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*APPLICATION NUMBER:*

**022526Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 022526  
Product Name: Addyi (flibanserin)

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PMR/PMC Description: Prospective Observational Study to Evaluate the Risk of Appendicitis with the Use of Addyi in Women Aged 18 to 44 (2939-2)

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/16
	Study Completion:	03/19
	Final Report Submission:	09/19
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Preapproval clinical trial data showed a numerical imbalance of acute appendicitis with Addyi compared to placebo. Appendicitis could be a class effect among drugs like Addyi that are antagonists at the serotonin 2A receptor. Given the low annual incidence estimates of acute appendicitis in U.S. women (11-13 cases per 10,000 among women aged 20-29, 8-11 cases per 10,000 among women aged 30-39, and 5-8 cases per 10,000 among women aged 40-49), it is not possible to fully assess this risk in the pre-approval setting.<sup>1</sup>

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue identified was an excess of reported cases of acute appendicitis in randomized, double-blind, placebo-controlled clinical trials. However, event rates were low and it remains unclear whether the observed imbalance reflects a chance finding or is attributable to drug. The goal of the observational study will be to determine if exposure to Addyi is associated with an increased risk of acute appendicitis among women in the indicated population.

<sup>1</sup> Buckius et al. Association For Academic Surgery: Changing Epidemiology of Acute Appendicitis in the United States: Study Period 1993-2008. J Surg Res 2012;175:185-190.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Applicant will conduct a prospective observational study in women exposed to Addyi.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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CHRISTINE P NGUYEN  
08/18/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 022526  
Product Name: Addyi (flibanserin)

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PMR/PMC Description: Enhanced Pharmacovigilance Study to Assess and Analyze the Risks of Hypotension, Syncope, and Accidents or Injuries and Fatal Outcomes with the use of Addyi (flibanserin) (2939-1)

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/15</u>
	Study Completion:	<u>10/20</u>
	Program Reassessment Report	<u>04/21</u>
	Final Report Submission:	<u>04/24</u>
	Other: Interim reports	<u>04/16, 10/16,</u> <u>04/17, 10/17</u> <u>04/18, 10/18</u> <u>04/19, 10/19</u> <u>04/20</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Important safety concerns identified from the preapproval safety database of Addyi were the risks of central nervous system (CNS) depression, hypotension and syncope, and concerns of accidents and injuries resulting from these adverse reactions. These risks are further increased when Addyi is taken during waking hours or if Addyi is used with moderate or strong CYP3A4 inhibitors or alcohol. It is unclear whether the findings in the clinical trials will be representative of findings seen with real world use.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to assess the severity of the risks of hypotension and syncope, accidents and injuries and to understand the cause of fatal outcomes associated with Addyi in the real world setting. These postmarketing data would help to inform the safety profile and also the effectiveness of risk mitigation approaches, including labeling and the ETASU REMS.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk.

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Enhanced pharmacovigilance study to systematically assess and analyze postmarketing adverse events of hypotension and syncope, accidents and injuries, and fatal outcomes reported with Addyi use, regardless of indication, for at least 5 years from the date of approval.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Systematic assessment and analysis of systematic pharmacovigilance of adverse events of interest with Addyi
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHRISTINE P NGUYEN  
08/18/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA #                    022526  
Product Name:                Addyi (flibanserin)

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PMR/PMC Description:      Pregnancy Registry Study to Evaluate Adverse Pregnancy Outcomes and Birth Defects in Pregnancies Exposed to Addyi (2939-3)

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/16</u>
	Study Completion:	<u>06/21</u>
	Final Report Submission:	<u>12/21</u>
	Other: Interim Analysis	<u>06/17, 06/18,</u> <u>06/19, 06/20</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

It is expected that pregnancies will occur in women who use Addyi, given the drug's indication (treatment of hypoactive desire disorder) and target population (premenopausal women). The pre-approval safety database was too limited to draw any conclusions about the effect of Addyi on pregnancies, maternal and fetal/neonatal outcomes.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR registry study is to evaluate the effects of Addyi on pregnancy and maternal and fetal/neonatal outcomes. This will be a registry-based, observational exposure cohort study (b) (4)

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This required study will be designed as a prospective registry based observational exposure cohort study that compares maternal, fetal, and infant outcomes in Addyi-exposed pregnancies to unexposed control pregnancies.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHRISTINE P NGUYEN  
08/18/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 022526  
Product Name: Addyi (flibanserin)

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PMR/PMC Description: Maternal-Fetal Outcome Study to Evaluate Adverse Pregnancy Outcomes and Birth Defects in Pregnancies Exposed to Addyi (2939-4)

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/16
	Study Completion:	06/21
	Final Report Submission:	12/21
	Other: Interim submissions:	06/17, 06/18
		06/19, 06/20

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

It is expected that pregnancies will occur in women who use Addyi, given the drug's indication (treatment of hypoactive desire disorder) and target population (premenopausal women). The pre-approval safety database was too limited to draw any conclusions about the effect of Addyi on pregnancies, maternal and fetal/neonatal outcomes. This study will complement the postmarketing pregnancy registry study (PMR 2939-3).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this observational study is to evaluate the effects of Addyi on pregnancy and maternal and fetal/neonatal outcomes. (b) (4)

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This observational study will assess the fetal and neonatal outcomes in Addyi-exposed pregnancies compared to an unexposed control population.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHRISTINE P NGUYEN  
08/18/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 022526  
Product Name: Addyi (flibanserin)

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PMR/PMC Description: Alcohol Interaction Trial in the Target Female Population (Between Ages 18 and 44) to Evaluate the Interaction Between Addyi and Alcohol Through a “Worst Case Scenario” with Varying Quantities of Alcohol Intake (2939-5)

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2015</u>
	Trial Completion:	<u>08/2016</u>
	Final Report Submission:	<u>12/2016</u>
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Addyi-alcohol interaction trial conducted pre-approval indicated that the concomitant intake of alcoholic beverages with Addyi significantly increased the risk of severe hypotension and syncope. This trial enrolled 25 healthy subjects, 23 of whom were men. The dose of alcohol tested ranged from 0.4 g/kg to 0.8 g/kg. Four of 23 subjects experienced severe hypotension and syncope requiring some medical intervention when 0.4 g/kg alcohol (equivalent to 2 standard alcohol drinks) was consumed with Addyi over 10 minutes in the morning. In addition, 6 (25%) of the 24 subjects co-administered ADDYI 100 mg and 0.8 g/kg alcohol experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions in these 6 subjects ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. This trial showed a pharmacodynamic interaction between Addyi and alcohol intake in men, but there are insufficient data to inform risk in female subjects (which is the population that will use Addyi). Because the interaction of Addyi and alcohol could be different in women, a separate trial is needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is to characterize and quantify the known risk of severe hypotension and syncope when Addyi is administered with different doses of alcohol in women (the population who would use Addyi). These data will help to inform the safe use of Addyi in the indicated population of premenopausal women.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)
The trial will evaluate whether there is a pharmacodynamic interaction when Addyi is co-administered with (b) (4) alcohol (b) (4).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
  - Information cannot be gained through a different kind of investigation
  - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
  - The trial will emphasize risk minimization for participants as the protocol is developed
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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CHRISTINE P NGUYEN  
08/18/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA/BLA # 022526  
Product Name: Addyi (flibanserin)

---

PMR/PMC Description: Alcohol Interaction Trial in the Target Female Population (Between Ages 18 and 44) to Evaluate the Interaction of the Timing of Alcohol Intake Relative to Addyi Dosing (2939-6)

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2017</u>
	Trial Completion:	<u>10/2017</u>
	Final Report Submission:	<u>02/2018</u>
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Addyi-alcohol interaction trial conducted pre-approval indicated that the concomitant intake of alcoholic beverages with Addyi significantly increased the risk of severe hypotension and syncope. This trial enrolled 25 healthy subjects, 23 of whom were men. The dose of alcohol tested ranged from 0.4 g/kg to 0.8 g/kg. Four of 23 subjects experienced severe hypotension and syncope requiring some medical intervention when 0.4 g/kg alcohol (equivalent to 2 standard alcohol drinks) was consumed with Addyi over 10 minutes in the morning. In addition, 6 (25%) of the 24 subjects co-administered ADDYI 100 mg and 0.8 g/kg alcohol experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions in these 6 subjects ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. This trial showed a pharmacodynamic interaction between Addyi and alcohol intake in men, but there are insufficient data to inform risk in female subjects (which is the population that will use Addyi). Because the interaction of Addyi and alcohol could be different in women, a separate trial is needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is to characterize and quantify the known risk of severe hypotension and syncope when alcohol is administered at different times relative to Addyi dosing in women (the population who would use Addyi). These data will help to inform the safe use of Addyi in the indicated population of premenopausal women.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)  
This trial will evaluate whether there is a pharmacodynamic interaction when alcohol is ingested relative to the timing of Addyi dosing (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
  - Information cannot be gained through a different kind of investigation
  - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
  - The trial will emphasize risk minimization for participants as the protocol is developed
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHRISTINE P NGUYEN  
08/18/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA/BLA # 022526  
Product Name: Addyi (flibanserin)

---

PMR/PMC Description: Alcohol Interaction Trial in the Target Female Population (Between Ages 18 and 44) to Evaluate the Interaction Between Addyi and Alcohol Intake in a “Typical Real World Use” Setting (2939-7)

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/2017</u>
	Trial Completion:	<u>10/2017</u>
	Final Report Submission:	<u>02/2018</u>
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Addyi-alcohol interaction trial conducted pre-approval indicated that the concomitant intake of alcoholic beverages with Addyi significantly increased the risk of severe hypotension and syncope. This trial enrolled 25 healthy subjects, 23 of whom were men. The dose of alcohol tested ranged from 0.4 g/kg to 0.8 g/kg. Four of 23 subjects experienced severe hypotension and syncope requiring some medical intervention when 0.4 g/kg alcohol (equivalent to 2 standard alcohol drinks) was consumed with Addyi over 10 minutes in the morning. In addition, 6 (25%) of the 24 subjects co-administered ADDYI 100 mg and 0.8 g/kg alcohol experienced orthostatic hypotension when standing from a sitting position. The magnitude of the systolic blood pressure reductions in these 6 subjects ranged from 22 to 48 mmHg, and the diastolic blood pressure reductions ranged from 0 to 27 mmHg. This trial showed a pharmacodynamic interaction between Addyi and alcohol intake in men, but there are insufficient data to inform risk in female subjects (which is the population that will use Addyi). Because the interaction of Addyi and alcohol could be different in women, a separate trial is needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is to characterize and quantify the known risks of severe hypotension and syncope when Addyi is administered with alcohol in a typical real life setting, (b) (4)  
These data will help to inform the safe use of Addyi in the intended population of women.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

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*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)  
This trial will evaluate whether there is a pharmacodynamic interaction when Addyi is co-administered with alcohol in a “real-world setting.”

