	38.0	93.7	35.0
AUC_{0-24} [ng·h/mL]	109	38.7	187	58.0	---	---	---	---
AUC_{0-tz} [ng·h/mL]	109	39.5	187	58.0	47.1	38.4	93.7	35.0
$AUC_{0-\infty}$ [ng·h/mL]	129	48.1	228	60.9	64.3	55.4	131	58.5
$\%AUC_{tz-\infty}$ [%]	13.2	59.9	15.1	58.8	21.6	56.1	23.6	51.4
$RAUC_{0-\infty,Met}$ [ ]	0.137	34.2	0.135	35.0	0.130	42.3	0.137	41.7
C_{max} [ng/mL]	19.5	42.0	31.3	62.4	10.4	34.8	20.6	38.7
t_{max}[1] [h]	0.875	0.500-3.00	0.750	0.500-3.00	0.750	0.500-4.00	0.909	0.500-3.00
$t_{½}$ [h]	9.28[2]	35.2[2]	10.1	29.8	5.86[3]	46.1[3]	6.38	47.5
MRT_{po} [h]	11.3	39.6	12.6	35.9	8.40	47.7	8.98	49.5

Source Data: Section 15, Table 6.3: 1, Table 6.2.1: 3 and Table 6.2.1: 17

[1] median and range

[2] N=31, [3] N=34

Table 11.5.2.2.2: 2 Comparison of key pharmacokinetic parameters of BIMA 23 BS at steady state by dose group

Steady state	50 mg q.d. (N=30)		100 mg q.d. (N=29)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=31)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	145	50.5	314	51.3	97.2	63.0	210	53.1
$R_{A,AUC}$ [ ]	1.33[2]	15.1[2]	1.65[3]	67.5[3]	2.07[4]	35.2[4]	2.23	24.5
$RAUC_{\tau,ss,Met}$ [ ]	0.141	35.0	0.145	35.3	0.143	38.4	0.144	40.5
$Cmax,ss$ [ng/mL]	22.5	46.1	42.5	42.8	16.4	46.8	34.1	41.0
$R_{A,Cmax}$ [ ]	1.16[2]	25.3[2]	1.35[3]	63.6[3]	1.59[4]	45.6[4]	1.68	29.9
$t_{max,ss}$[1] [h]	0.875	0.417-4.00	0.750	0.500-3.00	1.00	0.500-3.00	0.750	0.500-4.00
$t_{½,ss}$ [h]	11.0	37.7	13.3	40.2	13.8	58.2	14.9	32.9
$MRT_{po,ss}$ [h]	12.9	40.2	15.5	34.4	15.6	44.9	17.5	35.3

Source Data: Section 15, Table 6.3: 1

[1] median and range

[2] N=28, [3] N=27, [4] N=32

The following are geometric mean plasma concentration-time profiles of BIMA 23 BS (M35) after multiple oral doses of flibanserin to HSDD patients

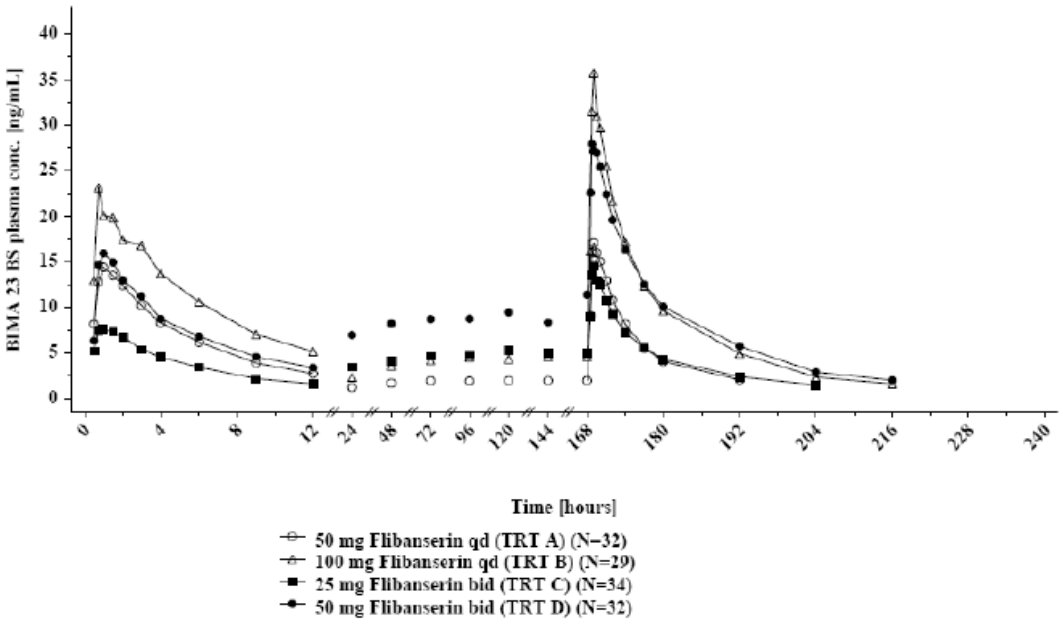


Table 11.5.2.2.3: 1 Comparison of key pharmacokinetic parameters of BIML 7 ZW after single dose by dose group

Single dose	50 mg q.d. (N=30)		100 mg q.d. (N=28)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=32)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-12} [ng·h/mL]	620	39.3	1070	72.2	282	31.8	580	29.0
AUC_{0-24} [ng·h/mL]	712	39.3	1250	68.6	---	---	---	---
AUC_{0-tz} [ng·h/mL]	711	39.3	1250	68.7	282	31.8	579	29.0
$AUC_{0-\infty}$ [ng·h/mL]	1000	72.1	1610	75.6	343	31.4	709	34.6
$\%AUC_{tz-\infty}$ [%]	15.0	117	14.9	87.1	13.3	68.1	13.1	82.7
$RAUC_{0-\infty,Met}$ [ ]	0.888	81.0	0.793	83.2	0.581	59.4	0.620	61.9
$RAUC_{0-\infty,MT/MR}$ [ ]	6.46	81.9	5.89	70.2	4.46	55.5	4.52	65.3
C_{max} [ng/mL]	314	48.2	506	86.3	139	48.9	301	39.0
t_{max}[1] [h]	1.00	0.500-2.00	1.00	0.500-3.00	1.00	0.750-2.00	1.00	0.500-3.00
$t_{½}$ [h]	19.4[2]	128[2]	16.2	86.1	7.22[3]	54.5[3]	7.76	64.7
MRT_{po} [h]	14.9	184	13.2	96.8	5.88	65.6	6.08	75.4

Source Data: Section 15, Table 6.3: 1, Table 6.2.1: 5 and Table 6.2.1: 19

[1] median and range

[2] N=31, [3] N=34

Table 11.5.2.2.3: 2 Comparison of key pharmacokinetic parameters of BIML 7 ZW at steady state by dose group

Steady state	50 mg q.d. (N=30)		100 mg q.d. (N=29)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=31)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	864	43.1	1760	36.7	446	27.8	943	26.2
$R_{A,AUC}$ [ ]	1.21[2]	13.6[2]	1.42[3]	65.3[3]	1.57[4]	29.1[4]	1.62	22.1
$RAUC_{\tau,ss,Met}$ [ ]	0.699	59.1	0.680	61.4	0.548	51.5	0.539	49.6
$RAUC_{\tau,ss,MT/MR}$ [ ]	4.97	49.8	4.69	51.0	3.83	52.4	3.75	48.5
$C_{max,ss}$ [ng/mL]	331	45.2	641	51.5	160	29.9	315	41.8
$R_{A,Cmax}$ [ ]	1.07[2]	37.6[2]	1.24[3]	75.4[3]	1.16[4]	39.3[4]	1.04	36.5
$t_{max,ss}$[1] [h]	1.00	0.500-3.00	1.00	0.750-3.00	1.00	0.750-3.00	1.00	0.750-2.00
$t_{½,ss}$ [h]	14.1	52.7	12.6	35.6	17.4	40.8	13.6	33.6
$MRT_{po,ss}$ [h]	9.48	41.5	10.4	38.4	12.6	39.3	12.6	27.7

Source Data: Section 15, Table 6.3: 1

[1] median and range

[2] N=28, [3] N=27, [4] N=32

The following are geometric mean plasma concentration-time profiles of BIML 7 ZW (M38) after multiple oral doses of flibanserin to HSDD patients

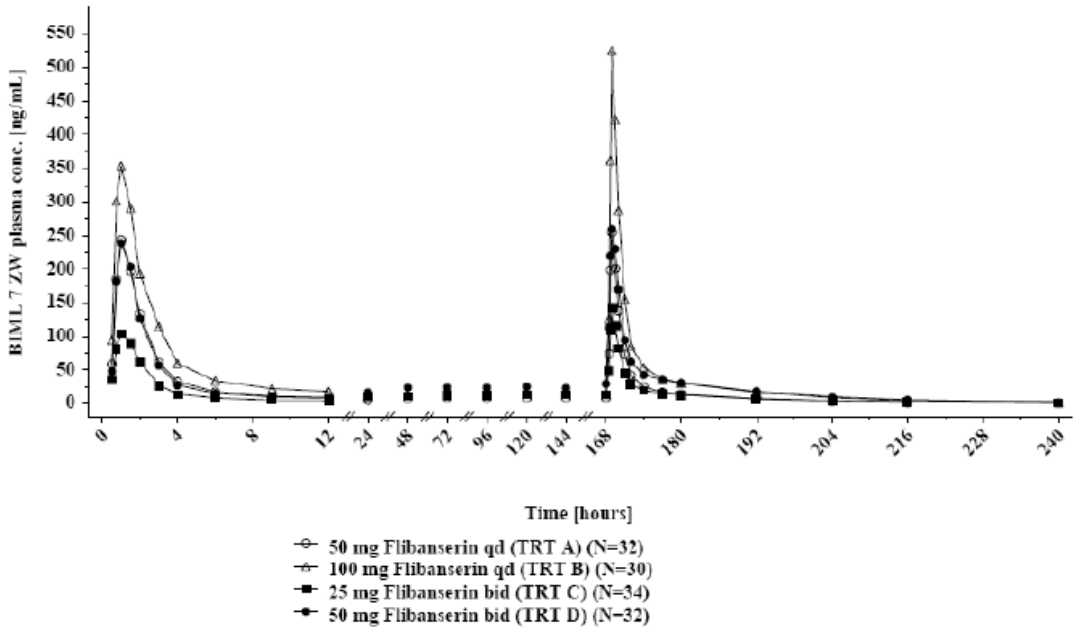


Table 11.5.2.2.4: 1 Comparison of key pharmacokinetic parameters of TFMPP after single dose by dose group

Single dose	50 mg q.d. (N=30)		100 mg q.d. (N=27)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=32)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-12} [ng·h/mL]	22.8	50.2	37.0	51.7	---	---	22.3	50.4
AUC_{0-24} [ng·h/mL]	29.7	52.3	49.0	53.4	---	---	---	---
AUC_{0-tz} [ng·h/mL]	24.9	64.9	43.8	63.7	11.6	71.7	21.9	54.4
$AUC_{0-\infty}$ [ng·h/mL]	33.2	56.3	55.4	56.3	---	---	31.5	58.9
$\%AUC_{tz-\infty}$ [%]	22.1	42.2	18.6	45.1	---	---	27.1	34.6
$RAUC_{0-\infty,Met}$ [ ]	0.0623	67.3	0.0546	70.1	---	---	0.0581	68.3
C_{max} [ng/mL]	3.56	49.7	5.69	56.2	1.97	45.9	3.64	40.3
t_{max}[1] [h]	3.00	1.00-6.00	3.00	1.00-6.00	3.00	0.750-9.00	2.00	0.750-6.00
$t_{½}$ [h]	6.68[2]	39.8[2]	7.17	32.5	---	---	6.08	45.6
MRT_{po} [h]	10.4	34.3	10.9	28.2	---	---	9.57	40.7

Source Data: Section 15, Table 6.3: 1, Table 6.2.1: 7 and Table 6.2.1: 21

[1] median and range

[2] N=31

Table 11.5.2.2.4: 2 Comparison of key pharmacokinetic parameters of TFMPP at steady state by dose group

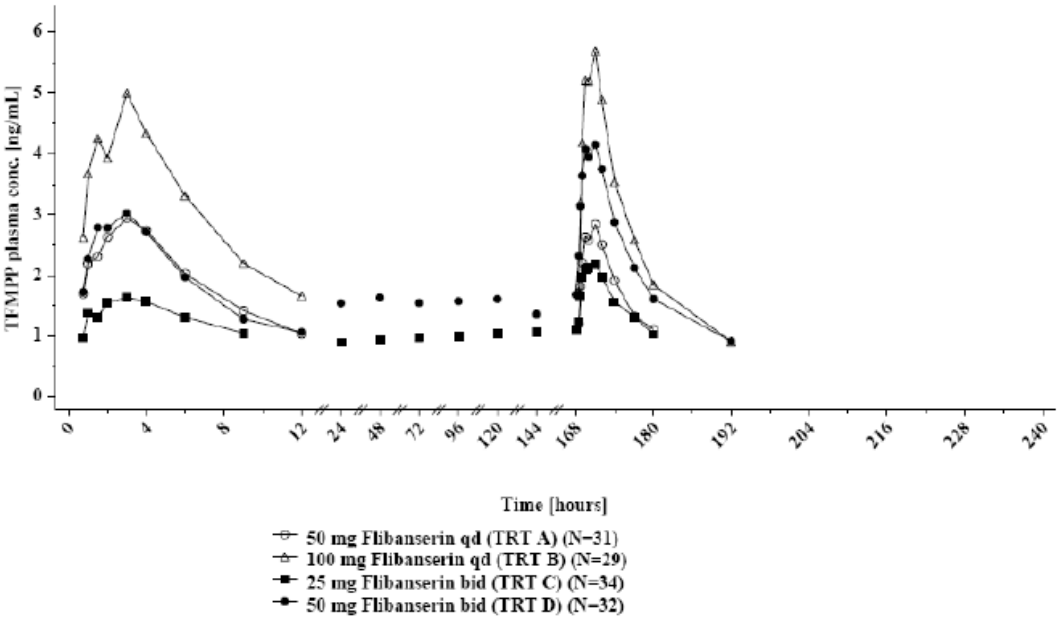
Steady state	50 mg q.d. (N=30)		100 mg q.d. (N=29)		25 mg b.i.d. (N=33)		50 mg b.i.d. (N=31)	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	30.5	52.4	57.2	46.3	18.7	51.0	34.6	53.2
$R_{A,AUC}$ [ ]	1.06[2]	25.0[2]	1.16[3]	23.2[3]	---	---	1.51	19.1
$RAUC_{\tau,ss,Met}$ [ ]	0.0521	65.8	0.0467	67.4	0.0485	73.0	0.0417	71.7
$C_{max,ss}$ [ng/mL]	3.40	44.0	6.39	45.4	2.50	42.6	5.01	53.9
$R_{A,Cmax}$ [ ]	0.985[2]	30.4[2]	1.09[3]	28.6[3]	1.29[4]	35.5[4]	1.35	30.6
$t_{max,ss}$[1] [h]	1.83	0.750-6.00	2.00	0.750-6.00	2.00	0.750-4.00	2.00	0.500-4.00
$t_{½,ss}$ [h]	9.32	74.3	9.49	47.3	10.9	71.6	11.1	66.6
$MRT_{po,ss}$ [h]	13.4	62.4	13.0	38.0	15.8	61.6	14.7	54.7

Source Data: Section 15, Table 6.3: 1

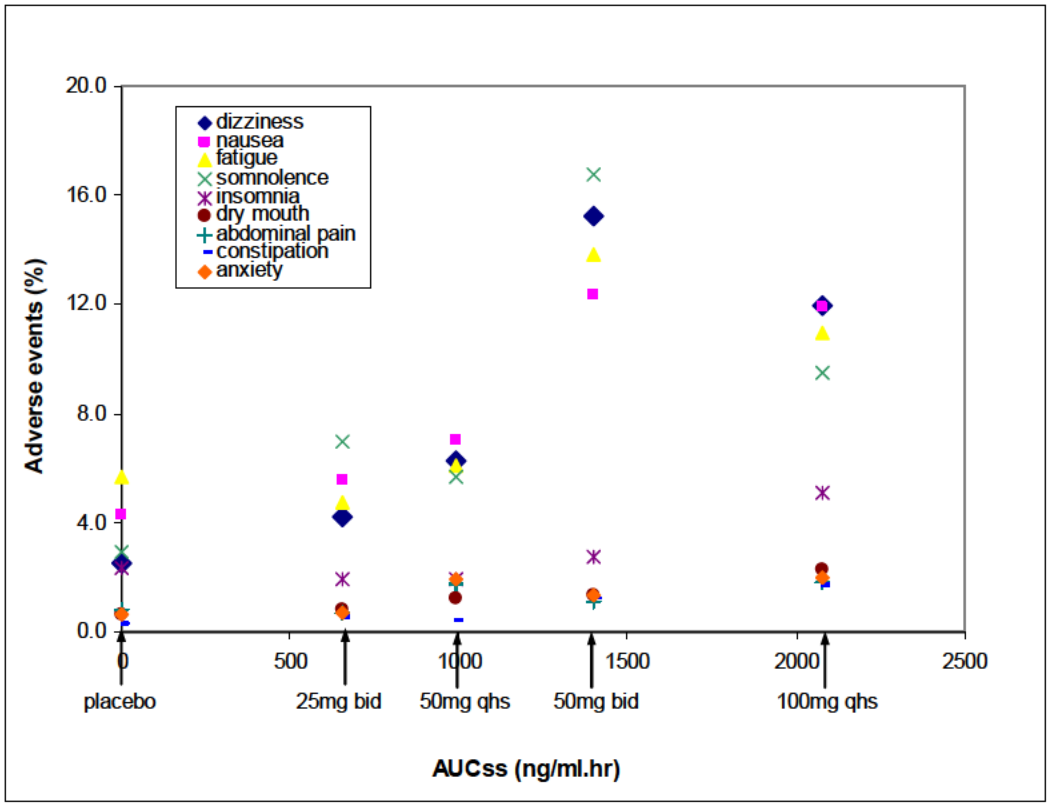
[1] median and range

[2] N=28, [3] N=26, [4] N=32

0-τThe following are geometric mean plasma concentration-time profiles of TFMPP (M30a) after multiple oral doses of flibanserin to HSDD patients



The figure below is an exposure (AUCss) vs adverse events profile for flibanserin. The adverse events in this figure are the same data from four phase 3 studies (511.70, 71, 75, and 77) being evaluated by the Medical Officer Olivia Easley. The most common treatment-emergent adverse events for subjects treated with flibanserin 100 mg qhs are dizziness, nausea, fatigue, and somnolence. The exposure data for each corresponding dose group (25 mg bid, 50 qhs, 50 mg bid, 100 mg qhs) are from this PK study in HSDD women. Patients in the phase 3 studies who received flibanserin once daily were given the drug at bedtime, not in the morning as in this PK study. At the same total daily dose (50 mg bid vs. 100 qhs), the qhs dosing strategy appears to lower the incidences of AEs such as dizziness, somnolence, and fatigue despite the higher exposure, especially for the 100 mg qhs group. That is the rationale for the qhs dosing regimen proposed in this NDA. Despite reducing the incidences of AEs by giving flibanserin at bedtime, there is a clear and possibly linear relationship in the incidences of adverse events and increase in flibanserin exposure, especially if comparison is made with the bid and qhs groups separately.



The following table summarizes the adverse events occurring in >1% and at least twice that of placebo in the flibanserin 100 mg group (according to randomized treatment) – Phase III placebo-controlled HSDD Trials[1]

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

1 - Includes trials 511.70, 511.71, 511.75 and 511.77; Source: Applicant submission, ISS, Table 2.1.2.1.1

Study 511.67

Title: Pharmacokinetics of flibanserin in subjects with liver impairment as compared to healthy subjects

Objective: The objective of this study was to assess the effect of mild-to-moderate liver impairment (Child-Pugh classification A/B; Child-Pugh score of 6-8 points) and moderate-to-severe liver impairment (Child-Pugh classification B/C, Child-Pugh score of at least 9 points) on the pharmacokinetics of flibanserin administered as a single oral dose of 50 mg.

Methods: This was an open-label, parallel group study. Thirty-two subjects completed the study (16 patients with liver impairment and 16 healthy subjects). Of the 14 people enrolled in the liver impairment group, 10 patients (5 females and 5 males) had mild liver impairment (Child-Pugh classification A) and 4 patients (1 female and 3 males) had moderate liver impairment (Child-Pugh classification B).

Flibanserin was administered as a single oral dose after 10 hours fast with about 240 mL of water in subject's standing position under supervision of the investigating physician. Subjects were kept under close medical surveillance until 24 hours following drug administration and were not allowed to lie down during the 2 hours following drug administration. Water was allowed ad libitum except for one hour before and one hour after drug administration.

Pharmacokinetic Sampling: Blood samples were taken pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48 and 72 hours following administration to determine PK parameters.

Results: The effect mild (10 patients) and moderate (4 patients) hepatic impairments on the PK of flibanserin administered as a single oral dose of 50 mg were evaluated by the sponsor in an open-label, parallel group study. Systemic exposure to flibanserin was significantly affected by hepatic impairment. The AUC0-inf of flibanserin was significantly higher (4.5-fold) in patients with mild hepatic impairment compared to matched subjects. The AUC0-inf of flibanserin was higher (2.6-fold) in patients with moderate hepatic impairment compared to matched subjects.

Compared to their matching control group, patients with mild hepatic impairment had a slightly reduced Cmax (9.5%), but it was significantly lower (63% decrease) in patients with moderate hepatic impairment, compared to healthy controls. Clearance decreased 78% and 62% in the mild and moderate hepatic impairment patients, respectively, compared to the healthy matched subjects.

The following table summarizes the PK parameters for mild and moderate hepatic impairment patients, and matched healthy subjects.

PK parameter*	Mild hepatic impairment	Mild healthy matched	Moderate hepatic impairment	Moderate healthy matched
AUC0-inf (ng.hr/ml)	3310 (43.0)	730 (39.5)	2420 (65.1)	925 (52.9)
Cmax (ng/ml)	191 (53.9)	211 (38.9)	88.0 (62.8)	243 (65.9)
Tmax (hr)[1]	0.50 (0.25 – 4.00)	0.75 (0.48 – 1.50)	1.75 (0.50 – 3.00)	0.87 (0.75 – 1.00)

$t_{1/2}$ (hr)	25.6 (47.4)	10.6 (25.2)	26.1 (57.3)	9.91 (31.4)
CL/F (ml/min)	252 (43.0)	1140 (39.5)	345 (65.1)	900 (52.9)

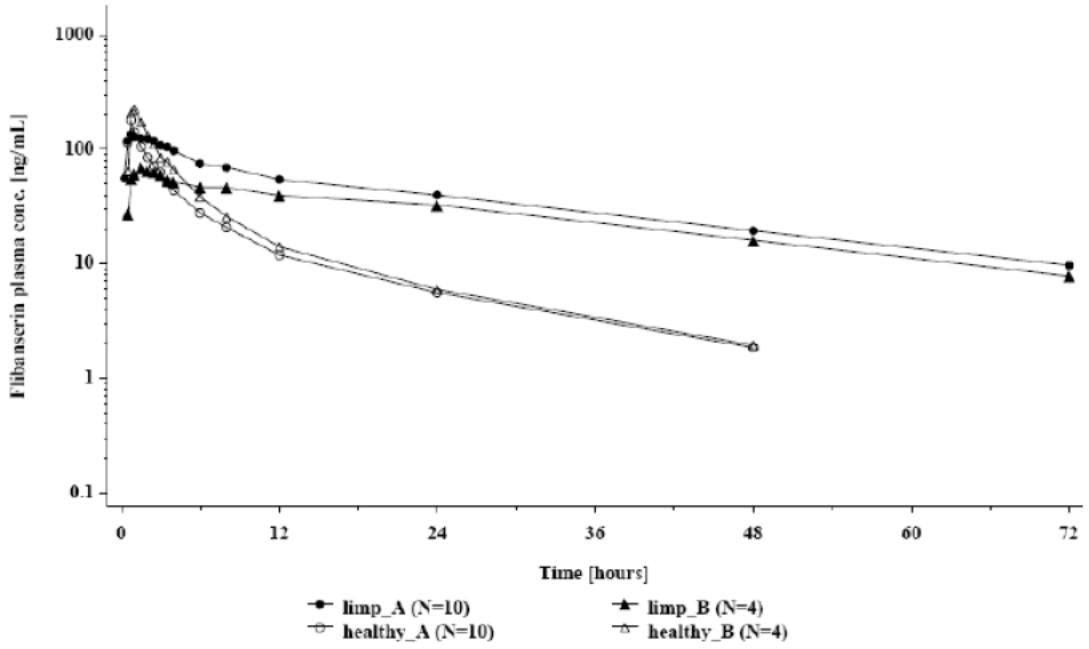
*geometric mean (%CV)
[1] median and range

Due to the small number of patients with moderate hepatic impairment (n=4) enrolled in the study, this reviewer cautions on the limitations of using data generated from that group in making regulatory decisions. The sponsor did not enroll patients with severe hepatic impairment.