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
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- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
  
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
  - Information cannot be gained through a different kind of investigation
  - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
  - The trial will emphasize risk minimization for participants as the protocol is developed
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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CHRISTINE P NGUYEN  
08/18/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology Review (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology Memo**

Date: 18 August 2015

Deputy Director: CDR David Moeny, RPH, MPH, USPHS  
Division of Epidemiology II

To: Dr. Hylton Joffe, Director  
Dr. Christine Nguyen, Deputy Director for Safety  
Division of Bone, Reproductive and Urologic Products

Subject: Recommendations regarding required post-marketing safety studies to detect a possible association between flibanserin and risk of breast cancer

Drug Name: Addyi (flibanserin)

NDA: 022526

The purpose of this memo is to document alignment between the Division of Epidemiology-II and the Division of Bone, Reproductive, and Urologic Products regarding the feasibility and potential path forward for required post-marketing safety studies to assess possible breast cancer risk associated with flibanserin use.

Based on Dr. Falconer's review, the proposed study using claims data will likely not adequately address the outstanding question of whether flibanserin use is associated with an increased risk of breast cancer in women). Dr. Falconer raises appropriate limitations as to why insurance-based data alone cannot address safety questions relating to cancer in the post-marketing setting. These include insufficient follow up time to assess an outcome with a likely long latency, the inability to validate outcomes, indications and covariates with linkage to cancer registry information rather than relying on unvalidated International Classification of Diseases (ICD) codes, and challenges in identifying appropriate comparator groups based on only claims data. Further, given that the signal arose from one sex in one animal species, she notes that there is no postulated biologic plausibility (unclear whether flibanserin acts as a cancer promotor or as an initiator) as the nonclinical data have uncertain relevance to humans.

Recently, the FDA hosted a public meeting to discuss data sources and methods to assess the risk of cancer outcomes associated with drug therapy in the post-approval setting. The following link provides the background package, agenda, transcripts and slides for the program:

<http://www.fda.gov/Drugs/NewsEvents/ucm401452.htm>. Many of the issues identified in this memo were discussed at that meeting, including specific information regarding the difficulties with evaluating cancer as an outcome and the limitations of claims data as a data source, especially in the US.

In addition to Dr. Falconer's concerns, there is the additional uncertainty relating to prescription coverage. Reimbursement for flibanserin prescriptions might vary among insurers, and should some insurance companies decline to cover flibanserin, it may not be possible to identify sufficient numbers of women exposed to flibanserin using insurance-based claims data. Even if coverage is widespread, the US healthcare systems that are more equipped to study a cancer outcome by linking to cancer registries (e.g. HMOs), also have limited numbers of enrollees, strict formularies, might be slow to provide coverage for flibanserin, or might require prior authorization to restrict usage of the product to certain populations. These factors would impact study feasibility and would limit generalizability. An additional factor that might limit the uptake of flibanserin after launch is the Risk Evaluation and Mitigation Strategy with Elements to Assure Safe Use (REMS with ETASU) that will be required.

DEPI has considered a number of sources of data and concludes that claims databases in the US are unlikely to be helpful. As one example, Medicare is a claims-based data resource often used for studies requiring long-term follow-up, and has been linked with cancer registry data. However, since the indicated population for flibanserin is pre-menopausal women, Medicare data are unlikely to be useful. Furthermore, it would be difficult to identify exposure as women transition from other insurance plans to Medicare. DEPI has also considered utilizing data from other countries, such as the long-term population-based ("cradle to grave") databases in Sweden and Denmark have frequently been used for cancer studies, but they are unlikely to be useful since flibanserin is not approved in any other country at this time.

For all of these reasons, DEPI recommends that any required post-marketing study to assess breast cancer risk be carefully designed to overcome these considerable challenges. However, it is highly unlikely that any US claims-based data system could be used to conduct such a study at this time.

Given the difficulties with US claims-based data studies to evaluate the risk of breast cancer, other options could include conducting a prospective epidemiologic study using primary data collection that captures both real-time exposure and cancer outcomes, as well as necessary confounders (medical history, and lifestyle factors such as obesity, smoking and alcohol use). However, such a study will also present substantial challenges such as the unknown uptake of the drug product, the identification of a suitable comparator cohort, and the expense and complexity of the effort needed for patient recruitment and long-term follow-up of large numbers of young women. DEPI anticipates that the effort and costs involved with conducting such a large, long-term prospective epidemiologic study would likely approach that of a clinical trial. Case-control studies would face similar and additional limitations.

DEPI-II concludes that a claims based study will likely be infeasible due to the potential limited uptake, uncertain insurance coverage for flibanserin, and the inability to validate outcomes and important covariates. Due to the lack of information on a mechanism for flibanserin associated breast cancer, the uncertain applicability of the mouse study to humans, and the probable long latency before cancer development, it is unclear whether the strength of the breast cancer signal supports the level of effort that would be required to conduct a prospective observational study. Further, the potentially low utilization of flibanserin due to uncertain insurance coverage and the impact of the REMS might limit uptake and study feasibility. Therefore, DEPI-II recommends closely monitoring available post-marketing surveillance and medical literature for additional evidence of a breast cancer safety signal. If FDA detects such evidence of new safety information of breast cancer in humans, DEPI-II recommends requiring the Sponsor to conduct an appropriately designed and powered post-marketing safety study to assess the risk of breast cancer associated with flibanserin use.

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/s/  
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DAVID G MOENY  
08/18/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** 08/17/2015  
**Requesting Office or Division:** Division of Bone, Reproductive, and Urologic Products (DBRUP)  
**Application Type and Number:** NDA 22526  
**Product Name and Strength:** Addyi (flibanserin) Tablets 100 mg  
**Submission Date:** 08/14/2015  
**Applicant/Sponsor Name:** Sprout Pharmaceuticals, Inc.  
**OSE RCM #:** 2015-48806-1  
**DMEPA Primary Reviewer:** Walter Fava RPh., MEd., Safety Evaluator  
**DMEPA Team Leader:** Danielle Harris, PharmD., BCPS

---

#### 1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised carton labeling and container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, and to comments communicated via email on August 12 and August 13, 2015.<sup>1</sup>

#### 2 CONCLUSIONS

The revised carton labeling and container labels are acceptable from a medication error perspective.

---

<sup>1</sup> Fava, W. Label and Labeling Review for Addyi (NDA 22526). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 10. 7 p. OSE RCM No.: 2015-425.

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/s/  
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WALTER L FAVA  
08/17/2015

IRENE Z CHAN on behalf of DANIELLE M HARRIS  
08/17/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 11, 2015

To: Hylton Joffe, MD  
Director  
**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Lynn Panholzer, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ADDYI (flibanserin)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 022526

Applicant: Sprout Pharmaceuticals, Inc.

## 1 INTRODUCTION

On February 14, 2015, Sprout Pharmaceuticals, Inc. submitted for the Agency's review a resubmission of New Drug Application (NDA) 022526 for ADDYI (flibanserin) Tablets. This resubmission is in response to the Complete Response letter issued by the Agency on September 27, 2013. Sprout Pharmaceuticals, Inc. initially submitted NDA 022526 for ADDYI (flibanserin) Tablets on October 27, 2009. A Complete Response letter was issued by the Agency on August 27, 2010 and a resubmission of the NDA was filed by Sprout Pharmaceuticals, Inc. on March 29, 2013. The proposed indication for ADDYI (flibanserin) Tablets is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on February 24, 2015 and February 23, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ADDYI (flibanserin) Tablets.

## 2 MATERIAL REVIEWED

- Draft ADDYI (flibanserin) tablets MG submitted on February 14, 2015, revised by the Review Division throughout the review cycle and received by DMPP on July 17, 2015.
- Draft ADDYI (flibanserin) tablets MG submitted on February 14, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on August 9, 2015.
- Draft ADDYI (flibanserin) tablets Prescribing Information (PI) submitted on February 14, 2015, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on August 7, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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KAREN M DOWDY  
08/11/2015

LYNN M PANHOLZER  
08/11/2015

MARCIA B WILLIAMS  
08/11/2015

LASHAWN M GRIFFITHS  
08/11/2015

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** August 5, 2015

**To:** Jennifer Mercier, CPMS  
Division of Bone, Reproductive and Urologic Products (DBRUP)

**From:** Lynn Panholzer, Pharm.D.  
Office of Prescription Drug Promotion (OPDP)

**Subject:** ADDYI (flibanserin) Tablets  
NDA 022526  
Labeling Consult Review

---

### Background

This consult review is in response to DBRUP's February 23, 2015, request for OPDP's review of the draft package insert (PI), carton/container labeling, and Medication Guide for ADDYI (flibanserin) Tablets. OPDP reviewed the version of the draft PI available in SharePoint on August 4, 2015. Our comments on the PI are included directly on the attached copy of the labeling. We reviewed the draft carton and container labels submitted by the applicant on February 14, 2015, available in the EDR. We have no comments on the carton/container labels (attached for reference). Our review of the Medication Guide will be conducted jointly with the Division of Medical Policy Programs and filed under separate cover.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Lynn Panholzer at 301-796-0616 or [lynn.panholzer@fda.hhs.gov](mailto:lynn.panholzer@fda.hhs.gov).

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/s/  
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LYNN M PANHOLZER  
08/05/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology: Review of Study Proposal**

Date: July 24, 2015

Reviewer: Monique Falconer, MD, MS  
Division of Epidemiology II

Team Leader Jie Li, PhD  
Division of Epidemiology II

Deputy Division Director CDR David Moeny, MPH, RPh, USPHS  
Division of Epidemiology II

Subject Surveillance and evaluation of a preclinical breast cancer signal

Drug Name(s): Flibanserin

Application Number: NDA 22526

Submission Number: eCTD 0065 (SDN 67)

Applicant/sponsor: Sprout Pharmaceuticals

OSE RCM #: 2013-861

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MONIQUE FALCONER  
07/24/2015

JIE J LI  
07/24/2015

DAVID G MOENY  
07/24/2015



Division of Pediatric and Maternal Health  
Office of New Drugs  
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**DIVISION OF PEDIATRIC AND MATERNAL HEALTH,  
MATERNAL HEALTH TEAM REVIEW**

**Date:** 07-23-2015

**From:** Leyla Sahin, M.D.  
Medical Officer,  
Division of Pediatric and Maternal Health, Maternal Health Team

**Through:** Lynne P Yao, M.D.  
Acting Director,  
Division of Pediatric and Maternal Health (DPMH)

**To:** Division of Bone, Reproductive and Urologic Products

**Drug:** Addyi (flibanserin) NDA 022526

**Applicant:** Sprout Pharmaceuticals

**Subject:** Post-Marketing Requirement (PMR) to assess safety in pregnancy

**Materials Reviewed:**

- Advisory committee (AC) briefing document
- Applicant's proposed labeling
- Division of Risk Management's draft review of applicant's proposed Risk Evaluation and Mitigation Strategy

**Consult Question:** Please provide guidance regarding a pregnancy registry PMR

## INTRODUCTION

On February 14, 2015, Sprout Pharmaceuticals submitted an original new drug application (NDA) for Addyi (flibanserin), a new molecular entity for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested on July 14, 2015, that the Division of Pediatric and Maternal Health (DPMH) and the Division of Epidemiology II assist in issuing a Post-Marketing Requirement (PMR) to assess outcomes following exposure in pregnant women.

## BACKGROUND

Addyi (flibanserin) is an agonist at the 5 hydroxytryptamine (5HT) type 1A receptor and an antagonist at the 5HT type 2A receptor. Flibanserin's mechanism of action in the treatment of HSDD is unknown. Flibanserin is not approved in any country; it is the first in class to treat this condition.

Addyi will be available only through a Risk Evaluation and Mitigation Strategy (REMS) program that includes a restricted distribution program due to the risks of hypotension and syncope caused by an interaction between Addyi and alcohol.

Addyi's Pregnancy subsection of draft labeling includes animal reproductive toxicity data that showed no teratogenicity in rats and rabbits administered 15 and 4 times, respectively, the clinical exposure based on AUC. There were increased resorptions and decreased fetal weight in rabbits administered 8 times the clinical exposure based on AUC.

The following pregnancy outcomes occurred in the flibanserin clinical development program:<sup>1</sup>

	Placebo	Flibanserin
Total number of subjects	1530	4804
No. of pregnancies	21	46
Live births	13	26
Congenital malformation/anomaly	0	0
Spontaneous abortion	0	5
Therapeutic abortion	4	5
Unknown	4	10

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<sup>1</sup> Personal communication from Dr. Christine Nguyen, DBRUP Deputy Director for Safety

## DISCUSSION AND CONCLUSIONS

Because Addyi's indicated population is females of reproductive potential, and half of all pregnancies are unintended, it is likely that exposures during pregnancy will occur. In addition, because pregnant women were excluded during the clinical development program, and very limited outcome data are available on the women who became pregnant in the trials, safety data regarding exposure during pregnancy are lacking. Therefore, post-approval studies to assess outcomes following exposure in pregnancy are important to help characterize flibanserin's safety in pregnancy.

A pregnancy exposure registry is the Agency's preferred method for post-marketing data collection in pregnant women due to the prospective method of data collection, which minimizes the biases of retrospective data collection.<sup>2</sup> In addition, pregnancy registries allow collection of patient level detailed data on potential confounders. However pregnancy registries are limited by their lack of power to assess specific (rare) birth defects and the long duration that may be needed to accumulate data. As discussed by the expert panel at the 2014 FDA public meeting on pregnancy registries and other post-approval safety studies in pregnant women, combining two study methods addresses limitations inherent to each study design.<sup>3</sup> It is possible that Addyi's restricted distribution may affect its uptake following marketing approval, and result in low enrollment in a pregnancy registry. Combining a pregnancy registry with a complementary study with a different study design that relies on large databases may address the potential low enrollment in a registry. Examples of complementary study designs include a case control study or a retrospective cohort study using claims or electronic medical record data.

## RECOMMENDATIONS FOR THE APPLICANT

DPMH recommends the following PMR language:

FDA has determined that you are required to conduct the following post-approval safety studies in pregnant women:

*“A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Addyi during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.*”

*And*

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<sup>2</sup> FDA Guidance for Industry Establishing Pregnancy Exposure Registries

<sup>3</sup> FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>

*An additional study that uses a different study design (for example a case control study or a retrospective cohort study using claims or electronic medical record data) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to Addyi during pregnancy compared to an unexposed control population.*

*Collect information to include, but not limited to, the following data elements (to the extent possible):*

- *Age, demographics, body mass index*
- *Exposure to smoking, alcohol, drugs*
- *Medical history, concomitant medications, prenatal vitamins, obstetrical history*
- *Current pregnancy: date of last menstrual period/gestational dating, prenatal tests and ultrasound results; pregnancy status*
- *Flibanserin exposure data (timing of exposure in pregnancy, dose, duration)*

*For guidance on how to establish a pregnancy exposure registry, the applicant should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>. For information on complementary study methods, the applicant should review the FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>.*

*Draft study protocols should be submitted three months after product approval.”*

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LEYLA SAHIN  
07/23/2015

LYNNE P YAO  
07/24/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology: Review of Study Proposal**

Date: July 17, 2015

Reviewer(s): Monique Falconer, MD, MS  
Division of Epidemiology II

Team Leader: Jie Li, PhD  
Division of Epidemiology II

Deputy Division Director: CDR David Moeny, MPH, RPh., USPHS  
Division of Epidemiology II

Subject: Appendicitis and Flibanserin Use

Drug Name(s): Flibanserin

Application Number: NDA 22526

Submission Number: eCTD 0065 (SDN 67)

Applicant/sponsor: Sprout Pharmaceuticals

OSE RCM #: 2013-861

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MONIQUE FALCONER  
07/17/2015

JIE J LI  
07/17/2015

DAVID G MOENY  
07/17/2015



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF NEUROLOGY PRODUCTS**

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**CONSULT M E M O R A N D U M**

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DATE: March 9, 2015

TO: Jennifer Mercier, Bone, Reproductive and Urologic Products

THROUGH: Billy Dunn, MD, Director, Division of Neurology Products

FROM: Ronald Farkas, MD, PhD, Clinical Team Leader, Division of Neurology Products

RE: Flibanserin, NDA 22526

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## **1. Background**

The Division of Bone, Reproductive and Urologic Products (DBRUP) noted the following background information about flibanserin in the consult request to the Division of Neurology Products (DNP):

Flibanserin is a 5-HT<sub>1A</sub> receptor agonist and 5-HT<sub>2A</sub> receptor antagonist being developed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. It is a new molecular entity that has undergone two NDA review cycles and a formal dispute resolution request (FDRR). With the Complete Response action taken in September 2013, DBRUP concluded that the modest treatment responses shown with flibanserin were not adequate to offset substantial safety concerns that have been identified. The long half-life of flibanserin, combined with the recommended dosing at bedtime, raises concerns about next-day somnolence and sedation, which may impair activities requiring mental alertness, such as driving. DBRUP recommended that a complete response application include a driving study to assess next-day impairment. DNP provided recommendations on the design of the driving impairment study in a memorandum of consultation to DBRUP dated July 22, 2014. On February 18, 2015, the sponsor submitted a response to the complete

response of September, 2013. Included in the new submission is the report of the recommended Phase I study assessing the next-day residual effects of flibanserin on simulated driving performance in normal premenopausal female volunteers (study SPR-14-01).

DBRUP's consult request is as follows:

Please review study SPR-14-01, "A Phase I, Randomized Double-Blind, placebo-controlled, 4-period, cross-over study assessing the next day residual effects of flibanserin on simulated driving performance in normal pre-menopausal female volunteers."

1. Do you believe that the study adequately assess the effects of flibanserin on next-day impairment?
2. Do you concur with the sponsor's conclusion that flibanserin has no adverse effects on next-day performance?
3. Do you agree that the study supports the notion that concomitant use of hormonal contraceptives with flibanserin does not exacerbate next-day impairment?
4. Based on the study findings, do you recommend any specific labeling language regarding driving while using flibanserin?

## 2. Driving Study Protocol

Study SPR-14-01 is titled '*A Phase I, Randomized, Double-Blind, Placebo-Controlled, 4-Period, Cross-Over Study Assessing the Next-Day Residual Effects of Flibanserin on Simulated Driving Performance in Normal Premenopausal Female Volunteers.*'

An initial draft of the study protocol was submitted to FDA for review and prior to being conducted the final protocol was deemed by FDA to have adequately incorporated recommendations.

As summarized by the sponsor, the primary objective of the study was to determine the next-day residual effects of acute and steady-state nighttime dosing of flibanserin 100 mg and the acute effect of a suprathreshold dose of flibanserin (200 mg) compared to placebo and positive control (zopiclone 7.5 mg) on simulated driving performance in healthy premenopausal female subjects as measured by standard deviation of lateral position (SDLP) using a driving simulator. Secondary endpoints included other measures of simulated driving performance (e.g., speed deviation, lane exceedance, lane position, speed control, cornering, collisions, and divided attention), Symbol Digit Coding (SDC) test, and self-report measures (i.e., Karolinska Sleepiness Scale [KSS], Visual Analog Scales addressing motivation and performance, and if the subject felt safe to drive).

The study was placebo-controlled with a full 4-period crossover design in which each subject completed each of the 4 treatments, as follows:

- Treatment A: flibanserin 100 mg + zopiclone placebo, night 1; flibanserin 100 mg only on nights 2 – 6; flibanserin 100 mg + flibanserin placebo + zopiclone placebo on night 7
- Treatment B: zopiclone 7.5 mg + flibanserin placebo, night 1; flibanserin placebo only on nights 2 – 6; flibanserin placebo (2) + zopiclone 7.5 mg on night 7
- Treatment C: zopiclone placebo + flibanserin placebo, night 1; flibanserin placebo only on nights 2 – 6; flibanserin placebo (2) + zopiclone placebo on night 7
- Treatment D: flibanserin 100 mg + zopiclone placebo, night 1; flibanserin 100 mg only on nights 2 – 6; flibanserin 100 mg (2) + zopiclone placebo on night 7

Study drug was administered by site staff on the evening of Days 1 and 7. Subjects self-administered drug at home at bedtime on Days 2 – 6.

Blood samples for flibanserin levels were collected on the first and last days of each treatment arm, pre-dosing and 8 hours after dosing.

### 3. Results

#### Enrolled subjects

Eighty-three healthy adult female subjects were enrolled, and 72 completed the four study periods. Mean age was 32 years, with a range of 19-49 years.