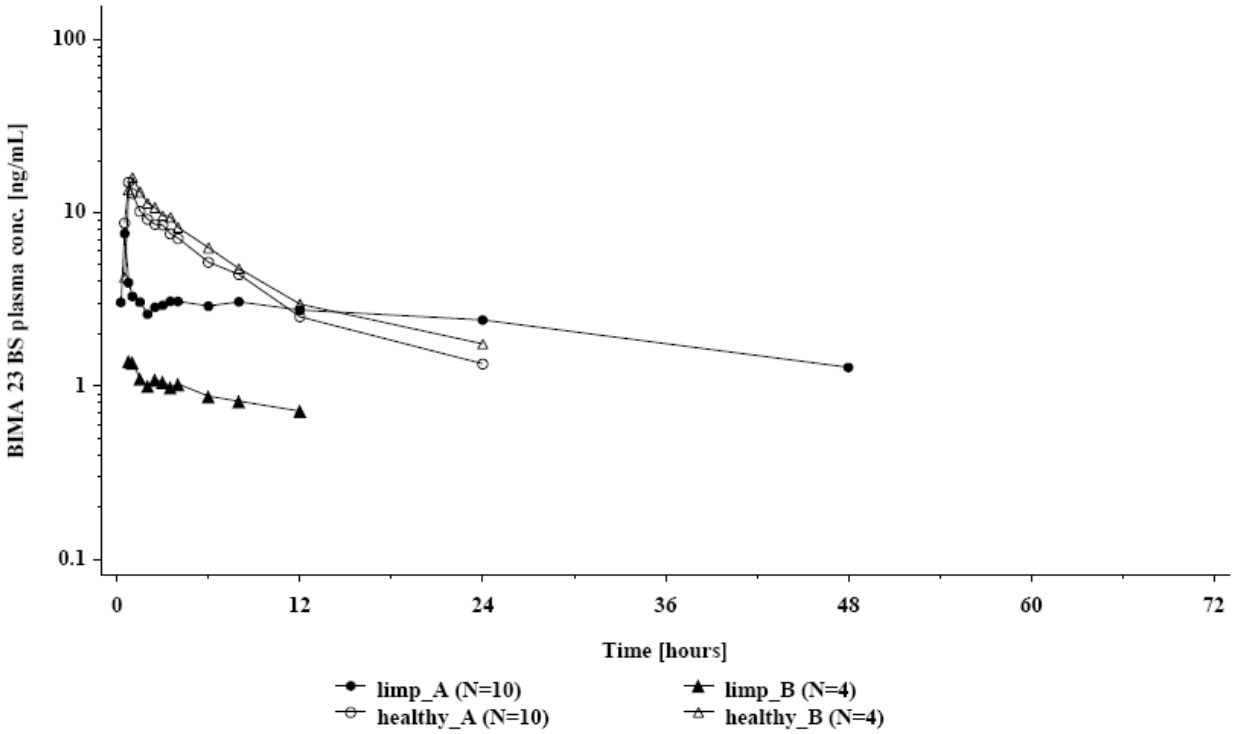
(b) (4)

For the targeted premenopausal population, this reviewer agrees with the sponsor in contraindicating the use of flibanserin in patients with hepatic impairment. If the patient population is expanded to include women older than 45 years, the sponsor will be advised to address how severe hepatic impairment will affect flibanserin exposure and to consider dose adjustment in patients with mild and/or moderate hepatic impairment.

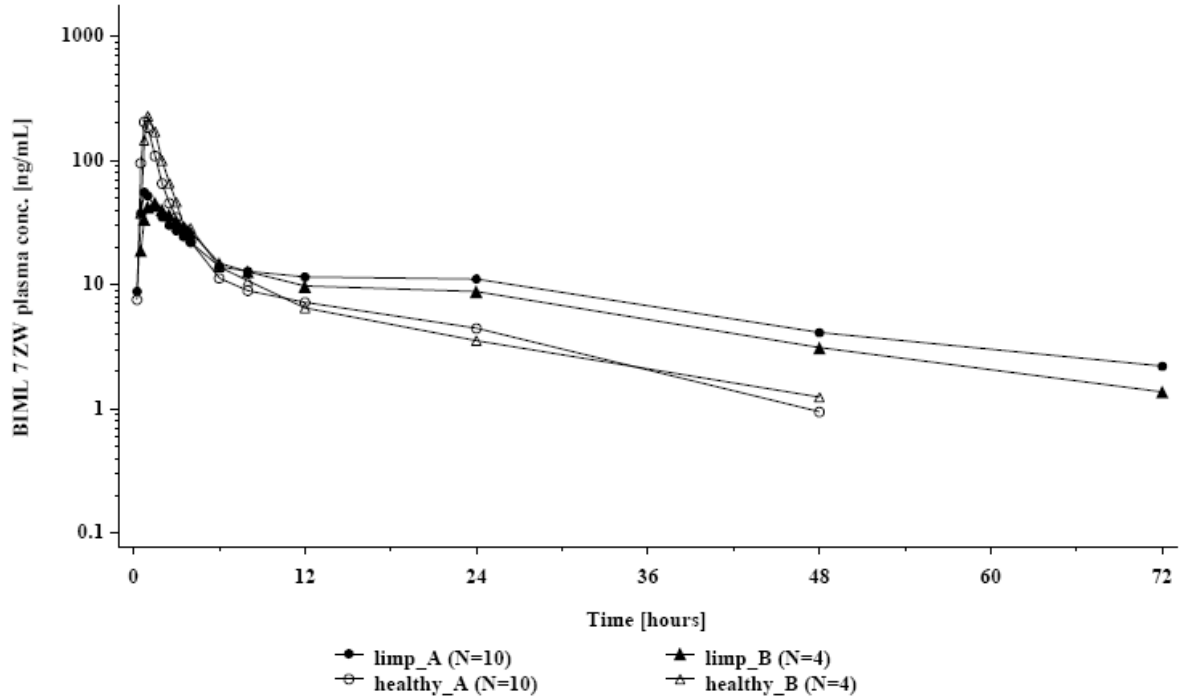
The following is a geometric mean plasma concentration-time profiles of flibanserin after a single oral dose of 50 mg flibanserin to subjects with hepatic impairment and matched healthy volunteers (semi logarithmic scale)



The following is a geometric mean plasma concentration-time profiles of BIMA 23 BS (M35) after a single oral dose of 50 mg flibanserin to subjects with hepatic impairment and matched healthy volunteers (semi logarithmic scale)



The following is a geometric mean plasma concentration-time profiles of BIML 7ZW (M38) after a single oral dose of 50 mg flibanserin to subjects with hepatic impairment and matched healthy volunteers (semi logarithmic scale)



The following is a geometric mean plasma concentration-time profiles of TFMPP (M30a) after a single oral dose of 50 mg flibanserin to subjects with hepatic impairment and matched healthy volunteers (semi logarithmic scale)

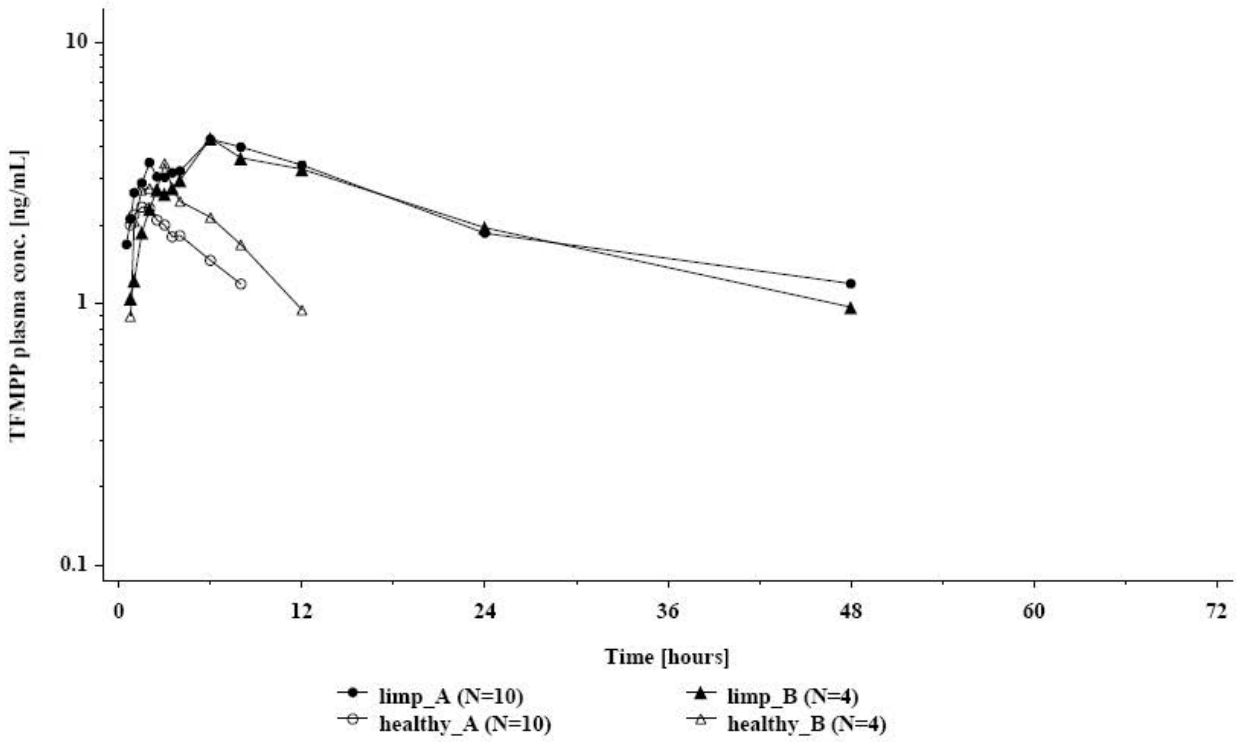


Table 11.5.2.2.1: 1 Comparison of key pharmacokinetic parameters of flibanserin by analysis group

		Patients with mild hepatic impairment (N=10)		Patients with moderate hepatic impairment (N=4)		Subjects matched to mild hepatic impairment group (N=10)		Subjects matched to moderate hepatic impairment group (N=4)	
PK parameter		gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-tz}	[ng·h/mL]	2760	26.7	1960	44.1	691	42.1	894	54.1
$AUC_{0-\infty}$	[ng·h/mL]	3310	43.0	2420	65.1	730	39.5	925	52.9
$\%AUC_{tz-\infty}$	[%]	10.8	128	12.2	148	4.37	62.5	3.12	47.9
C_{max}	[ng/mL]	191	53.9	88.0	62.8	211	38.9	243	65.9
t_{max}[1]	[h]	0.500	0.250-4.00	1.75	0.500-3.00	0.750	0.483-1.50	0.867	0.750-1.00
$t_{½}$	[h]	25.6	47.4	26.1	57.3	10.6	25.2	9.91	31.4
MRT_{po}	[h]	33.6	56.5	38.1	61.2	10.0	30.9	8.83	25.4
CL/F	[mL/min]	252	43.0	345	65.1	1140	39.5	900	52.9
V_z/F	[L]	557	14.0	778	26.5	1040	28.6	772	31.1

[1] median and range

Study 511.96

Title: Pharmacokinetics of flibanserin in subjects with renal impairment as compared to healthy subjects

Objective: Although flibanserin itself is not detected in urine due to its extensive metabolism, metabolites are excreted about 40% via the kidney. The objective of this clinical study was to assess the effect of mild-to-moderate renal impairment and severe renal impairment on the pharmacokinetics of flibanserin administered as a single oral dose of 50 mg.

Methods: In an open-label, single dose, parallel group comparison study, the sponsor assessed the effect of mild-to-moderate renal impairment (CrCL 30-80 mL/min) and severe renal impairment (CrCL <30 mL/min) on the pharmacokinetics of flibanserin administered as a single oral dose of 50 mg. A total of 32 subjects were planned to participate in the clinical trial, of whom 16 were to be patients with renal impairment and 16 healthy subjects to serve as matched controls. Of the 20 patients who participated in the study, 11 patients (2 males; 9 females) were in the mild-to-moderate group and 9 patients (7 males; 2 females) were in the severe impairment group. There were 7 and 9 healthy subjects in the mild-to-moderate renal impairment and severe renal impairment group, respectively.

Flibanserin was administered as a single oral dose after a 10-hour fast with about 240 mL of water in subject's standing position under supervision of the investigating physician. Subjects were kept under close medical surveillance until 24 hours following administration of the investigational product and were not allowed to lie down during the 2 hours following drug administration. Water was allowed ad libitum except for one hour before and one hour after drug administration.

Pharmacokinetic Sampling: Blood samples were taken pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48 and 72 hrs following administration to determine PK parameters.

Results: The effect of mild-to-moderate renal impairment and severe renal impairment on the PK of flibanserin administered as a single oral dose of 50 mg in an open-label, single dose, parallel group comparison study were evaluated by the sponsor. Mild-to-moderate renal impairment did not significantly impact the systemic exposure to flibanserin (AUC0-inf increased by 12.0%), compared to subjects with normal renal function. Severe renal impairment had a moderate impact on the systemic exposure to flibanserin (AUC0-inf increased by 20.8%), compared to subjects with normal renal function.

Cmax decreased by 4.2% in mild-to-moderate renal impairment patients, compared to subjects with normal renal function. This is not significant given the level of variability in the data. Cmax increased 31.1% in severe renal impairment patients, compared to subjects with normal renal function.

The following table summarizes the PK parameters for mild-to-moderate and severe renal impairment patients, and matched healthy subjects.

PK parameter*	Mild-moderate renal impairment	Mild-moderate healthy matched	Severe renal impairment	Severe healthy matched
AUC0-inf (ng.hr/ml)	957 (69.3)	854 (45.7)	1220 (39.8)	1010 (41.9)

Cmax (ng/ml)	230 (53.6)	240 (35.3)	274 (41.8)	209 (64.2)
Tmax (hr)[1]	0.75 (0.53 – 1.50)	0.75 (0.50 – 0.75)	0.75 (0.27 – 1.00)	0.75 (0.48 – 2.00)
$t_{1/2}$ (hr)	9.85 (32.1)	10.1 (46.7)	10.9 (38.1)	11.2 (17.4)

*geometric mean (%CV)
[1] tmax: median and range

The dose evaluated in this renal impairment study was 50 mg, while the proposed dose is 100 mg. It is possible that a larger effect of renal impairment on flibanserin PK is possible at the higher clinical dose. Flibanserin is indicated for premenopausal women between the ages of 18 and 45 years. Considering this target population, these finding in increased AUC and Cmax with severe renal impairment will be an unlikely concern. However, if the use of flibanserin is extended to include patients older than 45 years, the sponsor may be advised to consider adjusting the dose in patients with severe renal impairment or to re-evaluate the effect of renal impairment on flibanserin PK with the 100 mg dose.

(b) (4)

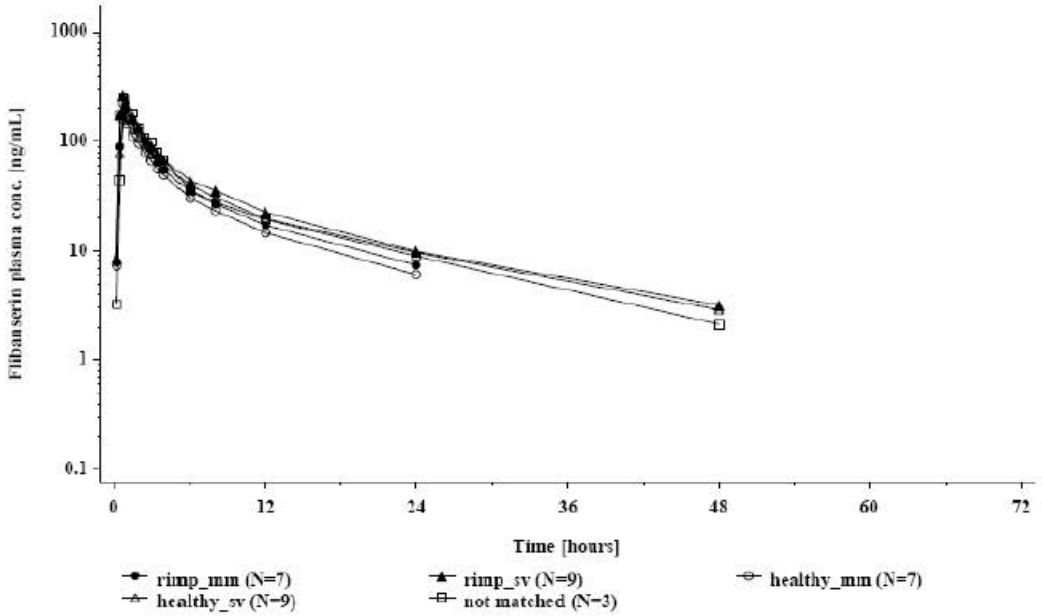
However, for the severe impairment group, an increase of 20.8% and 31.1% in AUC0-inf and Cmax, respectively, is not negligible considering the lower 50 mg dose evaluated in the study.

Table 11.5.2.2.1: 1 Comparison of key pharmacokinetic parameters of flibanserin by analysis group

		Patients				Healthy subjects			
		mm N = 7		sv N = 9		mm-matched N = 7		sv-matched N = 9	
PK parameter		gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-tz}	[ng·h/mL]	916	71.6	1160	41.4	816	46.5	966	45.3
$AUC_{0-\infty}$	[ng·h/mL]	957	69.3	1220	39.8	854	45.7	1010	41.9
$\%AUC_{tz-\infty}$	[%]	3.58	73.2	3.49	67.4	3.89	61.5	3.37	86.3
C_{max}	[ng/mL]	230	53.6	274	41.8	240	35.3	209	64.2
t_{max}[1]	[h]	0.750	0.533 – 1.50	0.750	0.267 – 1.00	0.750	0.500 – 0.750	0.750	0.483 – 2.00
$t_{½}$	[h]	9.85	32.1	10.9	38.1	10.1	46.7	11.2	17.4
MRT_{po}	[h]	9.85	41.4	11.1	45.9	10.0	59.5	11.8	22.7
CL/F	[mL/min]	871	69.3	686	39.8	976	45.7	825	41.9
V_z/F	[L]	743	36.6	646	42.9	853	29.0	797	28.3

[1] median and range (minimum – maximum)

The following figure is the geometric mean plasma concentration-time profiles of flibanserin after a single oral dose of 50 mg flibanserin to subjects with and without renal impairment per analysis group



Study 511.111

Title: An open-label, randomized two-period crossover trial to evaluate the effect of multiple doses of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of flibanserin.

Objective: To evaluate the influence of multiple doses of 400 mg QD of the CYP3A4 inhibitor ketoconazole on the pharmacokinetics of flibanserin and metabolites after a single oral dose of 50 mg flibanserin.

Methods: This was an open-label, randomized, two-period crossover study. Twenty-four healthy Caucasian female subjects were evaluated. The mean (range) age was 34.1 (19 to 47) years. The mean (range) weight was 62.8 (51 to 88) kg and the mean (range) BMI was 22.83 (18.7 to 28.4) kg/m^2.

Test group A (Test) received a single dose of flibanserin (25 or 50 mg) and ketoconazole 400 mg QD for 5 days. Test group B (Reference) received a single dose of flibanserin 50 mg. There was a washout period of at least 14 days. Flibanserin was administered about 9 am with 240 mL water about 1 hr after ketoconazole and a standardized light breakfast in group A. In test treatment group B, flibanserin was administered at about 9 am with 240 mL water 1 hr after a light breakfast. The Test group received oral administration of ketoconazole 400 mg qd for 5 days (days -3 to 2) together with a single morning dose of 50 mg of flibanserin on day 1. The Reference group received oral administration of a single morning dose of 50 mg of flibanserin on day 1.

Pharmacokinetic Sampling: Blood samples were taken pre dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 24, and 48 hrs following the administration of flibanserin to determine PK parameters of flibanserin and metabolites BIMA 23 BS (M35), BIML 7BZ (M38), BI 404016 ZW (M26) and TFMPP (M30a).

Results: The sponsor evaluated the influence of multiple doses of the strong CYP3A4 inhibitor ketoconazole on the PK of flibanserin and metabolites after a single oral dose of 50 mg flibanserin. Ketoconazole 400 mg daily for 5 days inhibited flibanserin metabolism leading to a 4.6-fold increase in flibanserin AUC0-inf. Cmax increased 1.8-fold. Tmax increased slightly from 1.25 to 1.50 hr and $t_{1/2}$ was significantly prolonged from 8.5 to 15.9 hrs. These results are more significant compared with a previous interaction study with itraconazole 200 mg daily for up to 8 days.

The following table summarizes flibanserin PK parameters with and without co-administration of ketoconazole.

	Flibanserin	
SD PK parameter*	With co-administration of ketoconazole	Without co-administration of ketoconazole
AUC0-inf (ng.hr/ml)	5260 (56.5)	1140 (43.5)
Cmax (ng/ml)	472 (24.6)	256 (27.4)
Tmax (hr)[1]	1.50 (0.75 – 4.00)	1.25 (0.75 – 2.00)

$t_{1/2}$ (hr)	15.9 (41.7)	8.54 (29.8)

*geometric mean (%CV)
[1] median and range

Based on findings from the food effect study 511.26, administration of flibanserin 1 hr after a light breakfast may increase exposure by 18%, compared to the fasted state. The exposure of flibanserin with ketoconazole co-administered is significantly higher than 18%; therefore the contribution to increase in AUC0-inf due to a light breakfast is minimal and mostly due to inhibition of CYP3A4 activity by ketoconazole. Knowing that flibanserin is extensively metabolized by CYP3A4, it is not surprising to observed significant inhibition by ketoconazole, a strong CYP3A4 inhibitor.

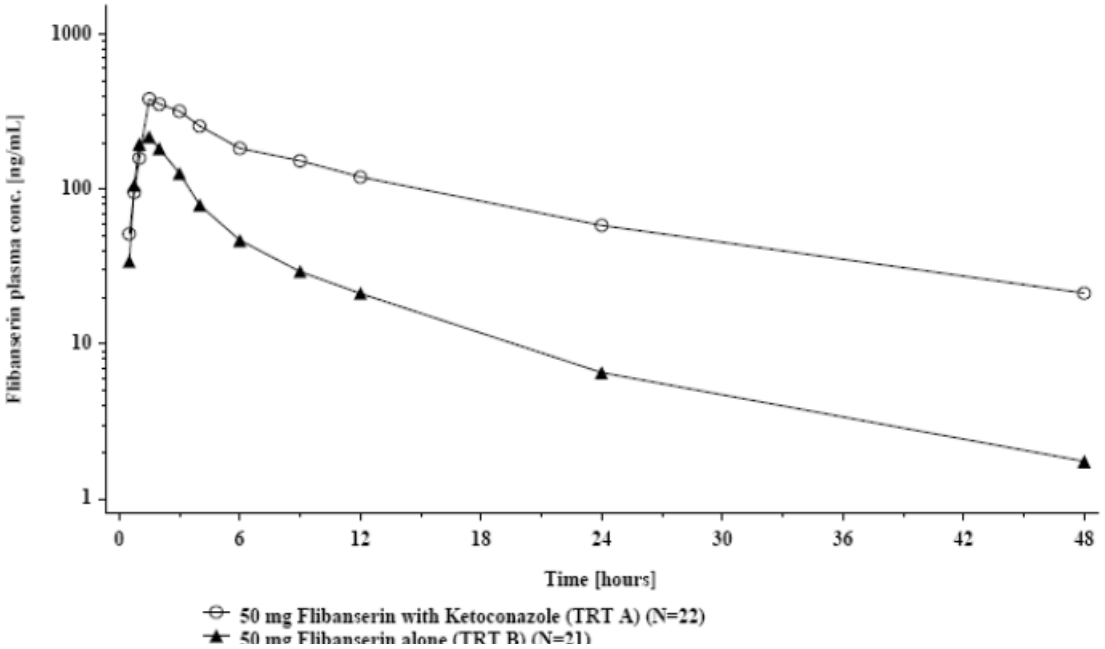
Due to the high degree of inhibition of flibanserin metabolism in the presence of a strong CYP3A4 inhibitor ketoconazole and the likely incidence of increased adverse events with increase flibanserin exposure, the unresolved question is whether and to what degree flibanserin metabolism will be inhibited by mild and moderate CYP3A4 enzymes.

In the Guidance to Industry: Drug Interaction Studies, there is a decision tree on page 27 encouraging sponsors to conduct in vivo studies with other inhibitors/inducers when in vivo studies with the most potent inhibitors/inducers show a significant interaction. Despite this available guidance, the sponsor did not evaluate the effect of mild or moderate CYP3A4 inhibitors on flibanserin PK. (b) (4) Additionally, CYP3A4 inhibitors, grapefruit juice, herbal medications and dietary supplements were excluded from many clinical trials. It is important to address the effect of mild and moderate CYP3A4 inhibitors considering the long list (5 pages) of excluded medications in the pivotal Phase 3 studies and its likelihood of use in HSDD women. One mechanism to address the potential for drug interactions with other CYP3A4s is to request the sponsor conduct studies with mild and moderate CYP3A4 inhibitors as a post-approval Phase 4 commitment.

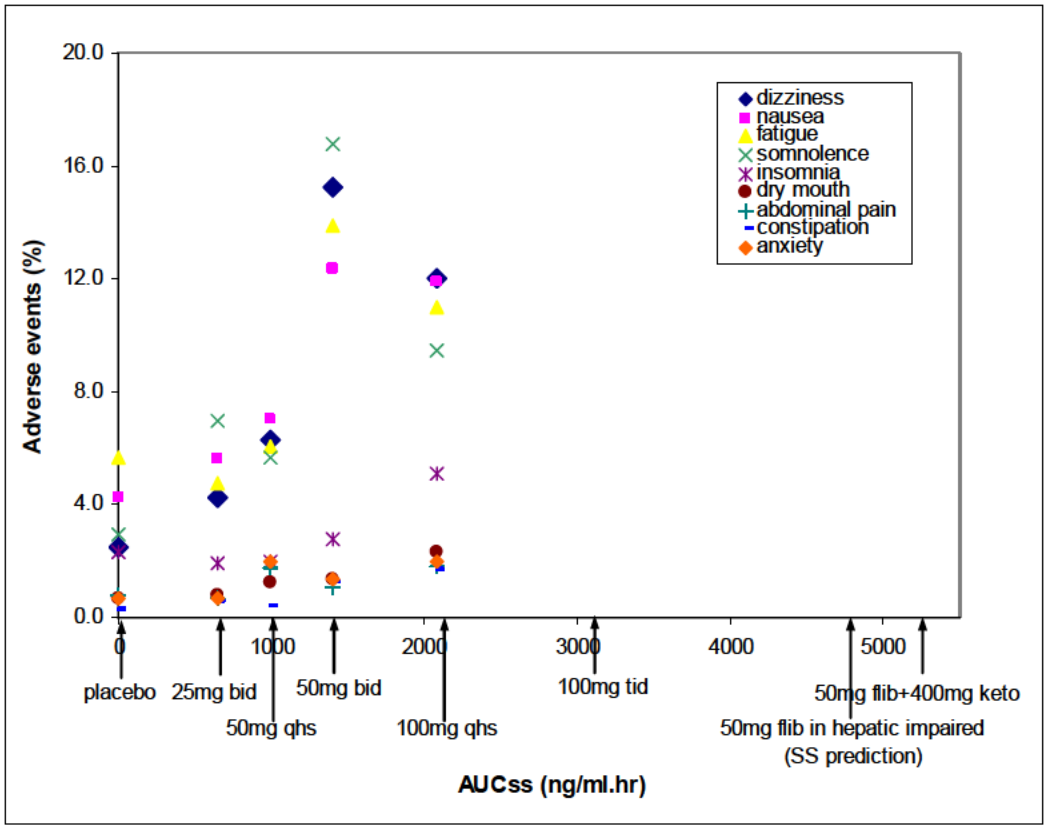
Table 11.5.2.2.1: 1 Comparison of key pharmacokinetic parameters of flibanserin by treatment

			Flibanserin			
			With co-administration of ketoconazole (TRT A)		Without co-administration of ketoconazole (TRT B)	
Parameter	Unit	N	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-12}	[ng·h/mL]	[20/20]	2480	27.9	873	34.6
AUC_{0-24}	[ng·h/mL]	[20/20]	3550	36.1	1030	39.2
AUC_{0-tz}	[ng·h/mL]	[20/20]	4420	47.0	1110	42.9
$AUC_{0-\infty}$	[ng·h/mL]	[20/20]	5260	56.5	1140	43.5
$\%AUC_{tz-\infty}$	[%]	[20/20]	9.01	160	1.95	57.1
C_{max}	[ng/mL]	[21/20]	472	24.6	256	27.4
t_{max}[1]	[h]	[21/20]	1.50	0.750-4.00	1.25	0.750-2.00
$t_{½}$	[h]	[20/20]	15.9	41.7	8.54	29.8
MRT_{po}	[h]	[20/20]	20.5	46.5	8.42	31.7
CL/F	[mL/min]	[20/20]	159	56.5	734	43.5
V_z/F	[L]	[20/20]	218	25.6	543	35.4

The following figure is the geometric mean plasma concentration-time profiles of flibanserin after a single oral dose of 50 mg flibanserin to healthy female volunteers with and without pre-treatment with 400 mg ketoconazole.



The figure below is an exposure vs adverse events profile from four phase 3 studies (Studies 511.70, 511.71, 511.75, and 511.77). The exposure of flibanserin in the presence of a strong CYP3A4 inhibitor is significantly higher than the exposure from the proposed clinical dose of 100 mg qhs, which was chosen over other doses due to tolerability.


20.0
16.0
12.0
8.0
4.0
0.0
Adverse events (%)
dizziness
nausea
fatigue
somnolence
insomnia
dry mouth
abdominal pain
constipation
anxiety
0
1000
2000
3000
4000
5000
placebo
25mg bid
50mg bid
100mg tid
50mg flib+400mg keto
50mg qhs
100mg qhs
50mg flib in hepatic impaired
(SS prediction)
AUCss (ng/ml.hr)

The mean steady state systemic exposure of flibanserin (AUCτ, ss) in HSDD women following once daily dosing of 50 mg and 100 mg dose is 991 and 2080 ng.hr/ml, respectively. Under conditions where the metabolism of flibanserin is altered such as through the concomitant use of a strong CYP3A4 inhibitor, the systemic exposures of a single 50 mg dose flibanserin were increased to 5260 ng.hr/ml. Based on the observed relationship between dose and adverse events, it is likely that patients using a CYP3A4 inhibitor will likely experience an increase in adverse events compared with healthy patients.

	Pharmacokinetics of flibanserin following different dosing regimens				
	25 mg flibanserin bid*	50 mg flibanserin qd*	50 mg flibanserin bid*	100 mg flibanserin qd*	50 mg flibanserin + 400 mg ketoconazole**
AUCτ, ss (ng.hr/ml)[a]	653 (60.1)	991 (47.7)	1400 (46.9)	2080 (46.6)	5260 (56.5)
Cmax, ss (ng/ml)[a]	168 (50.9)	234 (41.2)	346 (34.4)	469 (42.7)	472 (24.6)
Tmax (hr)[b]	1.00 (0.50-3.00)	1.00 (0.42-4.00)	0.75 (0.50-3.00)	1.00 (0.50-3.00)	1.50 (0.75-4.00)

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

Study 511.86

Title: An open, randomized two-period cross-over trial to evaluate the effect of multiple doses of rifampicin on the pharmacokinetics of flibanserin.

Objective: To evaluate the influence of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of flibanserin and relevant metabolites.

Methods: This was an open-label, single center, randomized, two-period cross-over study in healthy females.

Treatment A (Test): Oral administration of rifampicin 600 mg once daily in the evening (at about 8 pm) for 7 days (Study Days -7 to -1) followed by a morning dose (at about 8 am) of flibanserin 100 mg on Study Day 1 after an overnight fast of at least 10 hours. Two more evening doses of rifampicin 600 mg once daily were administered in the evening on Study Days 1 and 2. Flibanserin and rifampicin were given with 240 ml water.

Treatment B (Reference): Oral administration of flibanserin 100 mg once daily in the morning on Study Day 1. In the morning of study day 1, 100 mg flibanserin was administered close to 8 am after an overnight fast of at least 10 hours. Flibanserin was given together with 240 mL water.

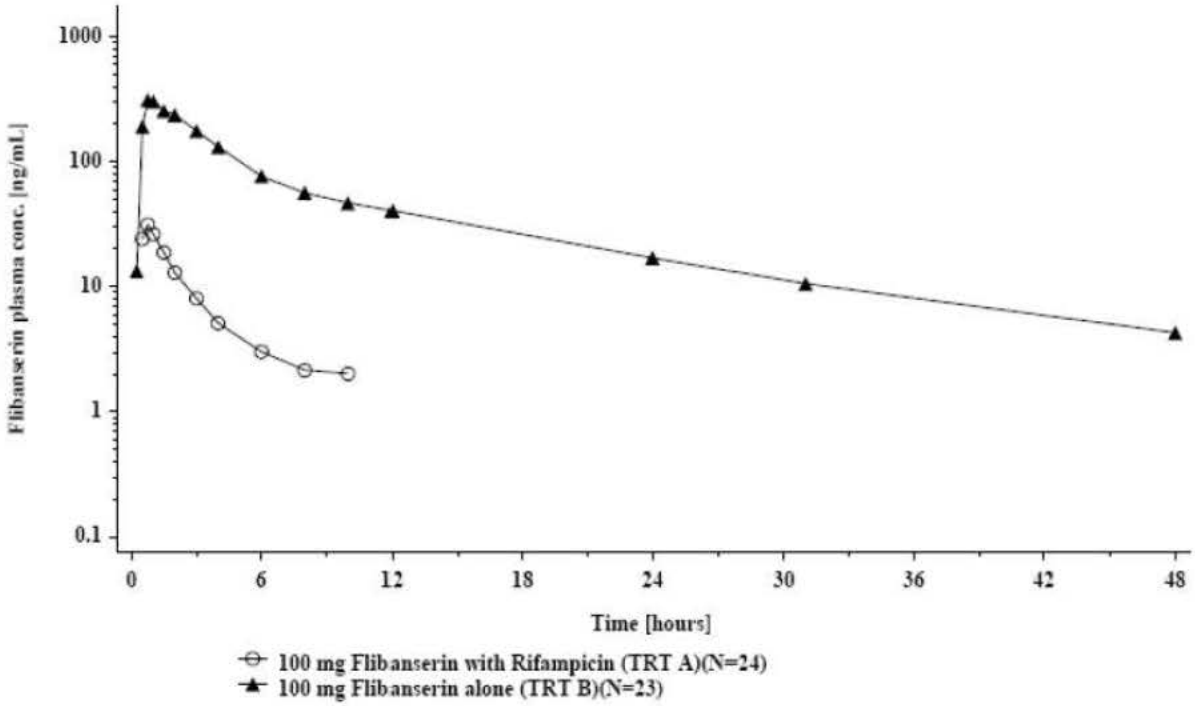
There was a washout period of four weeks, if Treatment A was the first treatment, and one week, if Treatment B was the first treatment following the last drug administration.

Pharmacokinetic Sampling: Blood samples were taken predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, and 48 hrs following the administration of flibanserin to determine PK parameters of flibanserin.

Results: The geometric mean flibanserin exposure AUC0-inf (%CV) was significantly lower when co-administered with rifampicin: 93.5 ng.hr/ml (54.8%), compared to 2080 ng.hr/ml (45.0%) without rifampicin. Flibanserin exposure (AUC0-inf) was reduced by 95.5% by rifampicin pre-treatment. Geometric mean flibanserin Cmax (%CV) was also significantly lowered when co-administered with rifampicin: 37.1 ng/ml (57.1%), compared to 377 ng.hr/ml (46.4%) without rifampicin. Cmax for flibanserin was reduced by 91%. BIMA 23 BS (M35) AUC0-t and Cmax decreased to 7.26% and 46.48%, respectively. BIML 7 ZW (M38) AUC0-t and Cmax decreased to 35.06% and 89.63%, respectively. And TFMPP (M30a) AUC0-t decreased to 63.86% while Cmax increased to 149.70%, respectively.

Table 11.5.2.2.1: 1 Comparison of key pharmacokinetic parameters of flibanserin by treatment

Treatment		A (Test)			B (Reference)		
		N	gMean	gCV (%)	N	gMean	gCV (%)
AUC_{0-tz}	[ng·h/mL]	24	85.2	54.0	23	1980	43.0
$AUC_{0-\infty}$	[ng·h/mL]	19	93.5	54.8	23	2080	45.0
$\%AUC_{tz-\infty}$	[%]	19	10.8	76.1	23	2.91	112
C_{max}	[ng/mL]	24	37.1	57.1	23	377	46.4
t_{max}*	[h]	24	0.750	0.500-1.50	23	0.750	0.500-2.00
$t_{1/2}$	[h]	19	5.05	101	23	10.7	34.8
CL/F	[mL/min]	19	17800	54.8	23	802	45.0
V_z/F	[L]	19	7790	60.0	23	740	40.5
MRT_{po}	[h]	19	5.08	85.5	23	11.2	47.6



(b) (4)

. This reviewer recommends the sponsor state more explicitly the level of reduction in flibanserin exposure (~95%) when flibanserin is co-administered with a strong CYP3A4 inducer.

Study 511.87

Title: Pharmacokinetics and pharmacodynamic of flibanserin in poor and extensive metabolizer of CYP2D6 and in combination with paroxetine.

Objective: To assess the effect of impaired CYP2D6 function on the pharmacokinetics of flibanserin when given to poor metabolizers of CYP2D6 or co-administered with an inhibitor of CYP2D6.

Methods: In an open-label, randomized, two-way crossover study with one additional parallel group There were 19 extensive metabolizers (EM), 9 intermediate metabolizers (IM), 1 ultra-rapid metabolizer (UM), and 12 poor metabolizers (PM). The two-way crossover study consisted of treatment A (flibanserin) and treatment B (flibanserin and paroxetine). Treatment C consisted of administration of flibanserin in poor PM. Subjects were given flibanserin tablets 50 mg bid for six days and a morning dose on the seventh day. In subjects who received paroxetine, the dose was up titrated with 20 mg in the morning on Day 1-3, followed by 40 mg (2x20 mg tablets) in the morning on Days 4-16. EM and PM status of CYP2D6 were assessed by genotyping. EMs were defined as carriers of two functional alleles (*1,*2) and PMs were defined as carriers of two non-functional alleles (*3, *4, *5, *6, *7, and *8).

Results: The sponsor evaluated the effect of impaired CYP2D6 function on the PK of flibanserin when given to poor metabolizers (PMs) of CYP2D6 or co-administered with an inhibitor of CYP2D6 in extensive metabolizers (EMs) in Study 511.86. Based on intra-individual comparison, no significant differences in flibanserin AUCτ,ss and Cmax,ss were noted in CYP2D6 EMs with or without co-administration of multiple doses paroxetine 20 mg. In EMs only, the geometric mean AUCτ,ss decreased by 2.5% and geometric mean Cmax,ss increased by 3.4% with co-administration of paroxetine; neither are considered significant.

Little differences in AUCτ,ss and Cmax,ss were seen between CYP2D6 PMs and EMs. In PMs the geometric mean AUCτ,ss increased by 18% and Cmax,ss decreased by 4.1%, compared to the EMs without paroxetine.

In CYP2D6 intermediate metabolizers (IMs), no significant differences in flibanserin AUCτ,ss and Cmax,ss were observed with or without co-administration of paroxetine. In IMs, the geometric mean AUCss decreased by 5.8% and Cmax increased by 8.9% with co-administration of paroxetine. These changes are not considered significant.

Overall, there were very small changes in flibanserin PK due to CYP2D6 polymorphism and co-administration of paroxetine. These findings are not surprising considering flibanserin is extensively metabolized by CYP3A4 and only to a minor extent by CYP2D6.

The following table summarizes the PK parameters for flibanserin in EMs (with or without paroxetine), IMs (with or without paroxetine) and PMs.

PK parameter*	EM without paroxetine	EM with paroxetine	IM without paroxetine	IM with paroxetine	PM
AUCτ,ss (ng.hr/ml)	1220 (31.8)	1190 (38.7)	1560 (40.8)	1470 (33.0)	1440 (62.7)

Cmax,ss (ng/ml)	358 (22.7)	370 (24.9)	403 (30.2)	439 (20.3)	344 (37.4)
Tmax,ss (hr)[1]	0.75 (0.50 – 2.00)	0.75 (0.50 – 2.00)	0.50 (0.50 – 1.50)	0.50 (0.50 – 1.50)	0.75 (0.50 – 2.00)
$t_{1/2,ss}$ (hr)	8.93 (21.2)	9.37 (25.0)	8.89 (28.2)	9.90 (37.8)	10.9 (26.2)

*geometric mean (%CV)
[1] median and range

Table 11.5.2.2: 1 Comparison of geometric mean pharmacokinetic parameters of Flibanserin by treatment and predicted CYP2D6 phenotype

		EM (N=17)		IM (N=9)		UM (N=1)		All (EM, IM, UM) (N=27)		PM (N=12)
Treatment		A	B	A	B	A	B	A	B	C
$AUC_{,ss}$	**gMean**	1220	1190	1560	1470	1350	1080	1330	1270	1440
[ng·h/mL]	**gCV (%)**	31.8	38.7	40.8	33.0	---	---	35.8	37.0	62.7
$C_{max,ss}$	**gMean**	358	370[+]	403	439	334	388	372	392[*]	344
[ng/mL]	**gCV (%)**	22.7	24.9[+]	30.2	20.3	---	---	25.2	24.1[*]	37.4
$t_{max,ss}$	**Median**	0.750	0.750[+]	0.750	0.750	0.750	0.950	0.750	0.750[*]	0.750
[h]	**Range**	0.500 – 2.00	0.500 – 2.00[+]	0.500 – 1.50	0.500 – 1.50	---	---	0.500 – 2.00	0.500 – 2.00[*]	0.500 – 2.00
$t_{1/2,ss}$	**gMean**	8.93	9.37	8.89	9.90	7.31	7.44	8.85	9.46	10.9
[h]	**gCV (%)**	21.2	25.0	28.2	37.8	---	---	23.1	29.1	26.2
$CL/F_{,ss}$	**gMean**	685	698	536	568	616	770	629	654	579
[mL/min]	**gCV (%)**	31.8	38.7	40.8	33.0	---	---	35.8	37.0	62.7
$MRT_{po,ss}$	**gMean**	8.24	8.76	9.49	9.36	7.82	7.50	8.62	8.90	11.4
[h]	**gCV (%)**	26.0	26.5	29.5	32.6	---	---	27.1	27.9	46.5

Source data: Tables 15.5.2.1: 1 to 9
[+] N=18
[*] N=28

The following table summarizes the PK parameters for metabolite TFMPP in EMs (with or without paroxetine), IMs (with or without paroxetine) and PMs.

Table 11.5.2.2: 4 Comparison of geometric mean pharmacokinetic parameters of TFMPP by treatment and predicted CYP2D6 phenotype

		EM (N=17)		IM (N=9)		UM (N=1)		All (EM, IM, UM) (N=27)		PM (N=12)
Treatment		A	B	A	B	A	B	A	B	C
$AUC_{,ss}$	gMean	28.3	141	58.9	125	---	67.0	36.5#	132	115
[ng·h/mL]	gCV (%)	49.5	59.3	97.1	60.1	---	---	78.4#	59.3	57.9
$C_{max,ss}$	gMean	4.66	17.6+	8.42	16.1	1.25	10.5	5.41	16.8*	13.5
[ng/mL]	gCV (%)	42.5	52.1+	77.8	56.2	---	---	71.4	52.4*	49.7
$t_{max,ss}$	Median	1.50	1.50+	1.50	1.50	1.50	1.50	1.50	1.50*	2.02
[h]	Range	0.750 – 3.00	0.750 – 3.00+	1.50 – 2.00	0.750 – 2.00	---	---	0.750 – 3.00	0.750 – 3.00*	0.750 – 6.00
$t_{1/2,ss}$	gMean	7.66	11.3	9.39	11.2	---	8.65	8.22#	11.2	12.0
[h]	gCV (%)	44.4	16.6	37.6	21.2	---	---	42.6#	18.3	34.8
$MRT_{po,ss}$	gMean	10.3	15.8	13.0	15.6	---	11.3	11.2#	15.5	18.0
[h]	gCV (%)	29.2	23.3	31.2	22.7	---	---	31.5#	23.1	37.0
$RAUC_{,ss,Met}$	gMean	0.0395	0.200	0.0642	0.144	---	0.105	0.0467#	0.175	0.136
[ ]	gCV (%)	50.2	50.9	75.9	50.1	---	---	64.2#	52.7	55.9

For the metabolite TFMPP (M30a), AUCτ,ss and Cmax,ss geometric mean ratios were significantly increased to 500.4% and 382.0%, respectively (90% CIs: 394.51-634.72% and 309.15-471.93%), in EMs co-administrated with and without paroxetine (txtmt B vs. txtmt A). Based on inter-individual comparison between PMs and EMs (txtmt C vs. txtmt A), there was also a significant increase in AUCτ,ss and Cmax,ss ratios - 407.6% (90% confidence interval: 296.15-560.94%) and 289.18% (90% CI: 218.85-382.11%), respectively. TFMPP is a phase 1 metabolite of flibanserin metabolism formed by CYP3A4, which is then further metabolized to BI 400296 ZW (M8) and BI 401703 ZW (M2) by CYP2D6. By exogenously blocking CYP2D6 metabolism through the co-administration of paroxetine or endogenously as evaluated in EMs, TFMPP have no metabolic pathway for its metabolism and thus its accumulation. Through receptor screening, TFMPP possesses some affinity to serotonergic receptors with approximately 5% molar exposure in plasma compared to flibanserin. Therefore, exposure of TFMPP can be increased to a significant degree, but there is little clinical concern regarding this accumulation as this metabolite is inactive.

Table 11.5.2.3: 4 Adjusted by-treatment geometric means and relative bioavailability for TFMPP - Intra-individual comparison of treatment B (test) and treatment A (reference) and inter-individual comparison of treatment C (test) and treatment A (reference)

Treatment comparison	N	gMean Test	N	gMean Ref.	Ratio[a] [%]	Lower 90% CI [%]	Upper 90% CI [%]	gCV [%]
$AUC_{\tau,ss}$ [ng•h/mL]								
B vs. A	17	142.520	17	28.481	500.40	394.506	634.722	40.3[b]
C vs. A	12	115.300	17	28.289	407.58	296.151	560.937	53.0[c]
$C_{max,ss}$ [ng/mL]								
B vs. A	18	17.680	17	4.629	381.97	309.154	471.933	35.8[b]
C vs. A	12	13.488	17	4.664	289.18	218.853	382.114	45.5[c]

[a] Test/Reference ratio
[b] intra-individual geometric coefficient of variation
[c] inter-individual geometric coefficient of variation
Source Data: Tables 15.5.6.5: 1 and 2, Tables 15.5.6.6: 1 and 2

This reviewer concurs with the sponsor in that flibanserin exposure was not significantly increased in CYP2D6 PMs or upon co-administration of paroxetine in CYP2D6 EMs indicating that CYP2D6 plays a minor role in the metabolism of flibanserin itself. A marked change in metabolite exposure was only observed for TFMPP with an increase in the geometric mean ratios of AUCτ,ss and Cmax,ss up to 500% and 382%, respectively with impaired CYP2D6 function. However, the geometric mean TFMPP exposure was still low with at maximum 17.5% relative to flibanserin.

Study 511.88

Title: An open, randomized, two-period crossover trial to evaluate the effect of multiple doses of flibanserin on the steady-state pharmacokinetics of bupropion.