The geometric mean plasma concentrations of flibanserin at ~8.25 hours after the last dose were 95 ng/mL and 190 ng/mL for the 100 mg and 200 mg qhs treatments, respectively. Thirty-three of the subjects were taking concomitant hormonal contraceptives, which increase flibanserin exposure: plasma concentrations for the hormonal contraception users vs. non-users were 26% higher the morning following the 100 mg dose, and 39% higher following the 200 mg dose.

#### Primary Endpoint, SDLP

SDLP was significantly increased by the positive control, zopiclone 7.5 mg, on both Day 1 (by 3.1 cm) and Day 8 (by 3.5 cm).

*Reviewer comment: This is similar to findings in other studies using zopiclone as a positive control, and establishes assay sensitivity.*

Flibanserin decreased mean SDLP vs. placebo, for both doses, and after both acute and chronic dosing: 100 mg acute dosing, -2.5 cm; 100 mg chronic dosing, -1.8 cm; acute 200 mg dosing, -1.4 cm. SDLP findings were similar between hormonal contraception users and non-users. Symmetry analysis gave similar results.

There was no apparent relationship between morning flibanserin blood levels and change in SDLP.

*Reviewer comment: There is no evidence of an adverse effect of flibanserin on ability to maintain lane position as measured by SDLP, the prespecified primary endpoint.*

### Secondary driving performance endpoints

There was either no change or improvement in most secondary driving performance endpoints, including lane exceedences and off-road collisions. Vehicle speed, particularly cornering speed, appeared to be decreased by flibanserin. Secondary driving performance endpoints were generally worsened by zopiclone.

*Reviewer comment: The decrease in speed was small and appears unlikely to be clinically meaningful. However, the decrease in speed may complicate interpretation of the decrease in SDLP and some other measures of driving performance.*

### Other psychomotor tests

Other tests of psychomotor function such as divided attention, reaction time, and digit symbol coding were not adversely affected by flibanserin, but were adversely affected by zopiclone.

### Subjective measures of alertness and driving ability

After acute dosing, more patients taking flibanserin than placebo reported feeling “not alert” prior to the driving test, as assessed by the KSS:

On Day 2, prior to the drive, 43% of the subjects taking zopiclone, 38% of subjects taking flibanserin 100 mg, and 26% of the subjects taking placebo reported KSS scores in the “not alert” range. Paired comparisons showed that the self-reported sleepiness ratings were higher pre-drive for both flibanserin 100 mg ( $p=0.0290$ ) and for zopiclone ( $p=0.0093$ ) compared to placebo.

After chronic dosing, there was a trend to greater feelings of “not alert” in the 200 mg flibanserin arm:

On Day 8, 38% of those who had received zopiclone, 35% of those subjects who had received flibanserin 100 mg, 43% of those who had received flibanserin 200 mg, and 35% of those who had received placebo reported KSS scores in the “not alert” range.

There was also a trend on day 8 towards a larger percentage of patients feeling unsafe to drive the morning after flibanserin.

In contrast, on Day 2 subjects self-rated their driving performance as better after 100 mg flibanserin vs. placebo (nominal  $p = 0.04$ ). On day 8, self-assessment of driving performance after 200 mg flibanserin was similar to placebo.

*Reviewer comment: Self-perception of sleepiness is not a reliable indicator of the likelihood of objective impairment of driving abilities, and the increase in subjective sleepiness from flibanserin, therefore, is not a reliable indicator of a safety risk. The increase in subjective sleepiness from flibanserin may, however, have affected the way patients performed the driving simulation tests, complicating interpretation of the decrease in SDLP and of some other measures observed following flibanserin dosing. For example, patient effort or caution might have been increased by flibanserin due to subjective feelings of sleepiness.*

### Spontaneous adverse events

Seemingly in contrast to the KSS findings, in which patients reported greater subjective sleepiness after flibanserin, there was no increase in reports of somnolence as an adverse event after flibanserin. However, there were a number of apparently dose-related adverse effects of flibanserin, including nausea, reported by almost a third of patients after 200 mg flibanserin, palpitations, abdominal pain, and dizziness. A number of other adverse events were higher for the flibanserin vs. placebo arms but did not show as strong a relationship to dose, including headache, which was reported by about a quarter of patients after both flibanserin 100 mg and 200 mg.

*Reviewer comment: Some types of adverse events, such as sudden loss of consciousness, would, on face, be of concern for driving safety even if other psychomotor skills were not adversely affected. However, the types of symptoms experienced by subjects after flibanserin (e.g. nausea, headache) do not clearly present this type of risk. The adverse events associated with flibanserin may, however, have led to differences in conscious driving behavior that complicate interpretation of the decrease (improvement) in SDLP and some other secondary measures of driving performance following flibanserin dosing.*

### Statistical Issues

Dr. Tristan Massie from the Office of Biostatistics conducted an independent review of key driving endpoints, which is included in in the Appendix to this document.

In brief, his review raised the following issues:

- The number of dropouts was not large, but crossover studies are particularly sensitive to dropouts, decreasing confidence in the findings. However, analyses of first-period findings was reassuring, as was worst-case imputation of missing data
- There was unequal randomization of oral contraceptive users across sequences, which may have decreased ability to find an effect of oral contraceptives. However, there was no compelling evidence of a sequence effect, which is reassuring, although other sources of bias also could have been present.

*Reviewer comment: Dr. Massie's overall conclusion was that the study was adequately robust.*

### Discussion and conclusions

1. Do you believe that the study adequately assess the effects of flibanserin on next-day impairment?

*DNP Response: Yes. Study design and conduct were adequate, with assay sensitivity confirmed by zopiclone. The primary and key secondary endpoints did not reveal evidence of impairment of next-day driving ability after flibanserin. Interpretation of findings is complicated by subjective effects of flibanserin, including an increase in sleepiness (on KSS) and a number of adverse effects such as nausea and dizziness, all of which may have had an effect on the way subjects performed the tests, e.g. potentially increasing effort or cautiousness. However, the shift in the primary and key secondary endpoints was strongly in the direction opposite increased risk from flibanserin, suggesting that the results are robust despite these potentially confounding factors.*

2. Do you concur with the sponsor's conclusion that flibanserin has no adverse effects on next-day performance?

*DNP Response: Study SPR-14-01 did not identify adverse effects on next-day driving performance but (as is true for most, if not all, safety studies) broader conclusions about absence of potential adverse effects on next day performance would not be supported. Importantly, the study was designed primarily to identify impairment from somnolence, while flibanserin has other adverse effects unrelated to somnolence that might adversely affect driving performance, but that might not have been detected.*

3. Do you agree that the study supports the notion that concomitant use of hormonal contraceptives with flibanserin does not exacerbate next-day impairment?

*DNP response: The study did not show impairment of driving performance at the higher than average flibanserin exposures than can result from concomitant use of flibanserin with hormonal contraceptives. Post-hoc examination of dose-response data similarly did not suggest a correlation between higher exposure and driving impairment.*

4. Based on the study findings, do you recommend any specific labeling language regarding driving while using flibanserin?

*The proposed package insert describes the driving study results in section 14.2 Special Safety Studies. The proposed text is the following:*

*"In a (b) (4) study in (b) (4) following single and multiple doses of 100 mg once daily at bedtime or single doses of 200 mg at bedtime.*

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(b) (4)

*Reviewer Discussion: Labeling should indicate that the driving study was conducted the morning after bedtime dosing, and should include clear warnings about psychomotor impairment in the hours following dosing e.g. as were identified in previous studies such as Boehringer Ingelheim Trial No. 511.3, which showed slowing of response time of a magnitude likely to be clinically meaningful for driving for a duration at least 3.5 hours after dosing, and possibly longer (as discussed in the DNP review of July 2013, this study lacked key design features such as a positive control and therefore was not capable of accurately characterizing the duration of risk after dosing).*

### Statistical Appendix:

Of the 83 subjects randomized in the simulated-driving study, 72 (86.7%) completed the four period crossover and follow up Visit.

A higher proportion, 60% or 12/20, took oral contraceptives in the A-D-B-C (100-200-Zop-Pla) sequence as compared to just 30% (6/20), 37% (7/19) and 37% (7/19) for the other sequences. This difference is not nominally significant unless the latter three sequences are combined, which is probably not justified (although the difference in proportions is somewhat striking). This issue may make the assessment of whether there are any treatment differences between oral contraceptive users and non-users less conclusive.

Other demographics seem balanced between the randomized sequence groups.

The following table shows the frequencies of actually observed sequences, i.e., completed and missing treatment periods for each subject (among those providing SDLP data on day 8 of at least one period, where any period with no SDLP recorded has the treatment letter replaced with a '.' to indicate it is missing).

Observed Sequences with SDLP data (Day 8)

Assigned Sequence	Completed Sequence	N/Frequency	Percent	Cumulative Number of Subjects	Cumulative Percent
A-D-B-C	.-D-B-C	1	1.28	1	1.28
	A-.-.-	1	1.28	2	2.56
	A-D-B-.	2	2.56	4	5.13
	A-D-B-C	16	20.51	20	25.64
B-A-C-D	B-.-.-	1	1.28	21	26.92
	B-A-.-	1	1.28	22	28.21
	B-A-C-D	18	23.08	40	51.28
C-B-D-A	C-B-.-	1	1.28	41	52.56
	C-B-D-A	18	23.08	59	75.64
D-C-A-B	D-C-A-B	19	24.36	78	100.00

Note: A: Flibanserin 100 mg ; B: Zopiclone 7.5 mg ; C: Placebo; D: Flibanserin 200 mg (night 7)

The primary analysis of mean SDLP was done using a mixed effects model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence, a variance-component covariance structure, and the Kenward-Roger method for the degrees of freedom.

The conclusions of the primary analysis could be biased due to dropouts because while they are few in number the possible impact of missing data is greater in a crossover study. In case there are period or carryover effects interpretation of the results becomes very difficult if the analyzed sequences are not completely balanced in terms of missing data and demographics/baseline characteristics.

For a first period only analysis of the SDLP (day 8) nothing was significant compared to placebo (table below) but of course this, while easier to interpret, may be too conservative and underpowered. The same first period only analysis done using day 2 did detect a zopiclone effect.