Objective: To evaluate the influence of flibanserin on the steady-state pharmacokinetics of bupropion. Bupropion is indicated for the treatment of depression and as a non-nicotine aid to smoking, and is extensively metabolized. Three metabolites have been shown to be active: hydroxybupropion, threohydrobupropion and erythrohydrobupropion, which are approximately 50%, 20%, and 20% as active as bupropion. The sponsor has shown in vitro that flibanserin moderately inhibits CYP3A4 and CYP2B6 with Ki values of 7.5 µM and 6.4 µM, respectively. Published literature referenced by the sponsor indicates that relevant in vivo inhibition of bupropion metabolism to hydroxybupropion has been shown after co-administration with the CYP2B6 inhibitors clopidogrel and ticlopidine. The sponsor states that based on in vitro results, there was a possibility that flibanserin inhibits the metabolism of bupropion by CYP2B6, despite Ki for CYP2B6 that is comparable to CYP3A4 inhibition where the in vivo simvastatin (a sensitive CYP3A4 substrate) inhibition was not clinically significant. The sponsor decided to conduct an in vivo study, using bupropion as CYP2B6 substrate, to assess the extent of CYP2B6 inhibition by flibanserin.

Methods: Twenty-two healthy white women completed this two-way crossover study. Twenty-eight subjects were included in the study; of the six subjects who discontinued from the study, one subject discontinued on Day 3 due to severe syncope after receiving a total of 300 mg flibanserin.

Treatment A (test): flibanserin tablets 50 mg were given bid for 2 days followed by 100 mg qd for 13 days. Oral bupropion sustained release tablets (Zyban) 150 mg were given bid from Day 6 to 12 and 150 mg on the morning of Day 13.

Treatment B (reference): bupropion sustained release tablets (Zyban) 150 mg were given bid for 7 days and 150 mg on the morning of Day 8. Washout period between treatments was at least 10 days.

Pharmacokinetic Sampling: Blood samples were taken for measurement of flibanserin, bupropion, and hydroxybupropion.

For flibanserin measurement in treatment A, blood samples were taken pre-dose to flibanserin administration in the morning of day 1 and on days 6, 12, 13, 14 and 15 as well as 45 min and 1 hour after administration of flibanserin on day 13, and 24 h after the last administration on day 16.

For measurement of bupropion and hydroxybupropion in treatment A, blood samples were taken pre-dose in the morning of day 1 and on day 12 before morning and evening dose, and on day 13 pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60 and 72 hours following the last bupropion administration.

For measurement of bupropion and hydroxybupropion in treatment B, blood samples were taken pre-dose in the morning of day 1 and on day 7 before morning and evening dose, and on day 8 pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60 and 72 hours following the last bupropion administration.

Results: There was essentially no difference in geometric mean exposure AUCss (%CV) for bupropion at steady-state when co-administered with flibanserin - 540 ng.hr/ml (28.5%) - compared to when bupropion was given alone - 525 ng.hr/ml (31.2%). Bupropion Cmax was 73.3 and 71.0 ng/mL for treatment group A and B, respectively. Bupropion Tmax (median and range) was reached 3.00 hrs (1.13-4.00 hrs) and 3.00 (1.00-4.00 hrs) after the last dose for treatment group A and B, respectively. $T_{1/2}$,ss were similar at 24.3 and 25.0 hrs for treatment group A and B, respectively. For bupropion, the geometric mean ratio (90% CI) for AUCτ,ss and Cmax,ss between the test and reference groups was 102.7 (97.2-108.5%) and 102.5 (94.1-111.6%), respectively.

The geometric mean hydroxybupropion exposure AUCss (%CV) at steady-state was lower when co-administered with flibanserin - 8760 ng.hr/ml (50.3%) - compared to when bupropion was given alone -9660 ng.hr/ml (39.8%). Geometric mean hydroxybupropion Cmax (%CV) was 822 (50.0%) and 928 (39.7%) ng/mL for treatment group A and B, respectively. Hydroxybupropion Tmax (median and range) was reached 4.00 hrs (2.00-10.00 hrs) and 4.00 (1.00-8.00 hrs) after the last dose for treatment group A and B, respectively. $T_{1/2}$,ss were similar at 21.9 and 24.2 hrs for treatment group A and B, respectively

AUCτ,ss and Cmax,ss of hydroxybupropion were slightly lower than unity (100) as seen by the geometric mean ratio (90% CI) of 92.4 (83.3-102.4%) and 90.6 (81.7-100.5%), respectively. The metabolic ratio of hydroxybupropion to bupropion was similar with a geometric mean ratio (90% CI) of 90.03 (79.9-101.4%).

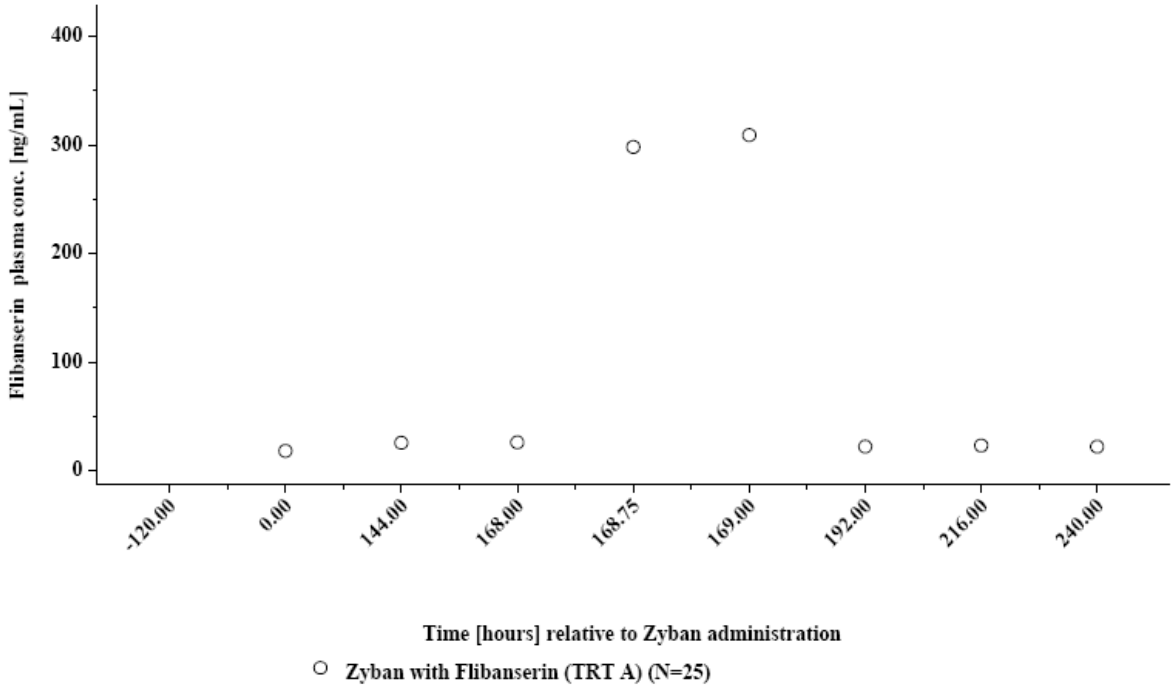
The following table is the PK parameters of bupropion and hydroxybupropion with and without flibanserin co-administration (sponsor's table 11.5.2.2:1).

		Bupropion with Flibanserin (TRT A)				Bupropion (TRT B)			
		Bupropion (N=22)		Hydroxy-bupropion (N=22)		Bupropion (N=23)		Hydroxy-bupropion (N=23)	
		gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$	[ng·h/mL]	540	28.5	8760	50.3	525	31.2	9660	39.8
$RAUC_{\tau,ss,Met}$	[ ]	---	---	15.2	64.1	---	---	17.2	52.9
$RAUC_{\tau,ss,T/R}$	[ ]	1.02	22.4	0.902	27.1	---	---	---	---
$C_{max,ss}$	[ng/mL]	73.3	30.9	822	50.0	71.0	32.9	928	39.7
$RC_{max,ss,T/R}$	[ ]	1.02	20.4	0.882	27.2	---	---	---	---
$t_{max,ss}$ [1]	[h]	3.00	1.13-4.00	4.00	2.00-10.0	3.00	1.00-4.00	4.00	1.00-8.00
$t_{½,ss}$	[h]	24.3	23.9	21.9	28.8	25.0	28.6	24.2	39.6
$CL/F_{,ss}$	[mL/min]	4020	28.5	---	---	4130	31.2	---	---
$MRT_{po,ss}$	[h]	18.6	19.1	34.6	24.6	19.6	20.1	36.3	27.9
$V_z/F_{,ss}$	[L]	8440	35.4	---	---	8920	38.2	---	---

Source data: Section 15. Table 6.3: 2
* median and range

The following figure is the flibanserin concentration-time profile following flibanserin administration in treatment group A. The range of geometric mean steady state trough plasma

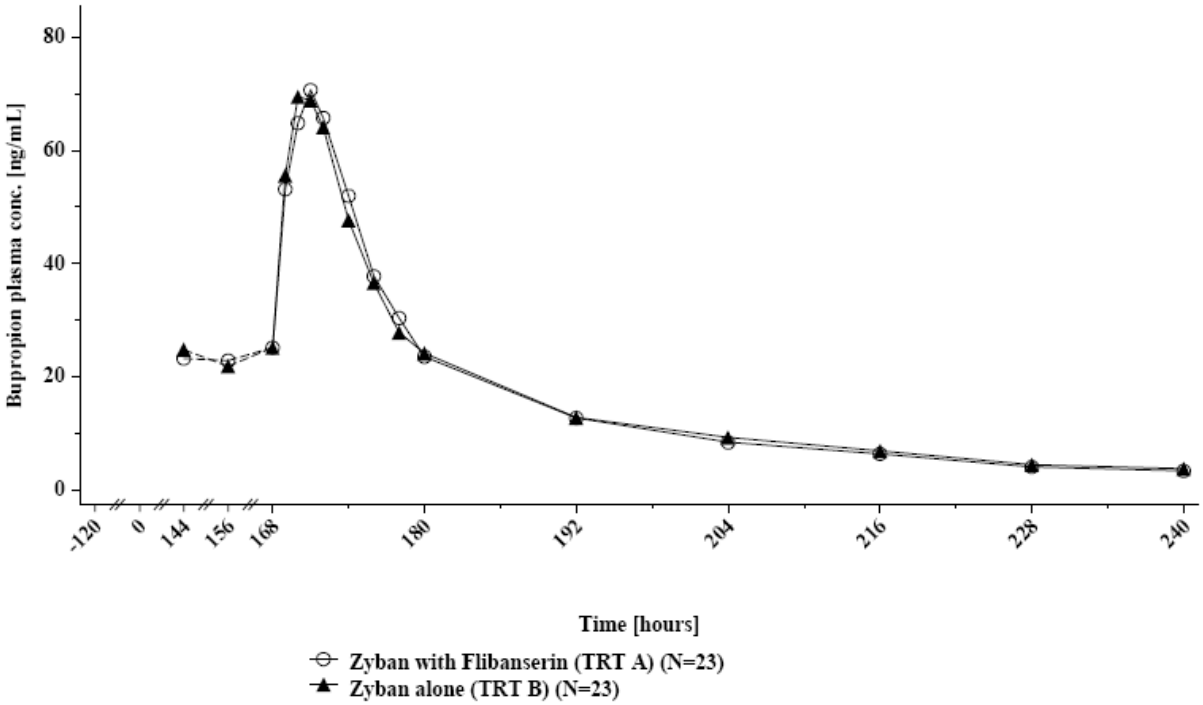
concentrations were 22.3 – 26.3 ng/mL (CV range: 59.9 – 89.5%) following pre-dose PK sampling at 0, 144 (Day 6), 168 (Day 7), 192 (Day 8), 216 (Day 9), 240 hours (Day 10) (relative to bupropion administration). The sponsor demonstrated through this PK profile of flibanserin that steady state has been attained. The geometric mean (%CV) flibanserin plasma concentrations at 168.75 and 169.00 hrs (45 min and 1 hr the Day 13 dose of flibanserin, respectively) were 298 ng/mL (69.9%) and 309 ng/mL (54.4%), respectively. These points are approximately the maximum flibanserin concentrations.



BI Trial No.: 0511.0088

Figure 15.6.5.3: 10 Geometric mean plasma concentration-time points of Flibanserin after multiple oral administration of 100 mg Flibanserin with Zyban bid to healthy female volunteers (linear scale)

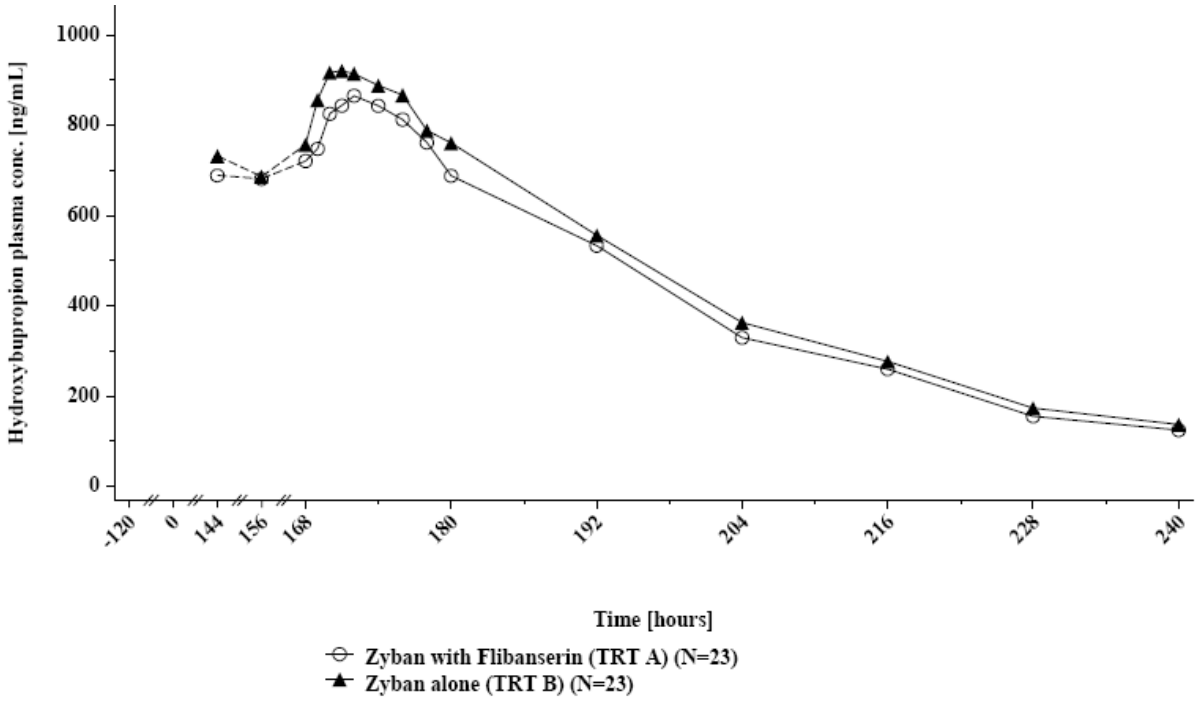
The following figure is the bupropion concentration-time profile following flibanserin and bupropion administration in treatment group A and bupropion only administration in treatment group B.



BI Trial No.: 0511.0088

Figure 15.6.5.3: 1 Arithmetic mean drug plasma conc. time-profiles of Bupropion after multiple oral administration of Zyban bid with or without Flibanserin to healthy female volunteers (linear scale)

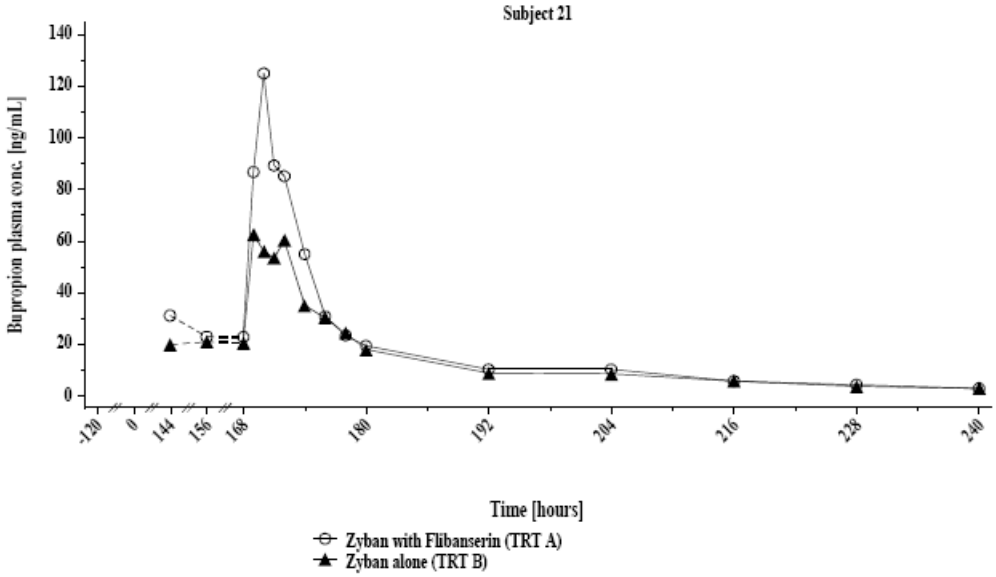
The following figure is the hydroxybupropion concentration-time profile following flibanserin and bupropion administration in treatment group A and bupropion only administration in treatment group B.

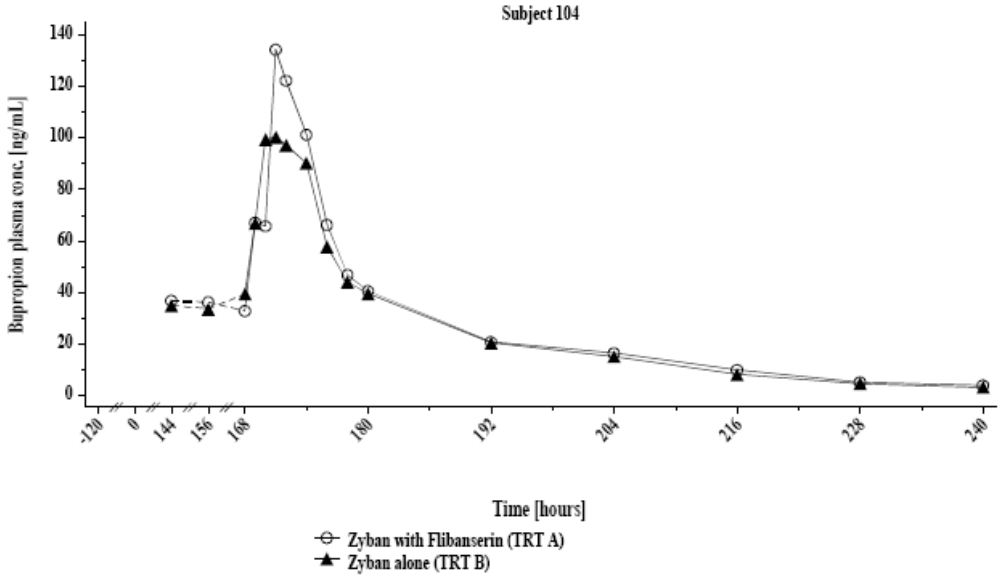


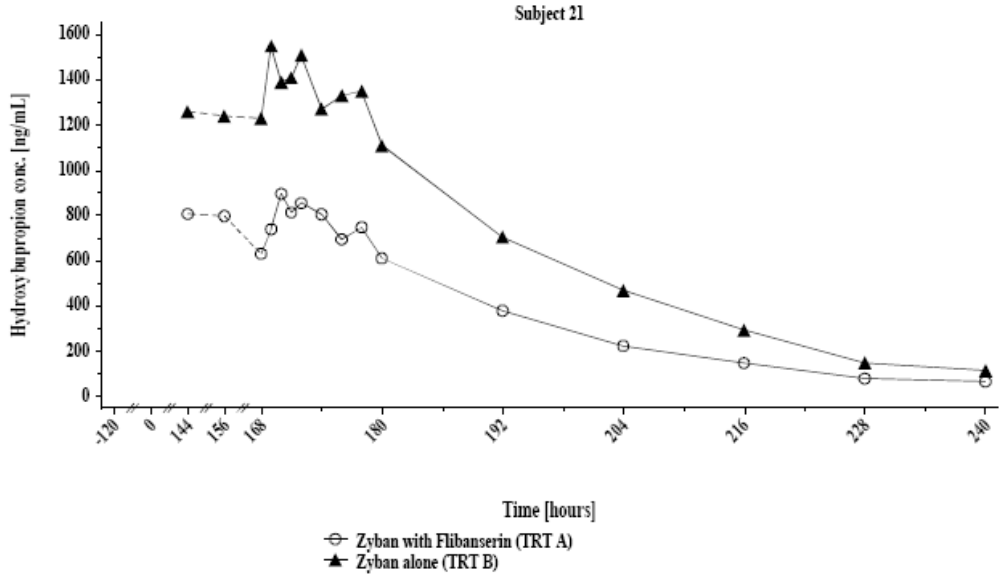
BI Trial No.: 0511.0088

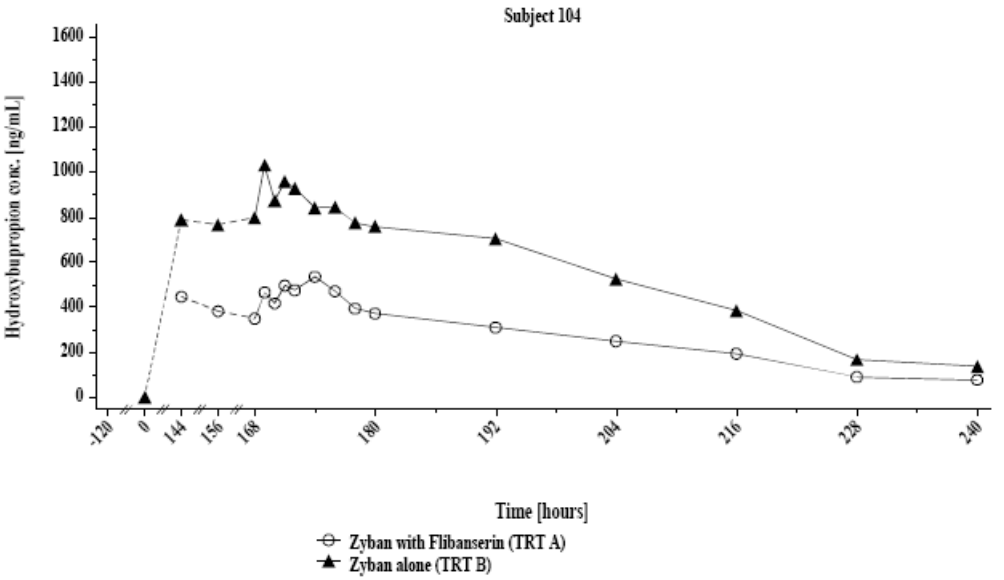
Figure 15.6.5.3: 3 Arithmetic mean drug plasma conc. time-profiles of Hydroxybupropion after multiple oral administration of Zyban bid with or without Flibanserin to healthy female volunteers (linear scale)

Based on the geometric mean ratios of AUC and Cmax for bupropion, it appears that flibanserin does not inhibit the metabolism of bupropion by CYP2B6. However, the geometric mean ratio of hydroxybupropion is lower than unity when comparing test to reference. The following individual profiles for subjects 21 and 104 appear to suggest that flibanserin may inhibit the metabolism of bupropion via CYP2B6. Bupropion plasma concentration is higher in treatment A (flibanserin and bupropion) compared with treatment B (bupropion alone). The reverse was observed with hydroxybupropion plasma concentrations: higher in treatment B compared with treatment A. **These findings suggest CYP2B6 <u>may</u> be inhibited by flibanserin. Because approximately 10% (two of twenty-two of subjects) evaluated in this study had lower than expected bupropion concentrations and higher than expected hydroxybupropion concentrations when bupropion was co-administered with flibanserin, this reviewer cannot absolutely rule out a potential of flibanserin to inhibit CYP2B6-mediated metabolism of bupropion. Overall, it does appear that flibanserin does not inhibit CYP2D6 activity.**


Subject 21
Bupropion plasma conc. [ng/mL]
140
120
100
80
60
40
20
0
-120
0
144
156
168
180
192
204
216
228
240
Time [hours]
Zyban with Flibanserin (TRT A)
Zyban alone (TRT B)


Subject 104
Bupropion plasma conc. [ng/mL]
140
120
100
80
60
40
20
0
-120
0
144
156
168
180
192
204
216
228
240
Time [hours]
Zyban with Flibanserin (TRT A)
Zyban alone (TRT B)





The following table is a summary of adverse events by treatment groups. **One subject (#4) withdrew from the study on Day 3 after receiving 300 mg (50 mg bid for 2 days and 100 mg qd) flibanserin due to severe syncope.** There was a significantly greater incidence of dizziness in treatment group A on flibanserin (37%) compared with subjects in treatment group B with bupropion only (0%). Dizziness does appear to subside following longer duration of flibanserin use (>5 days) as seen with the decrease in treatment group on flibanserin and bupropion (11.5%). Fatigue was higher in the treatment group A on flibanserin (48.1%) compared with subjects in treatment group B with bupropion only (0%). Gastrointestinal adverse events including diarrhea, dry mouth, and nausea and was higher in the treatment group A on flibanserin (25.9%) compared with subjects in treatment group B with bupropion only (4.2%)

These adverse events observed in this study are similar to those observed in the phase I dose finding study and affecting with greatest frequency the system organ classes psychiatric, nervous, general, and gastrointestinal.