#### First Period Analysis of SDLP (Day 8)

First Period Assignment	N	Mean SDLP	Diff from Placebo (S.E.)	Comparison to Placebo p-value
A/Flib 100	19	29.6	1.1 (2.0)	0.5696
D/Flib 200	19	30.1	0.6 (2.0)	0.7473
C/Pla	19	30.7	N/A	N/A
B/Zop	20	33.2	2.5 (2.0)	0.2152

As a sensitivity analysis for missing data, if one imputes the worst observed SDLP value of 66 for those missing some periods regardless of the assigned treatment then the zopiclone mean comparison just loses significance compared to placebo 1.97 (-0.0356, 3.985),  $p=0.0555$ . However, the symmetry analysis using the threshold of 2.5 (or 4.4) is still highly significant for zopiclone after that imputation as is the day 2 mean SDLP analysis and the Flibanserin symmetry analyses are similar to those for the observed (non-imputed) data results (both day 2 and day 8).

In terms of the average speed endpoint when analyzing only the first period on day 7 Flibanserin 100 mg was close to nominal significance compared to placebo, LSMean: 26.18 vs. 26.41  $p=0.0601$ , thus supporting the 4 period analysis result for this endpoint.

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RONALD H FARKAS  
07/01/2015

WILLIAM H Dunn  
07/01/2015



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

**Date:** June 24, 2015

**To:** Hylton Joffe, M.D., Director  
Division of Reproductive and Urologic Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** NDA review of abuse-related data  
Flibanserin (Addyi)  
NDA 22-526  
Indication: Treatment of hypoactive sexual desire  
disorder in premenopausal women  
Sponsor: Sprout Pharmaceuticals, Inc.

**Materials reviewed:** Abuse-related adverse events in NDA

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**1. Background**

This memorandum responds to a consult request by the Division of Reproductive and Urology Products (DRUP) to evaluate abuse-related information provided as part of the third re-submission of an NDA for flibanserin (NDA 22-526; Addyi). Flibanserin is a new molecular entity with 5-HT<sub>1A</sub> agonist/5-HT<sub>2A</sub> antagonist properties. It is also a ligand at 5HT<sub>2B</sub>, 5HT<sub>2C</sub> and dopamine D4 receptors, although no information has been provided to determine functionality at these sites. The Sponsor for this drug is Sprout Pharmaceuticals, Inc., which licensed flibanserin from Boehringer-Ingelheim for the

indication of hypoactive sexual desire disorder in premenopausal women. Flibanserin is not currently marketed in any country.

During the second submission of the NDA for flibanserin in 2012, the Sponsor submitted a human abuse potential study with flibanserin (“A Single-Dose, Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Relative Abuse Potential of Flibanserin in Healthy Recreational Poly-Drug Users”; Study #SPR-12-05, 3/29/13). In the CSS review of this study (DARRTS, August 23, 2013, Dr. Katherine Bonson), we concluded that the study was invalid for a number of methodological and outcome issues, including that the positive control did not statistically differentiate from placebo.

However, on September 26, 2013, CSS communicated to the Division that a new human abuse potential study would not be necessary, given that a re-analysis of the adverse event (AE) profile from Phase 1, 2 and 3 clinical studies was not suggestive of abuse potential (DARRTS, Dr. Katherine Bonson). The lack of an abuse potential signal in both preclinical and clinical studies was considered to mitigate CSS concerns during the first NDA review regarding the abuse potential of flibanserin. The conclusion that another human abuse potential study would not be required was conveyed to the Sponsor in the September 27, 2013, Complete Response letter.

Thus, in the present NDA submission, the Sponsor did not submit a new human abuse potential study. Therefore, the only data that CSS reviewed in the present NDA submission were AEs in the new clinical study conducted with flibanserin.

## 2. Conclusions

In the present NDA, CSS evaluated central nervous system (CNS)-related AEs for signals that flibanserin was inducing responses that are associated with abuse potential. When CNS depression terms (somnolence, sedation and fatigue) were summed, there was an incidence of 20.6% for patients. Conversely, there was a 4.9% incidence of insomnia, suggesting CNS stimulation in some patients. Notably for an abuse potential assessment, however, there were no euphoria-related AEs observed during this clinical study. This pattern of AEs is similar to those reported in the two previous NDA submissions.

Thus, while flibanserin produces both sedative and stimulant effects, in the absence of a euphoria signal, these responses are not indicative of abuse potential.

## 3. Recommendations

Given that there are no data demonstrating that flibanserin has abuse potential, CSS recommends the following:

- a) Flibanserin not be recommended for scheduling under the Controlled Substances Act.

- b)  (b) (4)

#### 4. Discussion

In the previous two submissions of the NDA for flibanserin, CSS determined that there were no abuse-related adverse events in Phase 1 and in Phase 2/3 clinical studies.

In the current NDA submission, Dr. Olivia Easley evaluated the most common adverse events that were observed in an additional Phase 3 clinical efficacy and safety study conducted by the Sponsor in support of their claim that flibanserin can be approved for the treatment of hypoactive sexual desire disorder in premenopausal women (as reported in the document “Clinical Background Document for the Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee”, June 4, 2015). As shown in Table 1 below, there were numerous CNS-related adverse events reported during this study.

**Table 1: Most common treatment-emergent adverse events, phase 3, placebo-controlled HSDD trials in pre-menopausal women**

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

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

When CNS depression terms (somnolence, sedation and fatigue) were summed, there was an incidence of 20.6% for these AEs (319 of 1543 patients). Conversely, there was a 4.9% incidence of insomnia (75 of 1543 patients). There was also an 11.4% incidence of dizziness (176 of 1543 patients).

Notably for an abuse potential assessment, however, there were no euphoria-related AEs observed during this clinical study. This pattern is similar to the responses reported in the two previous NDA submissions.

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KATHERINE R BONSON  
06/24/2015

SILVIA N CALDERON  
06/24/2015

MICHAEL KLEIN  
06/24/2015

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### **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** June 10, 2015

**Requesting Office or Division:** Division of Bone, Reproductive and Urologic Products (DBRUP)

**Application Type and Number:** NDA 22526

**Product Name and Strength:** Addyi (flibanserin) Tablets 100 mg

**Product Type:** Single Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Sprout Pharmaceuticals Inc.

**Submission Date:** February 12, 2015

**OSE RCM #:** 2015-425

**DMEPA Primary Reviewer:** Walter Fava, RPh., MEd., Safety Evaluator

**DMEPA Team Leader:** Danielle Harris, PharmD., BCPS

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## 1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the submitted container labels, carton labeling and prescribing information for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review identified areas in the container and carton labeling that could be improved from a medication error perspective. Specifically we are concerned about the risk of a prescription for “Addyi 100 mg” being incorrectly interpreted as “Addyi 1100 mg”. Inclusion of more information for the usual dosage statement on the labels and labeling, and using a darker font color for the strength statement to increase its prominence will reinforce the correct dose and decrease the risk of dosing errors. We also note the absence of the “Rx Only” statement on the professional sample labeling.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling for Addyi may be improved to promote the safe use of the product and provide recommendations in Section 4.1

#### **4.1 RECOMMENDATIONS FOR SPROUT PHARMACEUTICALS INC.**

We recommend the following be implemented prior to approval of this NDA:

##### **A. Container Label and Carton Labeling**

1. Revise the strength statement, '100 mg' to a darker font to increase its prominence.
2. Revise the dosage statement on the side panels of the container labels and carton labeling to read: 100 mg once daily at bedtime. Including this information on all packaging, will re-inforce the correct dosing for this product and help minimize the risk of written prescriptions for Addyi 100 mg tablets of being incorrectly interpreted as 'Addyi 1100 mg tablets'.
3. Include the 'Rx Only' statement on all professional sample labels and labeling.
4. Provide the NDC number on the revised labels and labeling as soon as it is available and include it on the revised labels and labeling with your next label and labeling submission.

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Addyi that Sprout Pharmaceuticals Inc. submitted on February 18, 2015.

<b>Table 2. Relevant Product Information for Addyi</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	flibanserin
<b>Indication</b>	Hypoactive sexual desire disorder (HSDD) in premenopausal women.
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablet
<b>Strength</b>	100 mg
<b>Dose and Frequency</b>	One tablet once daily at bedtime
<b>How Supplied/Container Closure</b>	Bottles of 30 tablets
<b>Storage</b>	25° (77°C); excursions permitted to 15°-30°C (59°-86°F)

**APPENDIX B. PREVIOUS DMEPA REVIEWS – N/A**

**APPENDIX C. HUMAN FACTORS STUDY - N/A**

**APPENDIX D. ISMP NEWSLETTERS – N/A**

**APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) N/A**

**APPENDIX F. N/A**

**APPENDIX G. LABELS AND LABELING**

**G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Addyi labels and labeling submitted by Sprout Pharmaceuticals Inc. on February 12, 2015.

- Container label
- Carton labeling
- Prescribing Information (no image)

**G.2 Label and Labeling Images**

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/IS) immediately following this page

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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WALTER L FAVA  
06/10/2015

DANIELLE M HARRIS  
06/10/2015

## STUDY ENDPOINT REVIEW

<b>STUDY ENDPOINTS TRACKING NUMBER IND/NDA/BLA NUMBER</b>	AT 2015-036 NDA 22526
<b>LETTER DATE/SUBMISSION NUMBER PDUFA GOAL DATE</b>	February 14, 2015 August 18, 2015 (AC Meeting planned for June 4, 2015)
<b>DATE OF CONSULT REQUEST</b>	February 20, 2015
<b>REVIEW DIVISION MEDICAL REVIEWER REVIEW DIVISION PM</b>	DBRUP Catherine Sewell and Olivia Easley Jennifer Mercier
<b>STUDY ENDPOINTS REVIEWER(S) ASSOCIATE DIRECTOR, STUDY ENDPOINTS (ACTING)</b>	Ashley Slagle Elektra Papadopoulos
<b>REVIEW COMPLETION DATE</b>	April 20, 2015
<b>ESTABLISHED NAME TRADE NAME APPLICANT</b>	Flibanserin N/A Sprout Pharmaceuticals, Inc.
<b>CLINICAL OUTCOME ASSESSMENT TYPE</b>	PROs
<b>ENDPOINT(S) CONCEPT(S)</b>	Satisfying sexual events; desire; distress
<b>MEASURE(S)</b>	Female Sexual Function Index (FSFI) desire domain; eDiary desire items; Satisfying Sexual Events eDiary; Female Sexual Distress Scale- revised (FSDS-R)
<b>INDICATION</b>	Hypoactive Sexual Desire Disorder (HSDD)
<b>INTENDED POPULATION(S)</b>	Premenopausal women with HSDD

## **A. EXECUTIVE SUMMARY**

This Study Endpoints review is provided as a response to a request for consultation by the Division of Bone, Reproductive, and Urologic Products (DBRUP) regarding NDA 22526. The applicant has used several patient-reported outcome (PRO) assessments as primary and secondary endpoints in clinical trials to evaluate treatment benefit of flibanserin in three clinical trials (511.71, 511.75, 511.147) of premenopausal women with hypoactive sexual desire disorder (HSDD). Note that the assessments used in 511.147 are the primary focus of this review, as 511.71 and 511.75 have already been reviewed during previous NDA cycles and an advisory committee asserted the findings from those studies did not provide an acceptable overall benefit/risk profile to support approval. The endpoints and assessments include:

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

The Division has consistently accepted and recommended the assessments of SSE using an eDiary and the assessment of desire using the FSDS-R item 13. The focus of this review is therefore primarily on the FSFI-SD. While the FSFI-SD used by the applicant may not be optimal, it may provide interpretable findings of efficacy if there is a reasonably large magnitude of effect for a particular product development program. However, given the very modest efficacy findings in the flibanserin program across all endpoints, we are concerned that limitations of the FSFI-SD outcome assessment used in this particular clinical trial context may have contributed to an observed treatment effect that may not represent clear evidence of treatment benefit.