Table 15.3.2: 3 Frequency [N (%)] of subjects with adverse events by treatment, primary system organ class and preferred term - treated set

System organ class/ Preferred term	Screening N (%)	A/flib N (%)	A/flib+bup N (%)	B/bup N (%)	Washout N (%)	Post-treat N (%)	Post-Study N (%)
Number of subjects	28 (100.0)	27 (100.0)	26 (100.0)	24 (100.0)	23 (100.0)	28 (100.0)	28 (100.0)
Total with adverse events	0 (0.0)	18 (66.7)	15 (57.7)	11 (45.8)	3 (13.0)	4 (14.3)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	2 (7.1)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (3.6)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	2 (7.7)	6 (25.0)	1 (4.3)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	1 (3.8)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nightmare	0 (0.0)	0 (0.0)	0 (0.0)	4 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Restlessness	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Sleep disorder	0 (0.0)	0 (0.0)	1 (3.8)	3 (12.5)	1 (4.3)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	13 (48.1)	8 (30.8)	4 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Disturbance in attention	0 (0.0)	2 (7.4)	1 (3.8)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	10 (37.0)	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	3 (11.1)	3 (11.5)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
Paraesthesia	0 (0.0)	1 (3.7)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Speech disorder	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dry throat	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version 10.1 was used for reporting

Table 15.3.2: 3 Frequency [N (%)] of subjects with adverse events by treatment, primary system organ class and preferred term - treated set

System organ class/ Preferred term	Screening N (%)	A/flib N (%)	A/flib+bup N (%)	B/bup N (%)	Washout N (%)	Post-treat N (%)	Post-Study N (%)
Gastrointestinal disorders	0 (0.0)	7 (25.9)	9 (34.6)	1 (4.2)	0 (0.0)	2 (7.1)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	2 (7.4)	1 (3.8)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Dry mouth	0 (0.0)	3 (11.1)	2 (7.7)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	3 (11.1)	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)
Menorrhagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	13 (48.1)	6 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	13 (48.1)	6 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Blood human chorionic gonadotropin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)

Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version 10.1 was used for reporting

Study 511.37

Title: A randomized, open label study to investigate the influence of CYP3A4 inhibitor itraconazole (oral 200 mg qd) on the pharmacokinetics of a single tablet administration of 50 mg flibanserin and the influence of 50 mg tablets flibanserin bid as a putative CYP3A4 inhibitor on the pharmacokinetics of oral administration of 40 mg simvastatin in two independent two way crossover studies in healthy female and male subjects.

Objective: The objectives of this study were to evaluate the effect of itraconazole at steady state on the pharmacokinetics of a single dose flibanserin (Group 1) and the effect of flibanserin at steady state on the pharmacokinetics of a single dose simvastatin (Group 2).

Methods: There were 24 subjects who completed the studies - 12 subjects (6 males, 6 females) in Group 1 and 12 subjects (6 males and 6 females) in Group 2. Both groups were open-label, randomized crossover studies.

In Group 1 (treatment A and B), 3 males and 3 females were randomized to sequence AB or BA with at least 14 days washout period.
For Treatment A: itraconazole + flibanserin
Day 0 evening: 400 mg itraconazole (loading dose)
Days 1-4 morning: 200 mg itraconazole qd
Day 5: 200 mg itraconazole + 50 mg flibanserin (2 hrs after itraconazole)
Days 6-7: 200 mg itraconazole qd
For Treatment B: flibanserin 50 mg alone
Day 1: 50 mg flibanserin

In Group 2 (Treatment C and D), 3 males and 3 females were randomized to sequence CD or DC with at least 14 days washout period. Treatment C: simvastatin 40 mg + flibanserin 50 mg. Treatment D: simvastatin 40 mg alone.
For Treatment C: flibanserin + simvastatin
Days 1-3 morning: 50 mg flibanserin bid
Day 4: 50 mg flibanserin bid + 40 mg simvastatin
For Treatment D: simvastatin alone
Day 1: 40 mg simvastatin

Pharmacokinetic Sampling: The sponsor took blood samples to assess plasma concentrations of flibanserin, itraconazole, and simvastatin/total simvastatin acid according to the following time schedule:

In Group 1:
For flibanserin in Treatment A: pre-dose on Day 5 and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hrs after flibanserin administration.
For flibanserin in Treatment B: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hrs after flibanserin administration.

In Group 2:
For simvastatin/simvastatin acid in Treatment C: pre-dose on Day 4 and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 after simvastatin administration.
For simvastatin/simvastatin acid in Treatment D: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 after simvastatin administration.

Itraconazole + Flibanserin Results:

The geometric means (%CV) of flibanserin AUC0-inf were 2810 (76.3%) and 1090 (57.5%) ng.hr/ml with and without itraconazole, respectively. The geometric means (%CV) of flibanserin Cmax were 342 (32.5%) and 201 (49.8%) with and without itraconazole, respectively. Itraconazole co-administered with flibanserin increased flibanserin exposure by 2.6-fold (AUC ratio range: 1.74-4.62) and Cmax by 1.7-fold (Cmax ratio range: 1.01-3.17). Half-life was extended by 4.2 hrs from 7.44 to 11.6 hrs in the presence of itraconazole.

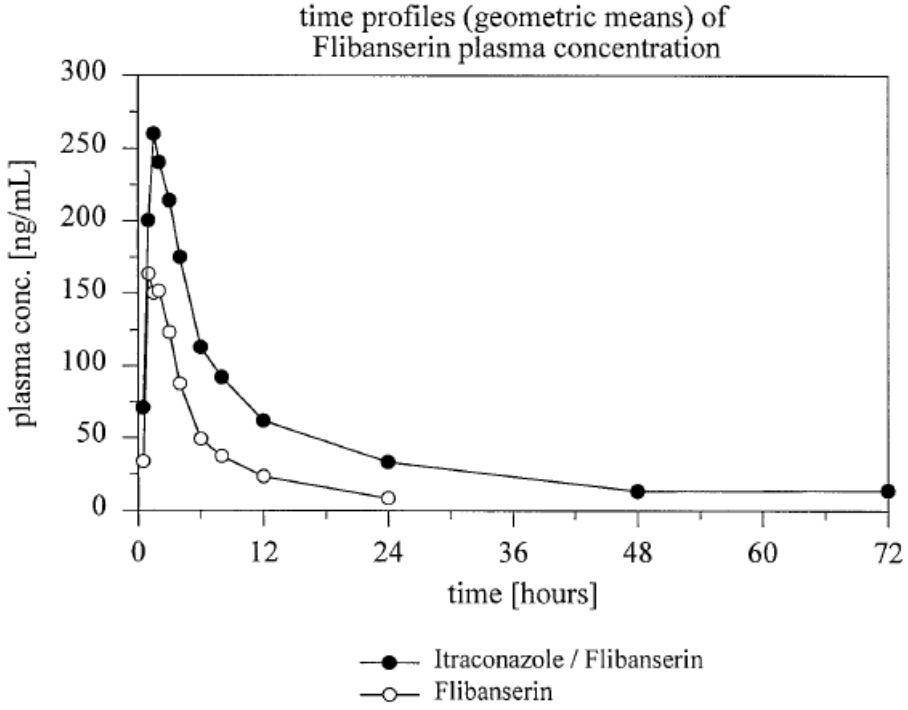
To assess whether and to what degree flibanserin would be affected by a CYP3A4 inhibitor, the sponsor selected 200 mg itraconazole. Although itraconazole is a suitable drug to evaluate potential CYP3A4 inhibition, the 200 mg dose selected for this study is lower than the recommended 400 mg dose and therefore the degree of inhibition by itraconazole is not maximized. Nonetheless, the results from this study show that flibanserin exposure increases in the presence of a strong CYP3A4 inhibitor and a significant drug interaction between itraconazole and flibanserin was demonstrated. Due to dose dependent increases in adverse events, it is likely to observe more adverse events when flibanserin is co-administered with a strong CYP3A4 inhibitor. The sponsor conducted another CYP3A4 inhibition study using ketoconazole 400 mg daily, a strong CYP3A4 inhibitor.

The following table is the PK parameters of flibanserin (geometric mean and CV) with and without itraconazole co-administration (sponsor's tables 11.4.2.2:1-2)

Pharmacokinetic characteristics [Unit]	Treatment A (Test) 100 mg itraconazole q.d., 50 mg flibanserin s.d.	Treatment B (Reference) 50 mg flibanserin	Estimated Ratio (intraindividual comparison)
	Analyte: flibanserin		
	day 5-7	day 1	
Primary Parameter			
$AUC_{0-\infty}$ [ng · h/mL]	2810 (76.3)	1090 (57.5)	2.565
C_{max} [ng/mL]	341 (32.5)	201 (49.8)	1.692

Pharmacokinetic characteristics [Unit]	Treatment A(Test) 100 mg itraconazole q.d., 50 mg flibanserin s.d.	Treatment B(Reference) 50 mg flibanserin	Estimated Ratio (intraindividual comparison)
	Analyte: flibanserin		
	day 5-7	day 1	
Secondary Parameter			
$t_{½}$ [h]	11.6 (46.5)	7.44 (27.0)	1.557
CL/F [mL/min]	297 (76.2)	761 (57.5)	
MRT_{tot} [h]	14.3 (51.9)	8.66 (30.0)	
V_z/F [L]	298 (37.9)	490 (54.3)	
t_{max} [h]	1.25 (1.00-4.00) #	1.25 (0.50-3.00) #	1.00 #

The following figure is the geometric mean concentration-time profiles for flibanserin with and without co-administration with itraconazole.



Flibanserin and Simvastatin Results:

The geometric means (%CV) of simvastatin AUC0-inf were 47.4 (36.1%) and 36.1 (38.1%) ng.hr/ml with and without flibanserin, respectively. The geometric means (%CV) of simvastatin Cmax were 19.0 (49.5%) and 16.6 (44.1%) with and without flibanserin, respectively. Flibanserin co-administered with simvastatin increased simvastatin exposure by 1.32-fold (90% CI: 1.08-1.61) and Cmax by 1.15-fold (90% CI: 0.95-1.39). Half-life was extended slightly from 2.16 to 2.60 hrs in the presence of flibanserin.

The following table is the PK parameters of simvastatin (geometric mean and %CV) with and without pre-treatment with flibanserin 50 mg bid for 4 days (sponsor's tables 11.4.2.2:3 & 11.4.2.2:5)

Pharmacokinetic characteristics [Unit]	Treatment C (Test) 50 mg flibanserin b.i.d., 40 mg simvastatin s.d.	Treatment D (Reference) 40 mg simvastatin s.d.	Estimated Ratio (intraindividual comparison)
	Analyte: simvastatin		
	day 4	day 1	
Primary Parameter			
$AUC_{0-\infty}$ [ng·h/mL]	47.4 (36.1)	36.1 (38.1)	1.315
C_{max} [ng/mL]	19.0 (49.5)	16.6 (44.1)	1.148

Pharmacokinetic characteristics [Unit]	Treatment C (Test) 50 mg flibanserin b.i.d., 40 mg simvastatin s.d.	Treatment D (Reference) 40 mg simvastatin s.d.	Estimated Ratio (intraindividual comparison)
	Analyte: simvastatin		
	day 4	day 1	
Secondary Parameter			
$t_{½}$ [h]	2.60 (41.7)	2.16 (24.6)	1.204
CL/F [mL/min]	14100 (36.1)	18500 (38.1)	
MRT_{tot} [h]	3.56 (32.6)	2.90 (16.2)	
V_z/F [L]	3160 (18.4)	3450 (36.4)	
t_{max} [h]	1.00 (0.50-4.00) #	1.00 (1.00-2.00) #	1.00 #

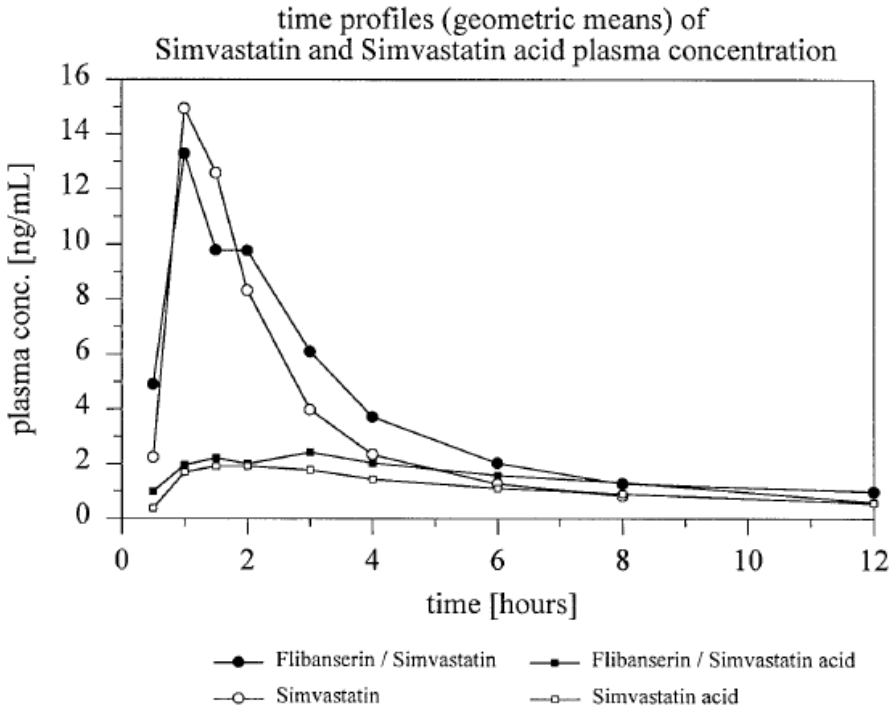
The geometric means (%CV) of the metabolite simvastatin acid AUC0-inf were 22.6 (57.9%) and 15.4 (71.2%) ng.hr/ml with and without flibanserin, respectively. The geometric means (%CV) of simvastatin acid Cmax were 3.56 (42.7%) and 2.61 (54.6%) with and without flibanserin, respectively. Flibanserin co-administered with simvastatin increased simvastatin acid exposure by 1.47-fold (90% CI: 1.10-1.97) and Cmax by 1.37-fold (90% CI: 1.17-1.59). Half-life was extended slightly from 3.55 to 4.31 hrs in the presence of flibanserin.

The following table is the PK parameters of simvastatin acid (geometric mean and %CV) with and without pre-treatment with flibanserin (sponsor's tables 11.4.2.2:4 & 11.4.2.2:6)

Pharmacokinetic characteristics [Unit]	Treatment C (Test) 50 mg flibanserin b.i.d., 40 mg simvastatin s.d.	Treatment D (Reference) 40 mg simvastatin s.d.	Estimated Ratio (intraindividual comparison)
	Analyte: simvastatin Acid		
	day 4	day 1	
Primary Parameter			
$AUC_{0-\infty}$ [ng·h/mL]	22.6 (57.9)	15.4 (71.2)	1.473
C_{max} [ng/mL]	3.56 (42.7)	2.61 (54.6)	1.368
AUC_{0-tf} [ng·h/mL]	18.0 (62.2)	12.5 (74.4)	1.438

Pharmacokinetic characteristics [Unit]	Treatment C (Test) 50 mg flibanserin b.i.d., 40 mg simvastatin s.d.	Treatment D (Reference) 40 mg simvastatin s.d.	Estimated Ratio (intraindividual comparison)
	Analyte: simvastatin Acid		
	day 4	day 1	
Secondary Parameter			
$t_{½}$ [h]	4.31 (39.0)	3.55 (39.2)	1.216
CL/F [mL/min]	30700 (57.9)	45200 (71.2)	
MRT_{tot} [h]	7.15 (32.9)	6.22 (29.2)	
V_z/F [L]	11500 (51.9)	13900 (70.5)	
t_{max} [h]	1.25 (0.50-6.00) #	1.75 (1.00-8.00) #	0.750 #

The following figure is the geometric mean concentration-time profiles for simvastatin and simvastatin acid with and without pre-treatment with flibanserin.



The most common adverse events were fatigue (14 subjects), dizziness (9 subjects), dry mouth (5 subjects), and nausea (4 subjects). These are all consistent with adverse events observed in other studies.

Study 511.93

Title: An open-label, randomized, two-way crossover trial to evaluate the effect of multiple doses of flibanserin on the single dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel.

Objective: The objective of this study was to evaluate the influence of multiple oral daily doses of 100 mg qd of flibanserin on the pharmacokinetics of ethinylestradiol (EE) and levonorgestrel (LNG).

Methods: Twenty-three healthy premenopausal female subjects completed the study. There was a washout period of 4 weeks between treatment groups.

Treatment Group A (Reference): subjects were given a single dose of 30 µg EE/150 µg LNG (Microgynon®) on the morning on Day 1.

Treatment Group B (Test): subjects were given a single 100 mg flibanserin qd (evening) for 14 days (Days -13 to Day -1 and a single oral dose of 30 ug EE/150 ug LNG (Microgynon®) on the morning of Day 1.

Pharmacokinetic Sampling:

Results:
EE increased slightly when OC was co-administered with flibanserin. Following flibanserin administration, the geometric mean AUC0-inf and Cmax increased 8.3% and 5.7%, respectively. Half-life increased by 0.6 hr from 13.0 to 13.6 hrs in the presence of flibanserin.

The following table summarizes PK parameters of EE with and without flibanserin.

	30 µg EE/150 µg LNG + flibanserin 100 mg qd for 14 days	30 µg EE/150 µg LNG
SD PK parameter*	EE	
AUC0-inf (ng.hr/ml)	708 (30.6)	654 (34.3)
Cmax (ng/ml)	68.3 (38.5)	64.6 (27.3)
Tmax (hr)[1]	1.50 (1.00 – 2.00)	1.50 (1.00 – 3.00)
$t_{1/2}$ (hr)	13.0 (21.4)	13.6 (39.0)

*geometric mean (%CV)
[1] median and range

LNG PK was essentially the same when OC was co-administered with flibanserin. AUC0-inf increased 1.2%. Cmax change of 0.02 ng/ml is negligible. Half-life increased by 0.3 hr from 26.0 to 26.3 hrs in the presence of flibanserin.

The following table summarizes PK parameters of LNG with and without flibanserin.

	30 µg EE/150 µg LNG + flibanserin 100 mg qd for 14 days	30 µg EE/150 µg LNG
SD PK parameter*	LNG	

AUC0-inf (ng.hr/ml)	49.2 (44.9)	48.6 (42.2)
Cmax (ng/ml)	4.73 (35.2)	4.75 (36.1)
Tmax (hr)[1]	1.00 (0.50 – 2.00)	1.00 (0.50 – 1.50)
$t_{1/2}$ (hr)	26.3 (33.3)	26.0 (39.0)

*geometric mean (%CV)
[1] median and range

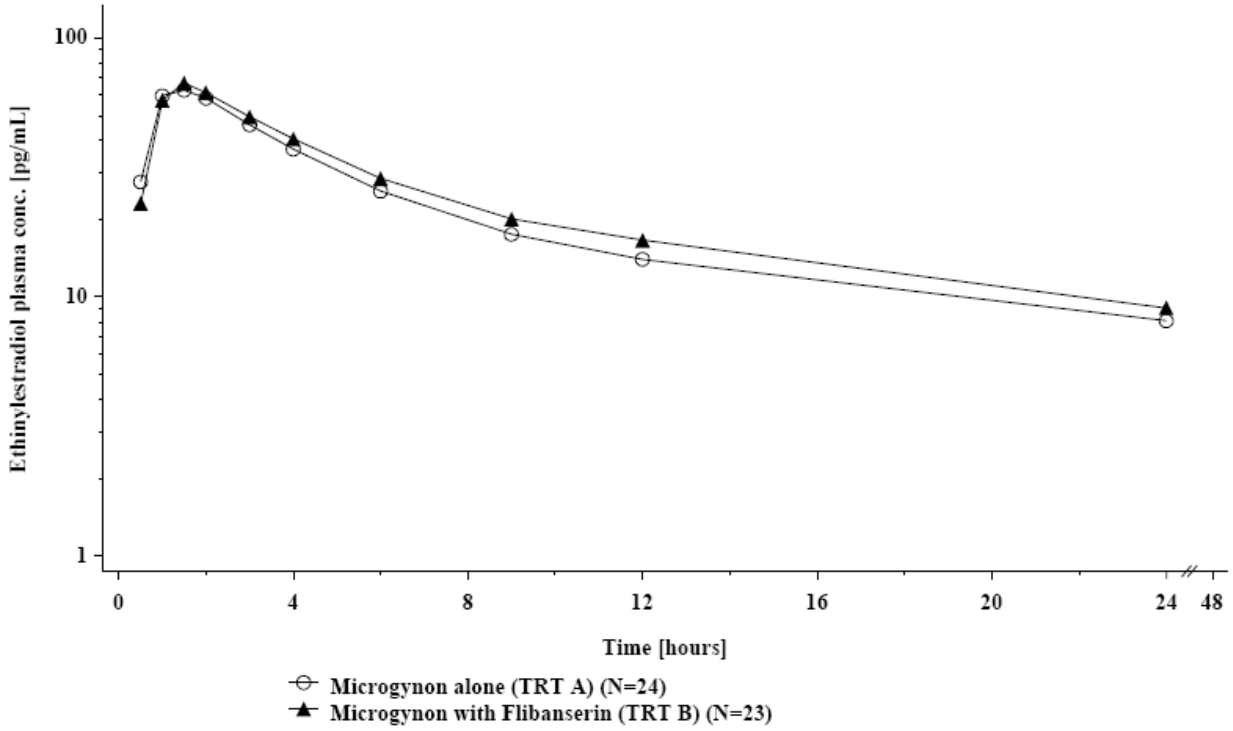
There appears to be a small increase in EE when the combination oral contraceptive Microgynon® was co-administered with flibanserin. Overall, flibanserin given daily does not appear to affect EE and LNG exposure.