We believe these concerns should be considered when interpreting efficacy findings and weighing those findings against the risks of the product. Specifically, key concerns that might be considered for discussion with the BRUPAC include:

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- The challenge of interpreting efficacy findings using the FSFI desire domain: this domain includes multi-barreled instructions making it unclear what is driving any change identified on the assessment (e.g., receptivity, sexual fantasies, and/or initiating sex). For example, if only one component (e.g., sexual fantasies) is actually improved in the women, but other components (e.g., wanting, initiating or feeling receptive to sex) have not improved, we could see a score change suggesting improvement, but it is unclear whether this represents true benefit. In addition, with a drug known to cause sedating effects, it is possible that receptivity due to sedation alone could be driving the modest score changes seen in the FSFI desire domain score. In light of this challenge with the validity of the measure (i.e., what in fact does a score change represent), and without a way to ensure key elements of desire that are important to women have in fact improved, we must be cautious in interpreting these findings of efficacy. Can we conclude the modest score changes on the FSFI desire domain represent meaningful benefit?
- There are concerns about concluding treatment benefit based on the response options in the FSFI. Is experiencing desire “all of the time” a true benefit, or might that represent a different concern to women?
- A 28-day recall period is used in the FSFI-SD. While it is possible that a longer recall period increases noise thus attenuating treatment effects, it is concerning that in studies 511.71 and 511.75, when a daily measure of desire was used, no significant improvements on desire were identified. It is possible that missing data with the daily assessment was the basis for this. However, the possibility exists that there was systematic bias introduced when the 28-day recall period was employed. For example, many women in qualitative research described their desire disorder in terms of how frequently they fought with or felt guilty about disappointing their partners about sexual activity. When recalling over time how bad their desire symptoms were, women may tend to anchor this in recalling experiences of fighting with or disappointing partners. If the drug product has an effect of minimizing patients’ concern with or memory of disagreements or guilt, there could be a systematic over-reporting of improvements on desire in the treatment arm with this longer recall period.
- Given the concerns above, and considering the anchor analyses using the PBE and PGI-I, what would the BRUPAC consider a meaningful amount of change on the FSFI and SSEs to conclude efficacy of the treatment?

Section C below provides suggested text for the AC background document, describing the outcome assessments used in Study 511.147.

## **B. BACKGROUND INFORMATION**

### Materials reviewed:

Previous NDA 22526 SEALD reviews and related submissions: AT 2013-060, AT 2014-201; Study Report for 511.147. No new information was provided for SEALD review in this 3<sup>rd</sup> cycle NDA review.

Background information:

The applicant submitted an NDA based on the findings from pivotal trials 511.71 and 511.75 previously, and received a Complete Response (CR) action in August 2010. An Advisory Committee meeting was held during this review cycle and the committee did not agree that the benefit/risk profile was acceptable to support approval.

Study 511.147 was completed and formed the basis of a second cycle NDA submission, for which a CR letter was sent to the applicant in August 2013. Following the 2013 CR, the applicant requested a dispute resolution. The dispute resolution request was denied, and a Type A meeting was held in March 2014. Following the CR letter and dispute resolution denial, the applicant was advised to provide additional safety information (e.g., results of a driving study). The applicant has now submitted those materials and is again seeking approval of flibanserin. An advisory committee meeting is planned for June 4, 2015, and the PDUFA goal date is August 18, 2015. While no new information about the clinical outcome assessments has been provided for consideration, this review was requested and is provided as a consolidation of previous review considerations and summary memo discussing key endpoints and outcome assessments to support the Division's preparation for the planned advisory committee meeting.

## **C. PROPOSED OUTCOME MEASURE TEXT FOR AC BACKGROUND PACKAGE**

### **1. Overview of Efficacy Measures**

Improvement of desire and satisfying sexual events have been assessed as co-primary endpoints in three pivotal studies 511.71, 511.75, and 511.147 using patient-reported outcome (PRO) assessments. Study 511.147 employed the Female Sexual Function Index Sexual Desire domain (FSFI-SD) with a 28-day recall, and an electronic daily diary assessing satisfying sexual events (SSE eDiary). Note that studies 511.71 and 511.75 also included the SSE eDiary, but used a daily electronic assessment of desire (Desire eDiary). Improvement of distress related to desire was assessed as a key secondary endpoint in all three studies using the Female Sexual Dysfunction Scale – Revised (FSDS-R) item 13.

Other PRO assessments were included as secondary and exploratory endpoints that can help in interpretation of clinically meaningful change. These include total scores of the FSFI and FSDS, as well as a patient global impression of improvement (PGI-I) and patient benefit evaluation (PBE).

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

The FSFI (Rosen et al., 2000) is a multidimensional 19 item self-report questionnaire developed to assess female sexual function in women with HSDD. A representation of the FSFI reproduced from the applicant's NDA submission is shown in Appendix A. As shown in Table 1, the

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instrument consists of 6 domains: sexual desire, arousal, lubrication, orgasm, satisfaction, pain. The version employed in study 511.147 uses a 4 week recall period. While this PRO assessment also produces a total score, only the sexual desire domain score was used as a co-primary endpoint in 511.147. Specifically, items 1 and 2 are used to support the primary endpoint related to change in sexual desire.

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

Note that studies 511.71 and 511.75 used an electronic daily diary assessment of sexual desire as a co-primary endpoint. The eDiary daily sexual desire question was: “Indicate your most intense level of sexual desire.” Possible responses were 0 (No desire), 1 (Low desire), 2 (Moderate desire), or 3 (Strong desire), with the resultant range for the monthly score from 0 to 84 if data were entered on all 28 days. Information from these studies was previously presented in the 2010 DRUP AC meeting, and thus this instrument is not described further here.

Table 1. FSFI Conceptual Framework

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

### b. eDiary of SSEs

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

Patients were instructed to complete the eDiary every morning, with up to a 7-day window allowed for recalling and reporting previous events.

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

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

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

### **c. FSDS-R item 13**

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

The FSDS-R (Derogatis et al., 2008) is a 13-item questionnaire that asks women to evaluate how often a given problem has “bothered you or caused you distress” over the past 7 days. Specifically, item 13 asks, “How often did you feel bothered by low sexual desire?”, with response options (0-4) that range from “never,” “rarely,” “occasionally,” “frequently,” to “always.” A representation of the FSDS-R reproduced from the applicant’s NDA submission is found in Appendix C.

### **d. Additional supportive PRO measures**

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

#### **i. PGI-I**

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

Response options include:

1=Very much improved

2=Much improved

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3=Minimally improved

4=No change

5=Minimally worse

6=Much worse

7=Very much worse

### **ii. PBE**

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

## **2. Evaluation of Efficacy Measures**

### **a. FSFI-SD**

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

#### **i. Development of the FSFI and Content Validity**

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

The applicant provided Study SPR-FSFI-01 that summarizes the evaluation and validation of the FSFI, including the 2-item sexual desire domain. Initial development work of the FSFI was completed using input from experts and patients with FSAD (not HSDD). Additional evaluation work in patients with HSDD has been subsequently completed or otherwise provided by the Applicant.

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

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The first study included premenopausal women aged 18-50 years with a diagnosis of generalized HSDD. Participants were required to have been in stable relationships, defined as a duration  $\geq 6$  months. Participants also needed a Female Sexual Distress Scale score  $\geq 15$  to qualify for inclusion. The second study used similar criteria, although it allowed recruitment of postmenopausal and premenopausal women, but excluded women who might have any other form of FSD.

Both studies were described as cognitive debriefings on the entire FSFI, augmented with general questions regarding the comprehensiveness of the instrument, and a few questions on the redundancy or completeness of the sexual desire items. The results of those queries suggested that 53% in one study and 70% in the other felt the FSFI captured their feelings about reduced sexual desire.

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

Study participants were also queried about their preference for a recall period that fit the most appropriate time frame over which to assess frequency and intensity of sexual desire. The findings were not wholly conclusive, as the authors report “[a]mong those who had preference, most women in both studies thought that a recall period of 4 weeks or 1-2 weeks was the most appropriate time frame over which to assess the frequency of sexual desire (question 1) or level of sexual desire (question 2)...Overall, there was no clear preference for 1-2 week recall, or a 4-week recall period.” It was clear that a minority of participants favored a 24-hour recall; the total across studies was 17%.

### Remaining Concerns about Content Validity

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

sexual advances due to sedation alone could be driving the modest score changes seen in the FSFI desire domain score. In light of this challenge with the validity of the measure (i.e., what in fact does a score change represent), and without a way to ensure various key elements of desire that are important to women have in fact improved, we are cautious in interpreting these findings of efficacy.

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

#### Questions about Recall Period

A 28-day recall period is used in the FSFI-SD. While it is possible that a longer recall period increases noise in the assessment, thus attenuating treatment effects, it is concerning that in studies 511.71 and 511.75, when a daily measure of desire was used, no significant improvements on desire were identified, and only the 28-day recall assessment shows significant change from baseline. It is possible that missing data with the daily assessment was the basis for this. However, the possibility exists that there was systematic bias introduced when the 28 day recall period was employed. For example, many women in qualitative research described their desire disorder in terms of how frequently they fought with, or felt guilty about disappointing, their partners about sexual activity. When recalling over time how severe their desire symptoms were, women are likely to anchor this by recalling experiences of fighting with or disappointing partners. If a drug product has central nervous system effects that could result in patients’ reduced concern or impaired memory of disagreements with partners or feelings of guilt, there could be a systematic over-reporting of “improvements” on desire in the treatment arm using longer recall periods.