The following table presents the pharmacokinetic parameters of EE by treatment group (sponsor's table 11.5.2.2.1:1)

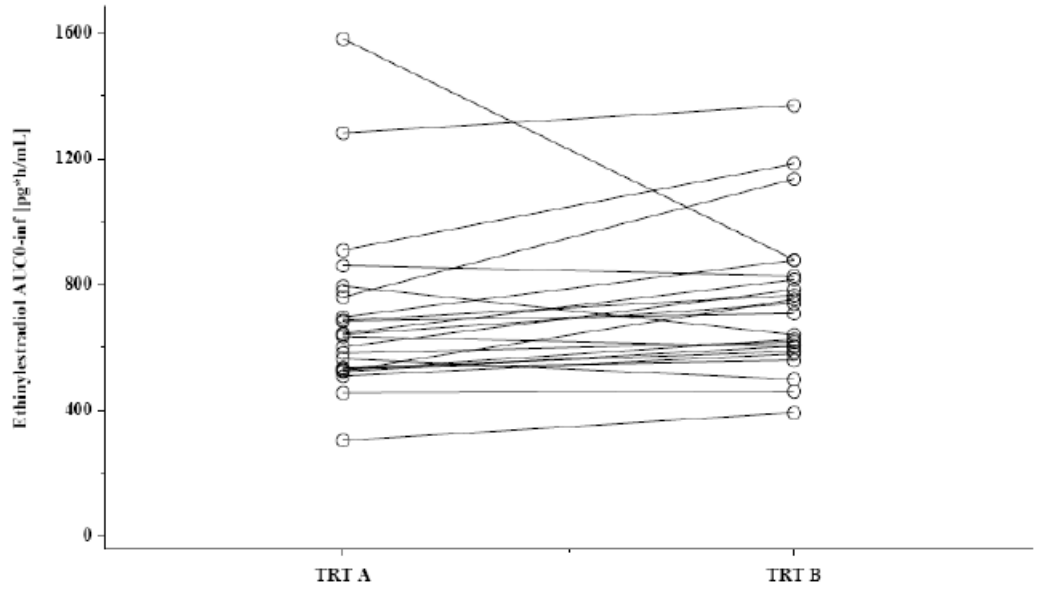
		A (Reference)			B (Test)		
Parameter	**Unit**	**N**	**gMean**	**gCV [%]**	**N**	**gMean**	**gCV [%]**
AUC_{0-24}	**[pg·h/mL]**	**24**	487	25.2	**23**	537	29.3
AUC_{0-48}	**[pg·h/mL]**	**24**	596	28.2	**23**	657	29.5
AUC_{0-tz}	**[pg·h/mL]**	**24**	490	29.6	**23**	543	35.6
$AUC_{0-\infty}$	**[pg·h/mL]**	**24**	654	34.3	**23**	708	30.6
$\%AUC_{tz-\infty}$	**[%]**	**24**	23.3	30.7	**23**	22.2	30.1
C_{max}	**[pg/mL]**	**24**	64.6	27.3	**23**	68.3	38.5
t_{max}#	**[h]**	**24**	1.50	1.00-3.00	**23**	1.50	1.00-2.00
$t_{½}$	**[h]**	**24**	13.6	39.0	**23**	13.0	21.4
MRT_{po}	**[h]**	**24**	16.7	38.4	**23**	16.4	21.3
CL/F	**[mL/min]**	**24**	764	34.3	**23**	706	30.6
V_z/F	**[L]**	**24**	897	26.4	**23**	794	28.8

Source data: Section 15, Table 6.3: 2
median and range

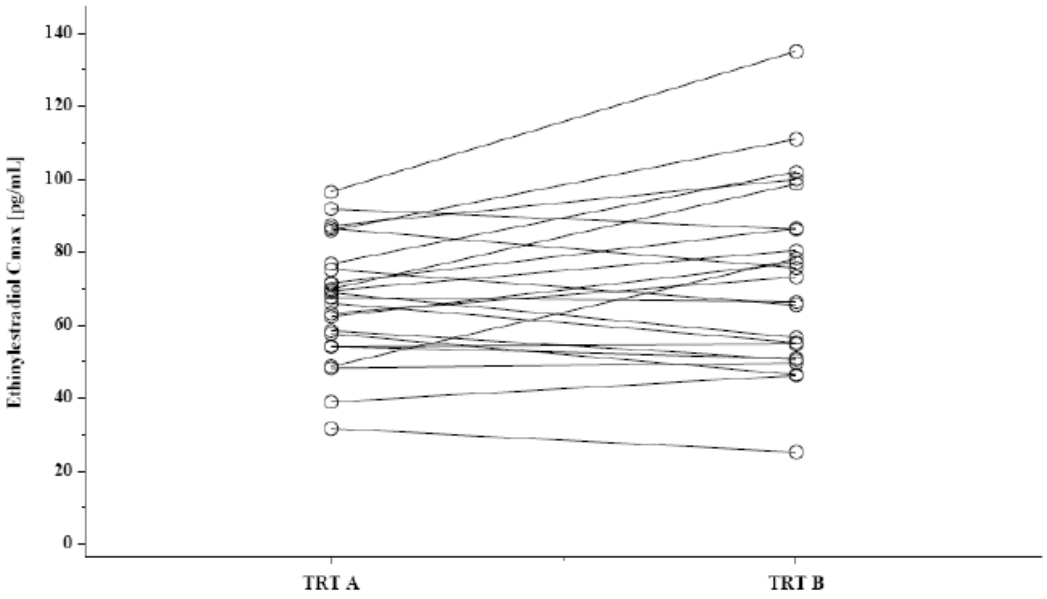
The following figure is a geometric mean plasma concentration-time profiles of EE after a single oral dose of Microgynon® to healthy female volunteers with and without pre-treatment with 100 mg flibanserin once daily evening dose (semi-logarithmic scale) (sponsor's figure 11.5.2.1:1)



The following figure is a comparison of individual AUC0-inf of EE by treatment groups (sponsor's figure 11.5.2.2.1:1).



The following figure is a comparison of individual Cmax of EE by treatment groups (sponsor's figure 11.5.2.2.1:2).

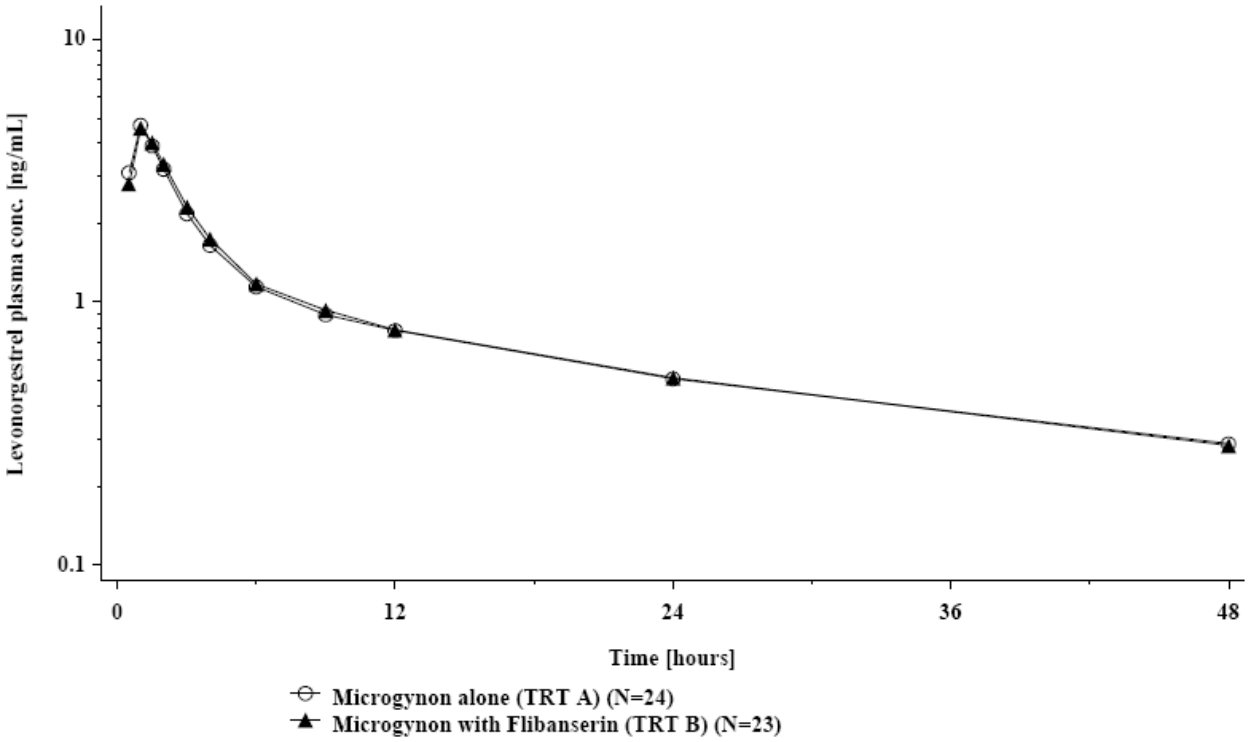


The following table presents the pharmacokinetic parameters of LNG by treatment group (sponsor's table 11.5.2.2.2:1)

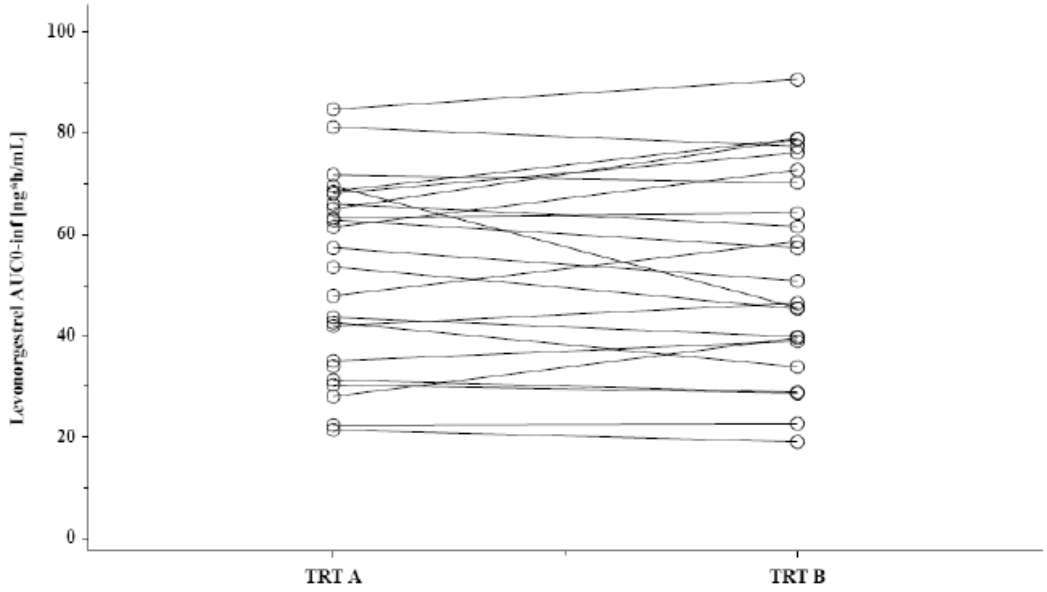
		A (Reference)			B (Test)		
Parameter	**Unit**	**N**	**gMean**	**gCV [%]**	**N**	**gMean**	**gCV [%]**
AUC_{0-24}	**[pg·h/mL]**	**24**	27.4	45.0	**23**	27.9	49.8
AUC_{0-48}	**[pg·h/mL]**	**24**	36.7	43.9	**23**	37.4	49.9
AUC_{0-tz}	**[pg·h/mL]**	**24**	36.4	42.9	**23**	37.4	49.9
$AUC_{0-\infty}$	**[pg·h/mL]**	**24**	48.6	42.2	**23**	49.2	44.9
$\%AUC_{tz-\infty}$	**[%]**	**24**	21.9	50.8	**23**	21.6	43.8
C_{max}	**[pg/mL]**	**24**	4.75	36.1	**23**	4.73	35.2
$t_{max}^{\#}$	**[h]**	**24**	1.00	0.500-1.50	**23**	1.00	0.500-2.00
$t_{½}$	**[h]**	**24**	26.0	39.0	**23**	26.3	33.3
MRT_{po}	**[h]**	**24**	31.1	40.7	**23**	31.3	33.7
CL/F	**[mL/min]**	**24**	51.5	42.2	**23**	50.8	44.9
V_z/F	**[L]**	**24**	116	59.2	**23**	116	67.5

Source data: Section 15, Table 6 3: 2
median and range

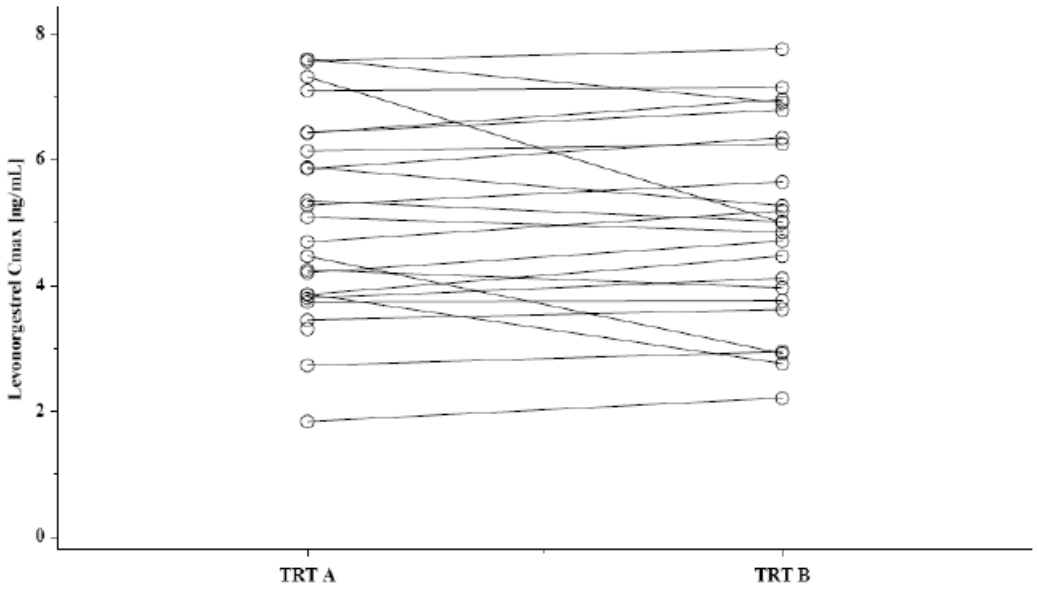
The following figure is a geometric mean plasma concentration-time profiles of LNG after a single oral dose of Microgynon® to healthy female volunteers with and without pre-treatment with 100 mg flibanserin once daily evening dose (semi-logarithmic scale) (sponsor's figure 11.5.2.1:2)



The following figure is a comparison of individual AUC0-inf of LNG by treatment groups (sponsor's figure 11.5.2.2.2:1).



The following figure is a comparison of individual Cmax of LNG by treatment groups (sponsor's figure 11.5.2.2.2:2).



The following table is the adjusted by treatment geometric means and relative bioavailability for EE and LNG – a comparison of intra-individual PK parameters with (Test) and without (Reference) flibanserin (sponsor's table 11.5.2.3:1)

	gMean Test (N=23)	gMean Reference (N=24)	Ratio Test: Reference [%]	90% CI lower limit [%]	90% CI upper limit [%]	Intra-indiv. gCV [%]
$AUC_{0-\infty}$						
EE	713.474	654.298	109.04	101.231	117.461	14.8
LNG	48.527	48.558	99.94	94.060	106.177	12.0
C_{max}						
EE	68.666	64.628	106.25	98.766	114.297	14.5
LNG	4.668	4.747	98.32	92.667	104.321	11.7

The sponsor states that flibanserin did not relevantly change the exposure to EE and LNG because the 90% CIs for the test to reference ratios of AUC0-inf and Cmax were within the 80-125% range. The sponsor also states there was no evidence for a flibanserin inductive effect on the metabolism of EE, LNG and flibanserin itself.

One potential concern about applying these findings to the general female population is that inclusion criteria for body mass index was limited to $\geq$ 18.5 and $\leq$ 29.9 kg/m^2 and drugs, herbals, and dietary supplements known to inhibit or induce CYPs, especially CYP3A4 were restricted.

The drug-related adverse events after flibanserin administration were mainly dizziness, nausea, and fatigue; all known to be associated with flibanserin use. One subject (#6) discontinued from the study due to reported dizziness, lightheadedness, nausea and fatigue following administration of 100 mg flibanserin.

Study 511.117

Title: Safety, tolerability and pharmacokinetics of single rising oral doses (25 and 50 mg) of flibanserin followed by multiple rising oral doses (25, 50, 100 mg per day) in healthy Japanese female volunteers.

Objective: The objective of this study was to evaluate safety, tolerability and pharmacokinetics after administration of flibanserin tablets.

Methods: This study was a randomized, double-blind, placebo-controlled within dose groups, single rising, single center study in Japanese women, mean (range) age of 26.4 (20-34) years. The mean (range) weight was 51.8 kg (42.9-72.5) and mean (range) BMI was 20.25 kg/m^2 (17.7-24.3). There were 12 subjects per dose group (9 on active treatment, and 3 on placebo) in single dose group and 15 subjects (12 on active treatment and 3 on placebo) in rising dose group; sixty-eight women completed the study. There were two groups that received a single dose and three groups that received 14 days of multiple dose (including first 7 days with lower doses and consecutive 7 days of up titration). There were 12 subjects in the 25 mg single dose group; 12 subjects in the 50 mg single dose group; 15 subjects in the 25 mg qd for 7 days followed by 25 mg bid for 7 days group; 15 subjects in the 50 mg qd for 7 days followed by 50 mg bid for 7 days group; and 15 subjects in the 50 mg qd for 7 days followed by 100 mg qd for 7 days group.

For single dose groups, following an overnight fast of at least 10 hours, the medication was administration with about 150 ml of water in the sitting position under supervision of the investigating physician or a designee. For multiple dose groups, the medication was administration about 2.5 hours after meal with about 150 ml of water in the sitting position under supervision of the investigating physician or a designee.

The table below is an outline of the trial design and plan (sponsor's table 9.1:1).

Dose group	A	B	C	D	E
Dose (mg)	25 mg	50 mg	1st week : 25 mg once daily (morning) 2nd week : 25 mg twice daily (morning, evening)	1st week : 50 mg once daily (morning) 2nd week : 50 mg twice daily (morning, evening)	1st week : 50 mg once daily (morning) 2nd week : 100 mg once daily (morning)
Duration	single	single	7 days + 7 days	7 days + 7 days	7 days + 7 days
No. of subjects	12	12	15	15	15
Subjects receiving drug	9	9	12	12	12
Subjects receiving placebo	3	3	3	3	3

Pharmacokinetic Sampling:
The following is the plasma sampling schedule in single dose groups:
Day 1: -1:00 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hrs after single administration
Day 2-5: 24, 33 and 48 hrs after single administration

The following is the plasma sampling schedule in multiple dose groups:
Day 1: -1:00 (or 0), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hrs after the first dose at Visit 2
Days 2-6: 24, 48, 72, 96 and 120 hrs after the first dose at Visit 2
Day 7: 144 (predose), 144.25, 144.5, 144.75, 145, 145.5, 146, 147, 148, 150, 152, 154 and 156 hrs after the first dose at Visit 2
Day 8: 168 hrs after the first dose at Visit 2
Days 12-13: 96 and 120 hrs after the first dose at Visit 3
Day 14: 144 (predose), 144.25, 144.5, 144.75, 145, 145.5, 146, 147, 148, 150, 152, 154 and 156 hrs after the first dose at Visit 3
Days 15-18: 168, 177 and 192 hrs after the first dose at Visit 3

Results: Following single dose of 25 mg and 50 mg flibanserin, median Tmax was reached at 0.75 hr. The geometric mean $t_{1/2}$ was 7.27 and 8.98 hrs following a single dose of 25 mg and 50 mg flibanserin, respectively. In Japanese women, geometric mean AUC0-inf is 607 and 988 ng.hr/ml following a single dose of 25 mg and 50 mg flibanserin, respectively. Geometric mean Cmax is 199 and 273 ng/ml following a single dose of 25 mg and 50 mg flibanserin, respectively.

The following table summarizes the PK parameters for flibanserin following a single dose of 25 mg and 50 mg flibanserin.

SD PK parameter*	25 mg	50 mg
AUC0-inf (ng.hr/ml)	607 (52.4)	988 (34.4)
Cmax (ng/ml)	199 (20.8)	273 (33.9)
Tmax (hr)[1]	0.75 (0.50 – 4.00)	0.75 (0.50 – 3.00)
$t_{1/2}$ (hr)	7.27 (21.7)	8.98 (24.3)

*geometric mean (%CV)
[1] tmax: median and range

Following multiple doses of 25 mg qd, 50 mg qd, 100 mg qd, 25 mg bid, and 50 mg bid, flibanserin concentration rapidly increased and reached the median Tmax,ss between 0.750 to 1.25 hrs. The geometric mean $t_{1/2,ss}$ of flibanserin was in the range of 8.81 to 9.68 hrs. The pharmacokinetics of flibanserin after single dose are comparable to multiple dose characteristics. The accumulation ratio is in the range of 1.05 to 1.34, based on 25 mg qd and 50 mg qd doses. A dose proportional increase in Cmax,ss and AUCτ,ss is observed after multiple oral administrations.

The following table summarizes the steady state PK parameters for flibanserin following multiple dose of 25 mg qd, 50 mg qd, and 100 mg qd flibanserin.

SS PK parameter*	25 mg qd	50 mg qd	100 mg qd
AUCτ,ss (ng.hr/ml)	639 (38.7)	1320 (54.5)	2940 (66.9)

Cmax,ss (ng/ml)	165 (38.7)	365 (42.3)	674 (51.3)
Tmax,ss (hr)[1]	1.25 (0.50 – 6.00)	0.75 (0.50 – 3.00)	1.00 (0.50 – 3.00)
$t_{1/2,ss}$ (hr)	NC	NC	9.68 (41.6)

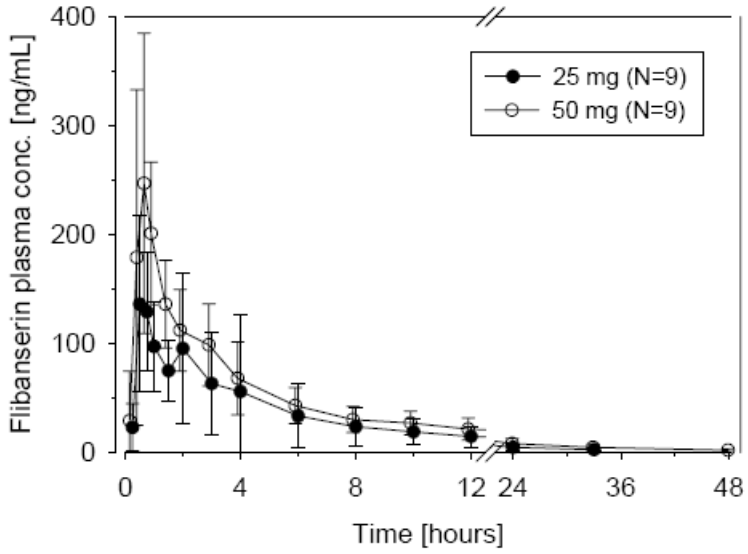
*geometric mean (%CV)
[1] tmax: median and range
NC: not calculated

The following table summarizes the steady state PK parameters for flibanserin following multiple dose of 25 mg bid and 50 mg bid flibanserin.

SS PK parameter*	25 mg bid	50 mg bid
AUCτ,ss (ng.hr/ml)	686 (34.8)	1540 (45.2)
Cmax,ss (ng/ml)	216 (24.8)	415 (39.2)
Tmax,ss (hr)[1]	1.25 (0.50 – 3.00)	0.88 (0.50 – 3.00)
$t_{1/2,ss}$ (hr)	9.26 (18.5)	8.81 (14.5)

*geometric mean (%CV)
[1] tmax: median and range

The following is the arithmetic mean (±SD) for plasma concentration-time profiles of flibanserin after single oral administration of 25 and 50 mg flibanserin (sponsor's figure 11.5.2.1.1: 1).

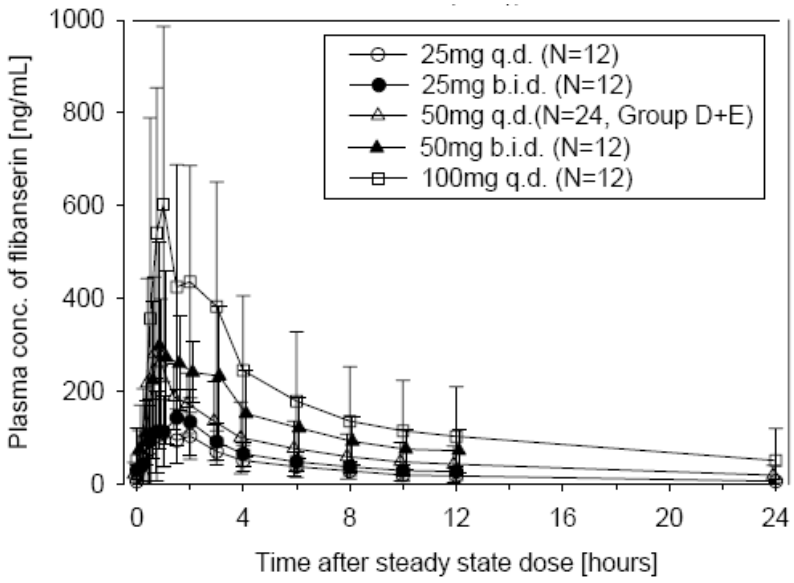


The following is a summary of pharmacokinetic parameters of flibanserin after single oral administration of 25 and 50 mg flibanserin (sponsor's table 11.5.2.1.3:1)

Flibanserin		Pharmacokinetic parameters after single dose					
		25 mg			50 mg		
		N	gMean	gCV%	N	gMean	gCV%
C_{max}	[ng/mL]	9	199	20.8	9	273	33.9
t_{max} [a)]	[h]	9	0.750	(0.500-4.00)	9	0.750	(0.500-3.00)
AUC_{0-tz}	[ng·h/mL]	9	595	53.0	9	965	33.9
$AUC_{0-\infty}$	[ng·h/mL]	9	607	52.4	9	988	34.4
$t_{1/2}$	[h]	9	7.27	21.7	9	8.98	24.3
MRT_{po}	[h]	9	7.77	24.1	9	9.04	31.9
CL/F	[mL/min]	9	686	52.4	9	843	34.4
V_z/F	[L]	9	431	46.8	9	655	31.2
fe_{0-tz}	[%]	9	0.00299	52.8	9	0.00449	46.3
$C_{max,norm}$	[ng/mL/mg]	9	7.97	20.8	9	5.46	33.9
$AUC_{0-\infty,norm}$	[ng·h/mL/mg]	9	24.3	52.4	9	19.8	34.4

BI Trial No.: 0511.0117
Source data: Table 15.6.2.1: 1 and Table 15.6.2.1: 2
a) Median (Min-Max)

The following is a comparison of arithmetic mean plasma concentration-time profiles of flibanserin after multiple oral administrations of flibanserin in different dosing regimen (sponsor's figure 11.5.2.2.1:1).