#### **ii. Other measurement properties of the FSFI-SD**

While other psychometric measurement properties (e.g., reliability, construct validity) cannot overcome concerns with, and may not be meaningful in the absence of, content validity, there is existing evidence of other measurement properties of the FSFI that are briefly described here. The tool, including the desire domain, is generally able to discriminate between women with HSDD and those without. Meston (2003) indicates that the FSFI desire domain has moderate internal consistency (Cronbach’s alpha = 0.58) among patients with HSDD. Rosen (2000) indicates the desire domain has good internal consistency (Cronbach’s alpha = 0.91) in women with female sexual arousal disorder (note this population is slightly different than the HSDD population). Rosen (2000) also provides evidence of adequate test-retest reliability, with a Pearson product-moment correlation coefficient of 0.80.

#### **iii. Interpreting meaningful change on the FSFI-SD**

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

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

Note that because content validity is in question (i.e., we don’t know exactly what has changed for the women to produce the identified score change), these numbers may be of limited value.

### **b. eDiary for SSEs**

The use of an electronic daily assessment of SSEs as a measure of satisfying sexual events has been consistently agreed upon by the Agency across multiple programs for HSDD. Additional details of this instrument were provided and discussed during the DRUP AC meeting in 2010, and are not reconsidered here. Note that in 511.147, while patients were asked to report daily, the participants had up to a 7-day maximum time period for reporting past events; however they could not enter events beyond the last entry.

While the method of assessment of SSEs is not in question, it is not yet clear what constitutes meaningful change in 28-day SSE scores. The applicant provided findings from an unpublished survey of 450 women, wherein 95% indicated that a change of 1-2 SSEs per month is meaningful. Other anchoring approaches using data from the flibanserin trial show a range of what might be considered a meaningful improvement, from >1 to 4.4 SSEs per month:

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

### **c. FSDS-R item 13**

The use of the FSDS-R, item 13 as a measure of distress related to desire, has been consistently agreed upon by the Agency across multiple programs for HSDD. Additional details of this instrument were provided and discussed during the DRUP AC meeting in 2010, and are not reconsidered here.

## **D. REFERENCES**

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## E. APPENDICES

### Appendix A. FSFI Instrument (sexual desire domain includes items 1-2)

*[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2019]*

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

In answering these questions the following definitions apply:

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

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

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

**CHECK ONLY ONE BOX PER QUESTION.**

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

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

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

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

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

## SEALD Review

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NDA 22526

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

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

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

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

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

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

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

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

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

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Ashley Slagle

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

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

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

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

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

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

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

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

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Ashley Slagle

NDA 22526

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Thank you for completing this questionnaire**

## Appendix B. e-Diary for SSEs

[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2019]

### 10.11 ELECTRONIC DIARY (E-DIARY FOR HSDD TRIALS)

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

1. Did you have sex. . .

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

NO

YES

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

*The following questions are asked only if the patient answers "yes" to the previous question.*

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

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

<Number spinner to increase by increments of 1>

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

3. Select the day of your sexual activity.

3a. Was the sex satisfying for you? <sup>1</sup>

NO

YES

3b. Did you have an orgasm?

NO

YES

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

**SEALD Review**

Ashley Slagle

NDA 22526

Flibanserin

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**Appendix C. FSDS-R**

*[Reproduced from the applicant's Study Protocol for 511.147, dated October 12, 2019]*

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

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INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST        7 DAYS        INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

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

NEVER      RARELY      OCCASIONALLY      FREQUENTLY      ALWAYS  
0              1                      2                      3                      4

---

**HOW OFTEN DID YOU FEEL:**

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| 1. Distressed about your sex life         | 0 | 1 | 2 | 3 | 4 |
| 2. Unhappy about your sexual relationship | 0 | 1 | 2 | 3 | 4 |
| 3. Guilty about sexual difficulties       | 0 | 1 | 2 | 3 | 4 |
| 4. Frustrated by your sexual problems     | 0 | 1 | 2 | 3 | 4 |
| 5. Stressed about sex                     | 0 | 1 | 2 | 3 | 4 |
| 6. Inferior because of sexual problems    | 0 | 1 | 2 | 3 | 4 |
| 7. Worried about sex                      | 0 | 1 | 2 | 3 | 4 |
| 8. Sexually inadequate                    | 0 | 1 | 2 | 3 | 4 |
| 9. Regrets about your sexuality           | 0 | 1 | 2 | 3 | 4 |
| 10. Embarrassed about sexual problems     | 0 | 1 | 2 | 3 | 4 |
| 11. Dissatisfied with your sex life       | 0 | 1 | 2 | 3 | 4 |
| 12. Angry about your sex life             | 0 | 1 | 2 | 3 | 4 |
| 13. Bothered by low sexual desire         | 0 | 1 | 2 | 3 | 4 |
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ASHLEY F SLAGLE  
04/20/2015

ELEKTRA J PAPADOPOULOS  
04/21/2015

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA**  
**CONSULT # 11209**

**Consultant Reviewer:** Lucas Kempf, M.D.  
Medical Officer  
Division of Psychiatry Products (DPP)

**Consultation Requestor:** Charlene Williamson  
Regulatory Project Manager  
DRUP

**Subject of Request:** NDA 22526 and IND (b) (4) – Flibanserin: assessment of suicidality boxed warning

**Date of Request:** November, 17, 2014

**Date Received:** Jan. 5, 2015

**I. Background**

**Regulatory:** Boehringer Ingelheim Pharmaceuticals submitted NDA 22-526 (flibanserin) to the Division of Reproductive and Urologic Products (DRUP) on October 27, 2009, seeking for the indication of hypoactive sexual desire disorder (HSDD) in pre-menopausal women. They received a complete response in 2010 because of modest response and significant safety concerns. May 12, 2010, Dr. Silvana Borges of DPP concluded that there was no suicidality or other psychiatric safety signal from the flibanserin safety analysis. DRUP's review also concurred. Based on the proposed possible antidepressant properties, DPP recommended that should flibanserin be approved, labeling would include the boxed warning for suicidality.

Another pharmaceutical company, Sprout, acquired the product from BI and resubmitted an NDA on March 29, 2013. The application received a complete response on September 29, 2013, for the same efficacy and safety concerns. There continued to be no signal for suicidality in the updated safety database. Sprout is planning to resubmit an application in First Quarter 2015. They believe they have adequately addressed the efficacy and safety issues identified by DRUP in the second cycle review.

**Clinical:** Flibanserin is a new molecular entity, acting preferentially as a post-synaptic 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist, having no relevant activity on 5-HT uptake and monoamine oxidases A or B. Flibanserin was originally developed for the treatment of major depressive disorder but failed to prove efficacy in Phase II trials. However, the sponsor observed that, in those failed Phase II depression trials, flibanserin was superior to placebo on improving the "sex drive" in women. This was their basis for pursuing the indication of HSDD in pre-menopausal women. Given flibanserin pharmacological profile, DRUP requested the sponsor to assess suicidality during its clinical development for HSDD. No suicidality assessment was performed in the MDD trials. The Beck Suicidality Scale was used in the early HSDD program and the most recent studies were all conducted with the C-SSRS after consultation with DPP in 2010.

**DBRUP is now consulting DPP for the question below:**

Because of flibanserin's mechanism of action and antidepressant properties, do you still recommend that a boxed warning for suicidality be included in the flibanserin product label should the drug be approved?

## II. Review of clinical issues

As stated previously, flibanserin failed to show efficacy in an antidepressant trial. Also, there continues to be no imbalance in completed suicides or suicidal thoughts/actions.

Boxed warnings for suicidality have been included in all antidepressants regardless of mechanism though the preliminary analysis was done with SSRIs, SNRIs and bupropion. SSRIs, SNRIs and bupropion used for other indications have also received the boxed warning because the increase in suicides was seen in the healthy population and in other non-Major Depressive Disorder populations exposed to these drugs in the meta-analysis.

Whether mechanistically either 5HT2A antagonists or 5HT1A agonists should receive boxed warnings as classes has been considered previously within DPP. Other drugs that are 5HT2A antagonists or 1A agonists have not received the boxed warning for examples Buspar (buspirone), Clozaril (clozapine), or Zyprexa (olanzapine) that have indications for non-depression psychiatric disorders. The anti-anxiety medication, Buspar, like the current compound, had a failed depression program and has a 5HT1A agonist profile. It carries no boxed warning. Clozaril was considered the first of the *atypical* antipsychotics. This designation was primarily based on the novel 5HT2A antagonism addition to the D2 antagonist. Due to the large risk profile of Clozaril due to agranulocytosis, their development program conducted an extremely large study demonstrating a *reduction* in suicides. The antipsychotic 5HT2A antagonists that carry the boxed warning had the warning added when they received the antidepressant indication not based on their activity at the 5HT2A receptor.

These factors were reviewed with consultation with Drs. Borges and Mathis and they concur with the reanalysis.

## III. Conclusions and Recommendations

- On face there appears to be no risk of suicidality safety signals arising from the flibanserin program. However, this is a first in class compound and it was only after a large meta-analysis of the SSRI, SNRI and bupropion programs that the suicidality signal was detected.
- Based on mechanism of action, we would not continue to recommend including the boxed warning in the case that DRUP decides to approve flibanserin for the treatment of HSDD.

Lucas Kempf, MD  
January 14, 2015

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/s/  
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LUCAS P KEMPF  
01/23/2015

MITCHELL V Mathis  
01/23/2015



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DIVISION OF NEUROLOGY PRODUCTS**

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**CONSULT M E M O R A N D U M**

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DATE: March 18, 2014

TO: Jennifer Mercier, Bone, Reproductive and Urologic Products

THROUGH: Billy Dunn, MD, Acting Director, Division of Neurology Products

FROM: Ronald Farkas, MD, PhD, Clinical Team Leader, Division of Neurology Products

RE: Flibanserin, NDA 22526

## **1. Background**

The Division of Bone, Reproductive and Urologic Products (DBRUP) noted the following background information about flibanserin in the consult request to the Division of Neurology Products (DNP):

Flibanserin is a 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist being developed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. It is a new molecular entity that has undergone two NDA review cycles and a formal dispute resolution request (FDRR). The applicant has now requested a Type A meeting to discuss the path forward following the denied appeal. This meeting is scheduled for March 12, 2014.