The following is a summary of pharmacokinetic parameters of flibanserin after multiple qd administrations of flibanserin in different dosing regimen (sponsor's table 11.5.2.2.3:1).

Flibanserin		Pharmacokinetic parameters after q.d. administrations					
			25 mg q.d.		50 mg q.d. (Group D+E)		100 mg q.d.
		N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
$C_{max,1}$	[ng/mL]	12	176 (33.4)	24	336 (47.6)		NC
$t_{max,1}$ [a)]	[h]	12	0.625 (0.500-3.00)	24	0.625 (0.250-4.00)		NC
$AUC_{0-24,1}$ [b)]	[ng·h/mL]	12	543 (34.8)	24	1120 (40.4)		NC
$C_{max,ss}$	[ng/mL]	12	165 (38.7)	24	365 (42.3)	12	674 (51.3)
$t_{max,ss}$ [a)]	[h]	12	1.25 (0.500-6.00)	24	0.750 (0.500-3.00)	12	1.00 (0.500-3.00)
$C_{pre,ss}$	[ng/mL]	12	5.20 (74.4)	24	13.9 (110)	12	30.7 (122)
$C_{min,ss}$	[ng/mL]	12	4.94 (89.5)	24	11.9 (105)	12	28.0 (134)
$AUC_{\tau,ss}$	[ng·h/mL]	12	639[c)] (38.7)	24	1320[c)] (54.5)	12	2940 (66.9)
$t_{1/2,ss}$	[h]		NC		NC	12	9.68 (41.6)
$MRT_{po,ss}$	[h]		NC		NC	12	10.7 (43.9)
$CL/F_{,ss}$	[mL/min]		NC		NC	12	568 (66.9)
$V_z/F_{,ss}$	[L]		NC		NC	12	476 (32.0)
$fe_{0-tz,ss}$	[%]	11	0.00440 (75.2)	23	0.00450 (48.9)	12	0.00790 (69.4)
$R_{A,AUC}$		12	1.18 (16.8)	24	1.17 (20.5)		NC
$R_{A,Cmax}$		12	0.940 (21.8)	24	1.08 (43.5)		NC
$C_{max,ss,norm}$	[ng/mL/mg]	12	6.61 (38.7)	24	7.29 (42.3)	12	6.74 (51.3)
$AUC_{\tau,ss,norm}$	[ng·h/mL/mg]	12	25.5 (38.7)	24	26.3 (54.5)	12	29.4 (66.9)

BI Trial No.: 0511.0117
Source data: Table 15.6.2.1: 3, Table 15.6.2.1: 8 and Table 15.6.2.1: 9
a) Median (Min-Max)
b) AUC_{0-tz} of the first dose (up to 24 hours) was used as a substitute for $AUC_{0-24,1}$ because half life was not determined at the first dose.
c) $AUC_{0-tz,ss}$ (up to 24 hours) was used as a substitute for $AUC_{\tau,ss}$ because half life was not determined at the first period.

The following is a summary of pharmacokinetic parameters of flibanserin after multiple bid administrations of flibanserin in different dosing regimen (sponsor's table 11.5.2.2.3:2).

Flibanserin		Pharmacokinetic parameters after b.i.d. administrations			
		25 mg b.i.d.		50 mg b.i.d.	
		N	gMean (gCV%)	N	gMean (gCV%)
$C_{max,1}$	[ng/mL]	12	176 (33.4)	12	341 (29.3)
$t_{max,1}$ [a)]	[h]	12	0.625 (0.500-3.00)	12	0.750 (0.500-2.00)
$AUC_{0-12,1}$	[ng·h/mL]	12	454 (32.4)	12	994 (31.6)
$C_{max,ss}$	[ng/mL]	12	216 (24.8)	12	415 (39.2)
$t_{max,ss}$ [a)]	[h]	12	1.25 (0.500-3.00)	12	0.875 (0.500-3.00)
$C_{pre,ss}$	[ng/mL]	12	28.1 (47.0)	12	64.4 (65.4)
$C_{min,ss}$	[ng/mL]	12	23.6 (64.3)	12	58.4 (60.2)
$AUC_{\tau,ss}$ [b)]	[ng·h/mL]	12	686 (34.8)	12	1540 (45.2)
$t_{1/2,ss}$	[h]	11	9.26 (18.5)	12	8.81 (14.5)
$fe_{0-tz,ss}$	[%]	11	0.00946 (41.1)	12	0.00872 (56.3)
$R_{A,AUC}$		12	1.51 (17.1)	12	1.55 (21.5)
$R_{A,Cmax}$		12	1.23 (32.1)	12	1.22 (27.4)
$C_{max,ss,norm}$	[ng/mL/mg]	12	8.64 (24.8)	12	8.31 (39.2)
$AUC_{\tau,ss,norm}$	[ng·h/mL/mg]	12	27.4 (34.8)	12	30.8 (45.2)

BI Trial No.: 0511.0117
Source data: Table 15.6.2.1: 3, Table 15.6.2.1: 4, Table 15.6.2.1: 5 and Table 15.6.2.1: 6
a) Median (Min-Max)
b) $AUC_{0-tz,ss}$ (up to 12 hours) was used as a substitute for $AUC_{\tau,ss}$ due to the evening dose.

Study 511.26

Title: An open-label, four-way, crossover study to evaluate a food effect on the pharmacokinetics of flibanserin after single oral administration of a 50 mg tablet following a light breakfast, a normal breakfast, and a high fat/caloric breakfast, compared with fasted state in healthy male volunteers.

Objective: The objective of the study was to evaluate the influence of food on the pharmacokinetics of flibanserin, compared with fasted state.

Methods: This study was a single dose, randomized, open-label, four-way crossover study. There were 16 healthy Caucasian male subjects in each of four treatment groups: flibanserin 50 mg after a light (low protein/low fat/low carbohydrate) breakfast (Light); flibanserin 50 mg after a normal (medium protein/medium fat/medium carbohydrate) breakfast (Medium); flibanserin 50 mg after a high fat/caloric (high protein/ high fat/high carbohydrate) breakfast (High); and flibanserin 50 mg in fasted state (Fasting). There was a 6 day washout period between treatment periods. The median (range) age was 29 (22-45) years.

Pharmacokinetic Sampling: Blood samples for determination of flibanserin concentrations were taken pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, and 32 hrs after flibanserin administration.

Results: The sponsor evaluated the effect of food on the pharmacokinetics of flibanserin after a single 50 mg dose of flibanserin tablet in an open-label, four-way, crossover study in 16 subjects. Compared to the fasted condition, the exposure of flibanserin was 17%, 41%, and 53% higher after administration of a light, medium, and high fat/caloric breakfast, respectively. The total flibanserin exposure increased with increasing fat/caloric content.

The Cmax was essentially the same between the light breakfast and fasted groups, with slight decrease of 3.9% in the light breakfast group. This is no meaningful considering the level of variability. In the medium and high fat/caloric breakfast groups, Cmax increased by 12 and 14%, respectively, compared with the fasted condition.

Tmax was prolonged slightly from 0.77 hr under fasted condition up to 2.03 hrs under high fat/caloric meal.

Note that the % changes are slightly different from those reported by the sponsor b/c the above values were calculated using the arithmetic mean values, not the geometric mean values used by the sponsor.

The following table are the PK parameters of flibanserin after administration of food with varying fat/caloric content:

	Meal Type			
PK parameter*	Fasted	Light Fat	Medium fat	High Fat
AUC0-inf (ng.hr/ml)	821 (52.0)	959 (50.1)	1160 (46.6)	1260 (49.1)
Cmax (ng/ml)	207 (34.7)	199 (33.1)	232 (43.9)	236 (38.7)

Tmax (hr)	0.77 (36.7)	1.78 (67.8)	1.19 (65.0)	2.03 (74.1)
$t_{1/2}$ (hr)	7.55 (37.1)	7.79 (33.2)	7.52 (27.0)	7.93 (30.5)

*Arithmetic mean (%CV)

Under the worst case scenario with high fat/caloric breakfast, the exposure increased by 53%. Cmax was influenced less by food, while Tmax was prolonged slightly. The recommendation dose for flibanserin in HSDD women is 100 mg at bedtime. It is possible that the exposure can increase more than 53% when patients are taking the recommended 100 mg dose, compared to 50 mg as evaluated in this study.

There was no mention by the sponsor with regard to the administration of food in the pivotal phase 3 studies 511.71 and 511.75. The protocols for these studies indicate that flibanserin tablets were given with 150 ml of fluid. The sponsor proposes in the label that flibanserin be given at bedtime with or without food. Even though there is an increase in exposure of up to 53% in the high fat/caloric breakfast group, it is unlikely patients taking this medication will consume a high fat/caloric meal prior to bedtime. Additionally, the dosing instruction for the phase 3 studies included 150 ml of fluid, not water. It is possible that patients consumed fluids (e.g. fruit juices) with varying levels of calories. Under the proposed dosing regimen at bedtime, this reviewer finds the sponsor's dosing recommendation with or without food acceptable.

Though the study was conducted in male subjects and flibanserin is indicated for premenopausal women, the findings on food effect is still applicable. The results in this study conducted in men clearly show a trend in increased exposure as the fat/calorie content increased, which is also applicable to women.

The sponsor conducted two additional studies to evaluate the effect of food on extended release formulation. In study 511.110, the sponsor evaluated the relative bioavailability and sedative effects of three modified release formulations compared to immediate release tablets. The relative bioavailability between immediate release tablet and nine extended release formulations was evaluated in study 511.115. The to-be-marketed and phase 3 clinical trials formulation is an immediate table; therefore, the studies evaluating the effect of food on extended release formulations were briefly reviewed.

The following table is a summary of pharmacokinetic parameters (Cmax, AUC0-inf, AUCtlast-inf (%)) following oral administration of flibanserin 50 mg after a light, a medium, a high fat/caloric breakfast, and under fasted conditions (sponsor's table 14.1:1).

	Treatment					
	Light			Medium		
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$AUC_{tlast-\infty}$ (%)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$AUC_{tlast-\infty}$ (%)
n	16	16	16	16	16	16
mean	199	959	5.92	232	1160	5.21
SD	65.8	481	3.37	102	542	3.56
CV%	33.1	50.1	57.0	43.9	46.6	68.3
min	86.3	498	2.63	118	544	2.43
median	184	824	5.10	204	1060	3.76
max	330	2230	13.6	519	2510	14.0
gmean	188	874	5.19	215	1060	4.45
gSD	1.42	1.53	1.68	1.48	1.53	1.71
gCV%	35.9	44.4	55.5	40.9	44.5	57.7

	Treatment					
	High			Fasted		
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$AUC_{tlast-\infty}$ (%)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$AUC_{tlast-\infty}$ (%)
n	16	16	16	16	16	16
mean	236	1260	5.53	207	821	6.56
SD	91.2	618	4.15	71.8	427	4.03
CV%	38.7	49.1	75.1	34.7	52.0	61.4
min	102	708	2.28	69.9	374	2.47
median	221	1060	3.90	222	680	5.21
max	460	3130	18.6	289	1810	15.5
gmean	219	1160	4.69	191	742	5.55
gSD	1.49	1.48	1.70	1.57	1.55	1.80
gCV%	41.8	41.1	57.3	47.9	46.3	64.2

The following table is a summary of pharmacokinetic parameters (Tmax, $t_{1/2}$, MRT, V_z/F, and CL/F) following oral administration of flibanserin 50 mg after a light, medium, high fat/caloric breakfast, and under fasted conditions (sponsor's table 14.1:2).

	Treatment									
	Light					Medium				
	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	CL/F (mL/min)	V_z/F (L)	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	CL/F (mL/min)	V_z/F (L)
n	16	16	16	16	16	16	16	16	16	16
mean	1.78	7.79	8.70	1030	635	1.19	7.52	8.63	848	517
SD	1.21	2.59	2.87	382	186	0.772	2.03	2.51	336	157
CV%	67.8	33.2	33.0	37.1	29.3	65.0	27.0	29.1	39.6	30.4
min	0.50	3.75	4.44	374	410	0.250	5.01	6.02	332	288
median	1.50	6.81	8.57	1020	596	0.875	7.16	8.29	787	518
max	4.00	12.7	14.6	1670	977	3.00	12.3	14.4	1530	805
gmean	1.43	7.40	8.29	954	611	0.962	7.28	8.33	783	494
gSD	2.00	1.40	1.38	1.53	1.33	2.00	1.29	1.31	1.53	1.38
gCV%	78.5	34.6	33.0	44.4	29.1	78.6	26.1	27.8	44.5	33.0

	Treatment									
	High					Fasted				
	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	CL/F (mL/min)	V_z/F (L)	t_{max} (h)	$t_{1/2}$ (h)	MRT (h)	CL/F (mL/min)	V_z/F (L)
n	16	16	16	16	16	16	16	16	16	16
mean	2.03	7.93	9.61	767	499	0.766	7.55	8.04	1220	727
SD	1.51	2.42	3.29	253	165	0.281	2.80	3.26	466	266
CV%	74.1	30.5	34.2	33.1	33.1	36.7	37.1	40.6	38.2	36.6
min	0.50	4.62	6.10	266	292	0.500	4.31	4.42	460	405
median	1.75	7.64	8.73	783	482	0.750	7.63	7.20	1230	689
max	5.00	13.3	19.6	1180	783	1.50	13.7	15.8	2230	1410
gmean	1.53	7.60	9.20	719	473	0.723	7.08	7.52	1120	688
gSD	2.22	1.34	1.34	1.48	1.40	1.41	1.45	1.44	1.55	1.40
gCV%	94.4	30.3	29.7	41.1	34.4	35.5	38.3	37.6	46.3	34.2

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22-526 **Applicant: Eli Lilly** **Stamp Date: October 27, 2009**

Drug Name: Flibanserin **NDA Type: Original**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		Studies 511.17, 511.19, 511.33
2	Has the applicant provided metabolism and drug-drug interaction information?	X		Studies 511.88, 511.93, 511.111
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			n/a
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			n/a
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			n/a
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			The sponsor is requesting a pediatric waiver.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			The sponsor is requesting a pediatric waiver.
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		

	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Potential Clinical Pharmacology Review Issues to be conveyed to the Sponsor:

- The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies did not demonstrate comparative dissolution studies according to the f2 value. If the sponsor decides to seek approval of the 50 mg tablets, a BE study may be needed.
- The hepatic impairment, renal impairment, and CYP2D6/paroxetine studies were conducted using a 50 mg dose and the ketoconazole study was conducted using 25 or 50 mg dose, while the recommended dose is 100 mg. [redacted] (b) (4)

LaiMing Lee — December 4, 2009
Reviewing Clinical Pharmacologist — Date

Myong-Jin Kim
Team Leader/Supervisor — Date

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-526**	**Brand Name**	**Girosa or (b) (4) (pending approval)**
OCP Division	**DCP3**	**Generic Name**	**Flibanserin (BIMT-17BS)**
Medical Division	**DRUP**	**Drug Class**	**serotonin 5-HT_{1A} agonist, 5-HT_{2A} antagonist**
OCP Reviewer	**LaiMing Lee, Ph.D.**	**Indication(s)**	**Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women**
OCP Team Leader	**Myong-Jin Kim, Pharm.D.**	**Dosage Form**	**Immediate Release Tablet**
		Dosing Regimen	**100 mg daily at bedtime**
Date of Submission	**October 27, 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Boehringer Ingelheim**
PDUFA Due Date	**August 27, 2010**	**Priority Classification**	**Standard**
Division Due Date	**July 16, 2010**	**Related IND**	(b) (4)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study 511.15**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**2**		**Study BB4.D184 (in animals, man & human serum albumin) Study A079.07FU (in human renal or hepatic insufficiency)**
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:	**X**	**4**		**Study 511.1 (single increasing oral dose), 511.9 (single increasing dose), 511.14 (single increasing iv dose), 511.15 (iv and oral C14)**
multiple dose:	**X**	**1**		**Study 511.2**
Patients-				
single dose:	**X**	**1**		**Study 511.105 (50 mg qd-> 100 mg qd, 25 mg bid-> 50 mg bid)**
multiple dose:	**X**	**1**		**Study 511.105 (50 mg qd-> 100 mg qd, 25 mg bid-> 50 mg bid)**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**4**		**Study 511.1 (SD PO), 511.2 (MD PO), 511.14 (iv), 511.97, 511.117 (Japanese women)**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**4**		**Study 511.37 (effect of MD itraconazole on flibanserin)** **Study 511.111 (effect of MD ketoconazole on flibanserin)** **Study 511.86 (effect of rifampicin on flibanserin)** **Study 511.87 (effect of paroxetine on flibanserin)**
In-vivo effects of primary drug:		**2**		**Study 511.88 (effect on SS PK of bupropion)** **Study 511.93 (effect on SD PK of EE & LNG)**
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**1**		**Study 511.117 (in healthy Japanese females)**
gender:				**n/a**
pediatrics:				**n/a**
geriatrics:				**n/a**
renal impairment:	**X**	**1**		**Study 511.96**
hepatic impairment:	**X**	**1**		**Study 511.67**
PD:				
Phase 2:	**X**	**1**		**Study 511.105**
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	**3**		**Study 511.105 (PK in HSDD patients)** **Study 511.68, 511.69 (Phase 2)**

Phase 3 clinical trial:	X	5		Study 511.70 (supportive), 511.71 (pivotal - 100 mg qhs), 511.74 (supportive), 511.75 (pivotal - up titration to 100 mg qhs), 511.77 (supportive)
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	2		Study 511.15
Relative bioavailability -				
solution as reference:	X			Study 511.17 (soln vs. caps)
alternate formulation as reference:	X	2		Study 511.19 (b) (4) DS) Study 511.33 (b) (4) DS)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		Study 511.33, 511.26
Dissolution:				
(IVIVC):	X	1		Study 511.108
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
QT Study	X	1		Study 511.90 (50 mg bid, 100 mg tid flibanserin x 5 days, 400 mf moxifloxacin)
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				n/a (waiver requested)
Literature References	X	42		
Total Number of Studies				
Filability and QBR comments				

	"X" if yes	Comments
Application fileable ?	**X**	**Advisory Committee meeting will be likely scheduled for early/mid June 2010.**
Comments sent to firm ?	**X**	**Potential Review Issues to be Conveyed to the Sponsor:** **- The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies did not demonstrate comparative dissolution studies according to the f2 value. If the sponsor decides to seek approval of the 50 mg tablets, a BE study may be needed.** **- The hepatic impairment, renal impairment, and CYP2D6/paroxetine studies were conducted using a 50 mg dose and the ketoconazole study was conducted using 25 or 50 mg dose, while the recommended dose is 100 mg.** **(b) (4)**
QBR questions (key issues to be considered)	**Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?** **What intrinsic factors (renal and/or liver impairment) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?** **Is the drug an inhibitor and/or an inducer of CYP enzymes?** **Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

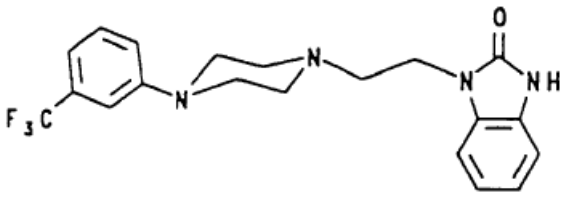
Filing Memo

Clinical Pharmacology Review

NDA: 22-526
Compound: Flibanserin
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Date: November 24, 2009
Reviewer: LaiMing Lee, Ph.D.

Background: Boehringer Ingelheim is seeking approval of flibanserin for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women (> 18 years of age). Flibanserin is a serotonin 5-HT_{1A} agonist and a 5-HT_{2A} antagonist. There is currently no FDA-approved pharmacologic therapy for HSDD. The proposed dose and dosing regimen is one - 100 mg oral tablet to be given daily at bedtime (qhs) with or without food.



HSDD is characterized by the lack or absence of sexual fantasies and desire for sexual activity for some period of time, and is the cause for marked distress or interpersonal difficulties. HSDD is not accounted for by another mental disorder, drug, or some other medical condition.

Boehringer Ingelheim (BI) developed flibanserin originally to treat depression, based on anti-depressant-like effects in preclinical models. Flibanserin failed to show efficacy on the primary endpoint in a Phase IIa depression clinical trial and virtually no sexual dysfunction was noted so a multi-dimensional measure, the Arizona Sexual Experiences Scale (ASEX), of sexual dysfunction was included in four Phase IIb depression studies. Again, flibanserin failed to show consistent efficacy as an antidepressant. The sponsor found that in one of the 4 studies, flibanserin was superior in women not only to the positive comparator, but also to placebo on the ASEX scale.

Clinical Trials: The sponsor states that in a Phase II depression trial that suggested efficacy for flibanserin in sexual dysfunction - the dose used was 50 mg twice daily (bid), up-titrated to 100 mg bid for patients whose depression did not improve. Patients showed improved sexual function on both dose regimens. Therefore, the dosage used in the two Phase II Proof-of-Concept trials for HSDD was 50 mg of flibanserin bid, with up-titration to 100 mg bid for patients not responding to the 50 mg bid dose.

In two 12-week proof-of-concept randomized, double-blind, placebo-controlled trials, the sponsor evaluated 50 mg twice daily and 100 mg twice daily flibanserin, compared to placebo (Studies 511.68 and 511.69). According to the sponsor, a pooled analysis of the two trials showed that flibanserin was superior over placebo in satisfying sexual events in the final evaluation period. Based on the multiple measure of efficacy, the proof-of-concept trials provided sufficient information to test flibanserin in Phase

III clinical trial. The data from these trials suggested flibanserin at doses of 50 mg bid or 100 mg qd would limit adverse events (i.e. sedation) and dropouts in the Phase III trials.

The sponsor evaluated multiple doses and dosing regimens of flibanserin in four pivotal, randomized, double-blind, placebo-controlled Phase III clinical trials (Study 511.70, 511.71, 511.75 and 511.77). The doses and dosing regimens examined were 25 mg bid, 50 mg qhs, 50 mg bid, and 100 mg qhs. Flibanserin tablets were administered with 150 mL water. The most common adverse events were constipation, dizziness, dry mouth, fatigue, insomnia, nausea, somnolence and vomiting. The sponsor noted that peak sedation occurred in close proximity to flibanserin t_{max}, but was generally absent within six hours of treatment. It appears that the sponsor chose to administer flibanserin at bedtime in order to minimize the effect of sedation.

The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies are manufactured at different sites (BI Reims, France vs. BI Roxane, Columbus, USA). The sponsor conducted comparative dissolution studies and failed according to the f2 value. Even though the sponsor is currently seeking approval of the 100 mg dose strength, this could, however, be a potential issue for us if the sponsor decides to seek approval of the 50 mg tablets or the dosing regimen changes from 100 mg qhs to 50 mg qhs then up-titrated to 100 mg qhs (one of the dosing regimens in one pivotal clinical trial). In the event the sponsor seeks approval of the 50 mg tablets or there is a dosing change, a BE study may be needed. The sponsor will be alerted that this could be a potential review issue.

Clinical Pharmacology:
The sponsor evaluated the PK in healthy men and premenopausal women in multiple Phase I studies using intravenous and oral formulations (Studies 511.1, 511.2, 511.14, 511.97, 511.105, and 511.117). The sponsor states that flibanserin shows linear and dose-proportional PK after single oral doses of 0.5 mg to 150 mg and after multiple oral administrations of total daily doses ranging from 60 mg to 300 mg. The sponsor also states that steady state is achieved after 3 days and the extent of exposure is increased 1.44-fold as compared to single dose during once-daily administration of 100 mg flibanserin.

According the sponsor, flibanserin is rapidly absorbed, with (b) (4)% of the dose reaching the systemic circulation as flibanserin or metabolites. After oral administration, maximum observed plasma concentrations (C_{max}) are usually achieved between 45 and 60 minutes. The absolute bioavailability of flibanserin following oral dosing is 33% (Study 511.15). The mean terminal elimination half-life of flibanserin ranging from 10.1 to 11.9 hours following doses of 25 bid, 50 mg qd, 50 mg bid, and 100 mg qd (Study 511.1.05).

In a teleconference meeting on May 10, 2007, DRUP and the sponsor discussed the choice of metabolites to be evaluated in the planned PK studies. At the time of the meeting, the sponsor indicated that PK sampling will not conducted in the Phase III studies due to poor quality data in prior Phase III PK sampling. It was agreed upon that the sponsor would measure M2, M8, M26, M30a, M35, and M38 in a Phase I study in 60 HSDD patients (Study 511.105). The doses selected for that study were: 50 mg qd, 100 mg qd, 25 mg bid, and 50 mg bid.

The sponsor conducted the following studies to evaluate intrinsic and extrinsic factors that may affect the PK of flibanserin: ethnicity (Study 511.117 Japanese women), food effect (Studies 511.26 and 511.33), renal impairment (Studies 511.96), hepatic impairment (Study 511.67), drug interaction with oral contraceptive containing EE/LNG (Study 511.93), drug interaction with bupropion (Study 511.88), drug interaction with ketoconazole (Study 511.111), drug interaction with rifampicin (Study 511.86) and drug interaction with paroxetine (Study 511.87).

Food effect on PK of flibanserin was evaluated in two separate studies. In both studies, $AUC_{0\text{-}inf}$ increased approximately 40% in the fed group; however, C_{max} decreased ~30% in one study and increased ~30% in the other study.

The impact of renal impairment on flibanserin PK was evaluated using the 50 mg tablets in severely impaired (CrCL <30 ml/min) and in mild to moderate ($\geq$30 to $\leq$ 80 ml/min) male and female subjects. The sponsor states that severe renal impairment did not impact the systemic exposure to flibanserin and its minor metabolite M30a. A potential review issue will be the implications of the renal impairment study using a 50 mg dose when the recommended dose is 100 mg.

The impact of hepatic impairment on flibanserin PK was evaluated using the 50 mg tablets. The sponsor states that systemic exposure to flibanserin was significantly affected by hepatic impairment. The $AUC_{0\text{-}inf}$ ratio of flibanserin was significantly higher (3 to 4.5 fold) in hepatically impaired patients, while the C_{max} ratio was slightly reduced in patients with mild hepatic impairment, but significantly lower in patients with moderate hepatic impairment, compared to healthy controls. The apparent clearance of flibanserin was significantly lower in hepatically impaired patients compared to healthy subjects. The sponsor does not recommend the use of flibanserin in patients with hepatic impairment. A potential review issue will be the implications of the hepatic impairment study using a 50 mg dose when the recommended dose is 100 mg.

Flibanserin is extensively metabolized by CYP3A4 and to a lesser extent CYP2D6. The sponsor evaluated the effect of 200 mg qd itraconazole, a potent CYP3A4 inhibitor, on flibanserin and conducted simulations at 200 mg bid itraconazole (Study 511.37). During a teleconference meeting with the sponsor on May 10, 2007, DRUP expressed concerns about the choice of CYP3A4 inhibitor as the Agency currently recommends a 400 mg qd dose of ketoconazole as a strong CYP3A4 inhibitor for drug-drug interaction studies. The Division also expressed concerns about the use of data from a physiologically-based pharmacokinetic model to predict flibanserin exposure after CYP3A4 inhibition if a dosing adjustment was needed in the light of safety concerns. Though there was no recommendation from the Division, the sponsor decided to conduct a drug-drug interaction study with ketoconazole (Study 511.111). The sponsor evaluated the effect of multiple dosed of 400 mg qd on the PK of 25 mg and 50 mg flibanserin. A potential review issue is the implications of the ketoconazole study using a dose lower than the 100 mg recommended dose.

The sponsor evaluated the effect of rifampicin, a potent CYP3A4 inducer, on flibanserin PK (Study 511.86). Subject were given a single dose flibanserin 100 mg and rifampicin 600 mg once daily for 9 days. The sponsor states that rifampicin caused a pronounced increase in flibanserin metabolism leading to a marked reduction in flibanserin exposure.

The sponsor evaluated the PK of flibanserin in poor and extensive metabolizers of CYP2D6 and effect of paroxetine, a potential for CYP2D6 inhibitor, on flibanserin (Study 511.87). 50 mg of flibanserin was given twice a day for 6 days followed by 20 to 40 mg paroxetine. The sponsor states that flibanserin exposure was not increased in poor metabolizers of CYP2D6 or with co-administration of paroxetine in extensive metabolizers of CYP2D6.

Drug Product: Flibanserin film-coated tablets are available [redacted]. The sponsor is seeking approval of the 100 mg strength only. The to-be-marketed product will be oval in shape and pink-colored, debossed on one side with "f100" and on the other side with [redacted] (b) (4) The following is the quantitative and qualitative formulation of the proposed 100 mg flibanserin tablets:

	Ingredient	Function	Amount (mg)
(b) (4)	Flibanserin	Active ingredient	100.000
	Lactose monohydrate	(b) (4)	
	Microcrystalline cellulose		
	Hypromellose (b) (4)		
	Croscarmellose sodium		
	Magnesium stearate		
	(b) (4) Pink		
	Total		347.0

Formulation Development:

The sponsor stated that a (b) (4) Phase I and Phase II clinical trials when they were pursing the initial indication of Major Depression Disorder. When the sponsor was evaluating the use of flibanserin for HSDD, higher doses and strengths (100 mg) were needed so the sponsor pursued the development of an immediate release film-coated tablet formulation (b) (4).

The film coat was initially (b) (4) then it was later changed to pink (b) (4)

(b) (4)

Flibanserin film coated-tablets were eventually developed in three strengths containing 25, 50 and 100 mg. All strengths (b) (4) have been used in phase III clinical trials.
The sponsor evaluated dose proportionality between the three strengths (Study 511.97) - 2 x 25 mg tablets and 1 x 50 mg tablets; and 2 x 50 mg tablets and 1 x 100 mg tablets. (b) (4)

Other Clinical Pharmacology Comments:

As requested in the pre-NDA clinical pharmacology comments, the sponsor submitted detailed information on the formulations and a summary listing of the formulations used in each flibanserin clinical trial.

Potential Review Issues to be conveyed to the Sponsor:

- The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies did not demonstrate comparative dissolution studies according to the f2 value. If the sponsor decides to seek approval of the 50 mg tablets, a BE study may be needed.

- The hepatic impairment, renal impairment, and CYP2D6/paroxetine studies were conducted using a 50 mg dose and the ketoconazole study was conducted using 25 or 50 mg dose, while the recommended dose is 100 mg. (b) (4)

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-526 is fileable.

_____ _____

LaiMing Lee, Ph.D. Reviewer Date

_____ _____

Myong-Jin Kim, Pharm.D., Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAI M LEE
08/25/2010

EDWARD D BASHAW
08/26/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	22-526	**Reviewer: Houda Mahayni, Ph.D.**	
Submission Date:	10/27/09		
Division:	DRUP	**Team Leader: Angelica Dorantes, Ph.D.**	
Sponsor:	Boehringer Ingelheim	**Supervisor: Patrick J. Marroum, Ph.D.**	
Trade Name:	Girosa	**Date Assigned:**	11/03/09
Generic Name:	Flibanserin	**Date of Review:**	05/15/10
Indication:	Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women	**Type of Submission: 505(b)(1) New Drug Application**	
Formulation/strengths	Immediate-Release, Film-Coated Tablet/ 100 mg		
Route of Administration	Oral		

SUBMISSION:

Flibanserin is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. Flibanserin film-coated tablet 100 mg is the strength intended for commercialization. The sponsor provided information on two additional strengths 25 mg and 50 mg which are not intended for commercialization.

BIOPHARMACEUTIC INFORMATION:

The composition of the core and the film-coat used in the formulation of flibanserin film-coated tablet is shown in Tables 1 and 2 below.

Table 1 : Composition of flibanserin film-coated tablets, 25 mg, 50 mg and 100 mg per tablet

(b) (4)

Table 2: Composition of (b) (4) Pink (b) (4)

Ingredient	mg per 25 mg tablet	mg per 50 mg tablet	mg per 100 mg tablet

(b) (4)

Biopharmaceutic areas to review in this submission are: dissolution method development and specification, and manufacturing site change.

1. Dissolution Method Development and Specification

a. Selection of Apparatus and Rotation Speed

(b) (4)

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Signature
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Signature
Patrick J. Marroum, Ph.D.
Biopharmaceutics Lead
Office of New Drugs Quality Assessment

cc: ADorantes, ZGe, DChristner, JDavid

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOUDA MAHAYNI
06/01/2010

PATRICK J MARROUM
06/02/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 22-526 **Applicant: Eli Lilly** **Stamp Date: October 27, 2009**

Drug Name: Flibanserin **NDA Type: Original**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		Studies 511.17, 511.19, 511.33
2	Has the applicant provided metabolism and drug-drug interaction information?	X		Studies 511.88, 511.93, 511.111
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			n/a
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			n/a
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			n/a
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			The sponsor is requesting a pediatric waiver.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			The sponsor is requesting a pediatric waiver.
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		

14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Potential Clinical Pharmacology Review Issues to be conveyed to the Sponsor:

- The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies did not demonstrate comparative dissolution studies according to the f2 value. If the sponsor decides to seek approval of the 50 mg tablets, a BE study may be needed.
- The hepatic impairment, renal impairment, and CYP2D6/paroxetine studies were conducted using a 50 mg dose and the ketoconazole study was conducted using 25 or 50 mg dose, while the recommended dose is 100 mg. (b) (4) [redacted]

LaiMing Lee — December 4, 2009
Reviewing Clinical Pharmacologist — Date

Myong-Jin Kim
Team Leader/Supervisor — Date

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-526**	**Brand Name**	**Girosa or (b) (4) (pending approval)**
OCP Division	**DCP3**	**Generic Name**	**Flibanserin (BIMT-17BS)**
Medical Division	**DRUP**	**Drug Class**	**serotonin 5-HT_{1A} agonist, 5-HT_{2A} antagonist**
OCP Reviewer	**LaiMing Lee, Ph.D.**	**Indication(s)**	**Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women**
OCP Team Leader	**Myong-Jin Kim, Pharm.D.**	**Dosage Form**	**Immediate Release Tablet**
		Dosing Regimen	**100 mg daily at bedtime**
Date of Submission	**October 27, 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Boehringer Ingelheim**
PDUFA Due Date	**August 27, 2010**	**Priority Classification**	**Standard**
Division Due Date	**July 16, 2010**	**Related IND**	**(b) (4)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study 511.15**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**2**		**Study BB4.D184 (in animals, man & human serum albumin) Study A079.07FU (in human renal or hepatic insufficiency)**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**4**		**Study 511.1 (single increasing oral dose), 511.9 (single increasing dose), 511.14 (single increasing iv dose), 511.15 (iv and oral C14)**
multiple dose:	**X**	**1**		**Study 511.2**

Patients-				
single dose:	**X**	**1**		**Study 511.105 (50 mg qd-> 100 mg qd, 25 mg bid-> 50 mg bid)**
multiple dose:	**X**	**1**		**Study 511.105 (50 mg qd-> 100 mg qd, 25 mg bid-> 50 mg bid)**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**4**		**Study 511.1 (SD PO), 511.2 (MD PO), 511.14 (iv), 511.97, 511.117 (Japanese women)**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**4**		**Study 511.37 (effect of MD itraconazole on flibanserin)** **Study 511.111 (effect of MD ketoconazole on flibanserin)** **Study 511.86 (effect of rifampicin on flibanserin)** **Study 511.87 (effect of paroxetine on flibanserin)**
In-vivo effects of primary drug:		**2**		**Study 511.88 (effect on SS PK of bupropion)** **Study 511.93 (effect on SD PK of EE & LNG)**
In-vitro:				
Subpopulation studies -				
ethnicity:	**X**	**1**		**Study 511.117 (in healthy Japanese females)**
gender:				**n/a**
pediatrics:				**n/a**
geriatrics:				**n/a**
renal impairment:	**X**	**1**		**Study 511.96**
hepatic impairment:	**X**	**1**		**Study 511.67**
PD:				
Phase 2:	**X**	**1**		**Study 511.105**
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	**3**		**Study 511.105 (PK in HSDD patients)** **Study 511.68, 511.69 (Phase 2)**
Phase 3 clinical trial:	**X**	**5**		**Study 511.70 (supportive), 511.71 (pivotal - 100 mg qhs), 511.74 (supportive), 511.75 (pivotal - up titration to 100 mg qhs), 511.77 (supportive)**
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**X**	**2**		**Study 511.15**
Relative bioavailability -				

solution as reference:	X			Study 511.17 (soln vs. caps)
alternate formulation as reference:	X	2		Study 511.19 (b) (4) DS) Study 511.33 (b) (4) DS)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		Study 511.33, 511.26
Dissolution:				
(IVIVC):	X	1		Study 511.108
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
QT Study	X	1		Study 511.90 (50 mg bid, 100 mg tid flibanserin x 5 days, 400 mf moxifloxacin)
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				n/a (waiver requested)
Literature References	X	42		
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application fileable ?	X	Advisory Committee meeting will be likely scheduled for early/mid June 2010.
Comments sent to firm ?	X	Potential Review Issues to be Conveyed to the Sponsor: - The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies did not demonstrate comparative dissolution studies according to the f2 value. If the sponsor decides to seek approval of the 50 mg tablets, a BE study may be needed. - The hepatic impairment, renal impairment, and CYP2D6/paroxetine studies were conducted using a 50 mg dose and the ketoconazole study was conducted using 25 or 50 mg dose, while the recommended dose is 100 mg. (b) (4)
QBR questions (key issues to be considered)	Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship? What intrinsic factors (renal and/or liver impairment) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? Is the drug an inhibitor and/or an inducer of CYP enzymes? Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?	

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

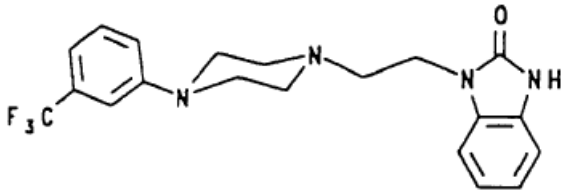
Filing Memo

Clinical Pharmacology Review

NDA: 22-526
Compound: Flibanserin
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Date: November 24, 2009
Reviewer: LaiMing Lee, Ph.D.

Background: Boehringer Ingelheim is seeking approval of flibanserin for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women (> 18 years of age). Flibanserin is a serotonin 5-HT_{1A} agonist and a 5-HT_{2A} antagonist. There is currently no FDA-approved pharmacologic therapy for HSDD. The proposed dose and dosing regimen is one - 100 mg oral tablet to be given daily at bedtime (qhs) with or without food.



HSDD is characterized by the lack or absence of sexual fantasies and desire for sexual activity for some period of time, and is the cause for marked distress or interpersonal difficulties. HSDD is not accounted for by another mental disorder, drug, or some other medical condition.

Boehringer Ingelheim (BI) developed flibanserin originally to treat depression, based on anti-depressant-like effects in preclinical models. Flibanserin failed to show efficacy on the primary endpoint in a Phase IIa depression clinical trial and virtually no sexual dysfunction was noted so a multi-dimensional measure, the Arizona Sexual Experiences Scale (ASEX), of sexual dysfunction was included in four Phase IIb depression studies. Again, flibanserin failed to show consistent efficacy as an antidepressant. The sponsor found that in one of the 4 studies, flibanserin was superior in women not only to the positive comparator, but also to placebo on the ASEX scale.

Clinical Trials: The sponsor states that in a Phase II depression trial that suggested efficacy for flibanserin in sexual dysfunction - the dose used was 50 mg twice daily (bid), up-titrated to 100 mg bid for patients whose depression did not improve. Patients showed improved sexual function on both dose regimens. Therefore, the dosage used in the two Phase II Proof-of-Concept trials for HSDD was 50 mg of flibanserin bid, with up-titration to 100 mg bid for patients not responding to the 50 mg bid dose.

In two 12-week proof-of-concept randomized, double-blind, placebo-controlled trials, the sponsor evaluated 50 mg twice daily and 100 mg twice daily flibanserin, compared to placebo (Studies 511.68 and 511.69). According to the sponsor, a pooled analysis of the two trials showed that flibanserin was superior over placebo in satisfying sexual events in the final evaluation period. Based on the multiple measure of efficacy, the proof-of-concept trials provided sufficient

information to test flibanserin in Phase III clinical trial. The data from these trials suggested flibanserin at doses of 50 mg bid or 100 mg qd would limit adverse events (i.e. sedation) and dropouts in the Phase III trials.

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The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies are manufactured at different sites (BI Reims, France vs. BI Roxane, Columbus, USA). The sponsor conducted comparative dissolution studies and failed according to the f2 value. Even though the sponsor is currently seeking approval of the 100 mg dose strength, this could, however, be a potential issue for us if the sponsor decides to seek approval of the 50 mg tablets or the dosing regimen changes from 100 mg qhs to 50 mg qhs then up-titrated to 100 mg qhs (one of the dosing regimens in one pivotal clinical trial). In the event the sponsor seeks approval of the 50 mg tablets or there is a dosing change, a BE study may be needed. The sponsor will be alerted that this could be a potential review issue.

Clinical Pharmacology:
The sponsor evaluated the PK in healthy men and premenopausal women in multiple Phase I studies using intravenous and oral formulations (Studies 511.1, 511.2, 511.14, 511.97, 511.105, and 511.117). The sponsor states that flibanserin shows linear and dose-proportional PK after single oral doses of 0.5 mg to 150 mg and after multiple oral administrations of total daily doses ranging from 60 mg to 300 mg. The sponsor also states that steady state is achieved after 3 days and the extent of exposure is increased 1.44-fold as compared to single dose during once-daily administration of 100 mg flibanserin.

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bupropion (Study 511.88), drug interaction with ketoconazole (Study 511.111), drug interaction with rifampicin (Study 511.86) and drug interaction with paroxetine (Study 511.87).

Food effect on PK of flibanserin was evaluated in two separate studies. In both studies, $AUC_{0\text{-}inf}$ increased approximately 40% in the fed group; however, C_{max} decreased ~30% in one study and increased ~30% in the other study.

The impact of renal impairment on flibanserin PK was evaluated using the 50 mg tablets in severely impaired (CrCL <30 ml/min) and in mild to moderate ($\geq$30 to $\leq$ 80 ml/min) male and female subjects. The sponsor states that severe renal impairment did not impact the systemic exposure to flibanserin and its minor metabolite M30a. A potential review issue will be the implications of the renal impairment study using a 50 mg dose when the recommended dose is 100 mg.

The impact of hepatic impairment on flibanserin PK was evaluated using the 50 mg tablets. The sponsor states that systemic exposure to flibanserin was significantly affected by hepatic impairment. The $AUC_{0\text{-}inf}$ ratio of flibanserin was significantly higher (3 to 4.5 fold) in hepatically impaired patients, while the C_{max} ratio was slightly reduced in patients with mild hepatic impairment, but significantly lower in patients with moderate hepatic impairment, compared to healthy controls. The apparent clearance of flibanserin was significantly lower in hepatically impaired patients compared to healthy subjects. The sponsor does not recommend the use of flibanserin in patients with hepatic impairment. A potential review issue will be the implications of the hepatic impairment study using a 50 mg dose when the recommended dose is 100 mg.

Flibanserin is extensively metabolized by CYP3A4 and to a lesser extent CYP2D6. The sponsor evaluated the effect of 200 mg qd itraconazole, a potent CYP3A4 inhibitor, on flibanserin and conducted simulations at 200 mg bid itraconazole (Study 511.37). During a teleconference meeting with the sponsor on May 10, 2007, DRUP expressed concerns about the choice of CYP3A4 inhibitor as the Agency currently recommends a 400 mg qd dose of ketoconazole as a strong CYP3A4 inhibitor for drug-drug interaction studies. The Division also expressed concerns about the use of data from a physiologically-based pharmacokinetic model to predict flibanserin exposure after CYP3A4 inhibition if a dosing adjustment was needed in the light of safety concerns. Though there was no recommendation from the Division, the sponsor decided to conduct a drug-drug interaction study with ketoconazole (Study 511.111). The sponsor evaluated the effect of multiple dosed of 400 mg qd on the PK of 25 mg and 50 mg flibanserin. A potential review issue is the implications of the ketoconazole study using a dose lower than the 100 mg recommended dose.

The sponsor evaluated the effect of rifampicin, a potent CYP3A4 inducer, on flibanserin PK (Study 511.86). Subject were given a single dose flibanserin 100 mg and rifampicin 600 mg once daily for 9 days. The sponsor states that rifampicin caused a pronounced increase in flibanserin metabolism leading to a marked reduction in flibanserin exposure.

The sponsor evaluated the PK of flibanserin in poor and extensive metabolizers of CYP2D6 and effect of paroxetine, a potential for CYP2D6 inhibitor, on flibanserin (Study 511.87). 50 mg of flibanserin was given twice a day for 6 days followed by 20 to 40 mg paroxetine. The sponsor states that flibanserin exposure was not increased in poor metabolizers of CYP2D6 or with co-administration of paroxetine in extensive metabolizers of CYP2D6.

Drug Product: Flibanserin film-coated tablets are available in three strengths - 25, 50, and 100 mg. The sponsor is seeking approval of the 100 mg strength only. The to-be-marketed product will be oval in shape and pink-colored, debossed on one side with "f100" and on the other side with [redacted]. The following is the quantitative and qualitative formulation of the proposed 100 mg flibanserin tablets:

	Ingredient	Function	Amount (mg)
[redacted]	Flibanserin	Active ingredient	100.000
	Lactose monohydrate	[redacted]	
	Microcrystalline cellulose		
	Hypromellose [redacted]		
	Croscarmellose sodium		
	Magnesium stearate		
	[redacted] Pink		
	Total		347.0

Formulation Development:
The sponsor stated that a [redacted] Phase I and Phase II clinical trials when they were pursing the initial indication of Major Depression Disorder. When the sponsor was evaluating the use of flibanserin for HSDD, higher doses and strengths (100 mg) were needed so the sponsor pursued the development of an immediate release film-coated tablet formulation [redacted].

The film coat was initially [redacted] then it was later changed to pink [redacted]

[redacted]

Flibanserin film coated-tablets were eventually developed in three strengths containing 25, 50 and 100 mg. All strengths [redacted] have been used in phase III clinical trials. The sponsor evaluated dose proportionality between the three strengths (Study 511.97) - 2 x 25 mg tablets and 1 x 50 mg tablets; and 2 x 50 mg tablets and 1 x 100 mg tablets. [redacted]

Other Clinical Pharmacology Comments:
As requested in the pre-NDA clinical pharmacology comments, the sponsor submitted detailed information on the formulations and a summary listing of the formulations used in each flibanserin clinical trial.

Potential Review Issues to be conveyed to the Sponsor:

- The 50 mg tablets used in the Phase III clinical trials and the batches of 50 mg tablets for primary stability studies did not demonstrate comparative dissolution studies according to the f2 value. If the sponsor decides to seek approval of the 50 mg tablets, a BE study may be needed.
- The hepatic impairment, renal impairment, and CYP2D6/paroxetine studies were conducted using a 50 mg dose and the ketoconazole study was conducted using 25 or 50 mg dose, while the recommended dose is 100 mg. [redacted] (b) (4)

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-526 is fileable.

_____ _____

LaiMing Lee, Ph.D. Reviewer Date

_____ _____

Myong-Jin Kim, Pharm.D., Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

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/s/

LAI M LEE
12/15/2009

MYONG JIN KIM
12/15/2009