With the Complete Response action taken in September 2013, DBRUP concluded that the modest treatment responses shown with flibanserin were not adequate to offset substantial safety concerns that have been identified. The long half-life of flibanserin, combined with the recommended dosing at bedtime, raises concerns about next-day somnolence and sedation, which may impair activities requiring mental alertness, such as driving. DBRUP recommended that a complete response application include a driving study to assess next-day impairment.

The sponsor submitted a protocol for a driving impairment study (protocol SPR-14-01), and asked the following questions:

1. Does the Agency agree that the design of this study is adequate to address the Agency's concerns regarding next-day impairment of mental alertness?
2. Does the Agency have any comments or concerns regarding the study design?

DBRUP requests that DNP comment on the proposed driving impairment study.

## 2. Driving Study Protocol

Study SPR-14-01 is titled '*A Phase I, Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study Assessing the Next-Day Residual Effects of Flibanserin on Simulated Driving Performance in Normal Premenopausal Female Volunteers.*'

The proposed driving study is a randomized, double-blind, placebo-controlled, multi-center crossover study [REDACTED] (b) (4)

[REDACTED] Blood levels of flibanserin will be determined in each period (see figure below).



Subjects will go to bed 30 minutes after dosing, and will be awakened 7.5 hours after dosing. Within 1 hour of waking, subjects will perform the following tests of psychomotor function:

- *Digit symbol substitution test (DSST)*; this is an electronic version called 'CogScreen Symbol Digit Coding (SDC)'

Subjects are asked to substitute digits for symbols at an electronic monitor screen. The test is designed to measure attention, visual scanning, working memory, and speed of information processing. Test endpoints are number of correct responses, response accuracy, and standard deviation of reaction time.

- *Karolinska Sleepiness Scale (KSS)*

KSS is self-reported 9-point Likert scale of sleepiness, ranging from '1, extremely alert' to '9, extremely sleepy – fighting sleep.'

Testing on the driving scenario will begin 9-hours post dosing. The study will use the 'CRCDS Country Vigilance-Divided Attention (CVDA) driving scenario', a 100 km, monotonous, two-lane highway driving task that includes a secondary visual vigilance task. The drive involves occasional long, wide curves, and mild changes in grade. The divided attention task is

presented throughout the entire drive, and involves responding to arrow targets presented in boxes on the left side mirror and right windshield column, and responding appropriately by either hitting or not hitting buttons to the left and right of the steering wheel (hit left button for left arrow, right button for right arrow, and no button for up arrow). The driver is asked to drive the entire scenario at 55 miles/hour.

The primary endpoint is a measure of ability to maintain steady lane position, Standard Deviation of Lateral Position (SDLP), (b) (4)

Other measures include the following:

- Lane exceedance; including number, maximum, duration, and area of exceedance
- Ratio above speed limit, excessive speed count, excessive speed ratio
- Average speed, speed deviation, speeding count, speeding ratio
- Excessive Ay (cornering speed threshold)
- Collision count, off-road crashes, total collisions
- Divided Attention (DA): Correct Vigilance, Omission Vigilance, Commissions
- Vigilance, Reaction Vigilance, Deviation Vigilance

After completing the driving scenario, drivers will be administered a Visual Analog Scale (VAS) to assess motivation and self-appraisal of their driving performance.

## Discussion and Conclusions

### *Flibanserin Exposure*

Studies of driving impairment should be designed to characterize drug effects at the high end of exposures expected to be encountered with use as directed, because such exposures are expected to be associated with the largest impairment. This should include exposures experienced by patients taking concomitant medications according to labelling. The following are some of the factors identified by clinical pharmacology as increasing flibanserin exposure:

- **Food effect:** compared to the fasted condition, exposure to flibanserin is increased 53% after a high fat/calorie breakfast, but only 17% after a light breakfast.
- **Oral contraceptives:** The adjusted geometric ratio of AUC of flibanserin was 1.42 following a single dose in patients using oral contraceptive, and CNS adverse effects such as dizziness and fatigue were more pronounced with concomitant administration of flibanserin and hormonal contraceptives.
- **Fluconazole,** a moderate CYP3A4 inhibitor, increased AUC of flibanserin 7-fold. CYP2C9 and CYP2C19 may also be involved.

Adequate characterization of risk associated with common blood levels might be possible by enrolling subjects on concomitant oral contraceptives, and dosing under

high fat fed conditions. Alternatively, studying a cohort dosed at 150 or 200 mg flibanserin would provide data about impairment from exposures at the high end of what is expected from the 100 mg recommended dose.

### **General Study Design**

The monotonous driving scenario and other proposed tests are acceptable for characterizing the effect of flibanserin on alertness/arousal, the main concern from this drug for driving safety. Patient self-perception of sleepiness will be measured before the driving test using the KSS, but DNP recommends additionally asking subjects to predict their ability to drive before the driving test, as this may be informative about patient ability to self-identify impairment.

The proposed design includes a positive control for assay sensitivity, but only in the first study period, which is not acceptable for a pharmacodynamic study that is expected to have large effects from learning/learning and subject effort. A positive control should be included in all test periods.

(b) (4)

The sponsor states that the 100 mg dose is highly likely to be impairing, but DNP concludes that the level of impairment will be too great to demonstrate that the study is sensitive to the lesser but clinically meaningful degrees of impairment that are of primary interest, e.g. an SDLP increase of about 2- to 3 cm. Driving studies similar to that proposed often use zopiclone 7.5 mg as a positive control. Zopiclone is a non-benzodiazepine hypnotic that is the most commonly prescribed drug for insomnia in Europe and that is similar to eszopiclone (Lunesta) that is approved in the US. Use of eszopiclone 4 mg as a positive control would lead to similar exposures of the active moiety, and would also be acceptable.

A full 4-way, 4-treatment period crossover design with the arms below is recommended by DNP. Each treatment period is 1 week in duration, with a one week washout period in between. Subjects should be randomized equally (1:1:1:1) into one of four treatment sequences that form an experimental design called a Latin square. Testing after acute dosing is conducted on day 1 (after HS dosing), and drug is then taken for the remainder of the week, with testing after chronic exposure the morning after the seventh dose:

(b) (4)

- Treatment A: Flibanserin 100 mg + zopiclone placebo, night 1 and 7; flibanserin only on night 2-6
- Treatment B: zopiclone 7.5 mg + flibanserin placebo, night 1 and 7; flibanserin placebo only on night 2-6
- Treatment C: zopiclone placebo + flibanserin placebo, night 1 and 7; flibanserin placebo only on night 2-6
- Treatment D: Flibanserin 200 mg + zopiclone placebo, night 1 and 7; flibanserin only on night 2-6

Dr. Tristan Massie from the Office of Biostatistics estimated study power based on data from previous driving studies, and concludes that a sample size of 54 or 60 would be adequate (sample size should be a multiple of 6 for the DNP-proposed design).

#### *Endpoints and Statistical Analysis*

The proposed safety endpoints are reasonable. However, as a descriptive safety study, there is less distinction between primary and secondary endpoints. In particular, lane exceedences, particularly if large or prolonged, appear to have considerable face-validity as indicators of risk. The specific pre-specified analyses and cutoffs for secondary endpoints should be described in detail in the final protocol.

The sponsor has proposed studying the *average* effects of the 100 mg recommended dose on measures of driving impairment, but such an approach does not allow determination of the degree of impairment of patients at the higher end of exposure, and may yield negative findings even if a meaningful proportion of patients are significantly impaired. Some of the shortcomings of an endpoint based on average effects can be addressed by a responder analysis that assesses the *proportion* of patients on drug vs. placebo that exceed the <sup>(b) (4)</sup> increase in SDLP commonly used as a threshold for clinically meaningful impairment, or other thresholds, larger and smaller, that are of interest in understanding the degree of impairment. The statistical test used for such an analysis has been called a 'symmetry analysis' because it tests if the distribution of changes (drug minus placebo) in SDLP above the threshold and below the threshold is symmetric around zero.

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/s/  
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RONALD H FARKAS  
03/18/2014

WILLIAM H Dunn  
07/22/2014



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**CONSULT M E M O R A N D U M**

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DATE: July 26, 2013 *Date incorrect*  
TO: Jennifer Mercier, Bone, Reproductive and Urologic Products  
THROUGH: Billy Dunn, MD, Acting Director, Division of Neurology Products  
FROM: Ronald Farkas, MD, PhD, Clinical Team Leader, Division of Neurology Products  
RE: Flibanserin, NDA 22526

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## **1. Background**

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1. Does the Agency agree that the design of this study is adequate to address the Agency's concerns regarding next-day impairment of mental alertness?
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[REDACTED] Blood levels of flibanserin will be determined in each period (see figure below).

Subjects will go to bed 30 minutes after dosing, and will be awakened 7.5 hours after dosing. Within 1 hour of waking, subjects will perform the following tests of psychomotor function:

- *Digit symbol substitution test (DSST)*; this is an electronic version called 'CogScreen Symbol Digit Coding (SDC)'

Subjects are asked to substitute digits for symbols at an electronic monitor screen. The test is designed to measure attention, visual scanning, working memory, and speed of information processing. Test endpoints are number of correct responses, response accuracy, and standard deviation of reaction time.

- *Karolinska Sleepiness Scale (KSS)*

KSS is self-reported 9-point Likert scale of sleepiness, ranging from '1, extremely alert' to '9, extremely sleepy – fighting sleep.'

Testing on the driving scenario will begin 9-hours post dosing. The study will use the 'CRCDS Country Vigilance-Divided Attention (CVDA) driving scenario, a 100 km, monotonous, two-lane highway driving task that includes a secondary visual vigilance task. The drive involves occasional long, wide curves, and mild changes in grade. The divided attention task is presented throughout the entire drive,

and involves responding to arrow targets presented in boxes on the left side mirror and right windshield column, and responding appropriately by either hitting or not hitting buttons to the left and right of the steering wheel (hit left button for left arrow, right button for right arrow, and no button for up arrow). The driver is asked to drive the entire scenario at 55 miles/hour.

The primary endpoint is a measure of ability to maintain steady lane position, Standard Deviation of Lateral Position (SDLP), (b) (4)

Other measures include the following:

- Lane exceedance; including number, maximum, duration, and area of exceedance
- Ratio above speed limit, excessive speed count, excessive speed ratio
- Average speed, speed deviation, speeding count, speeding ratio
- Excessive Ay (cornering speed threshold)
- Collision count, off-road crashes, total collisions
- Divided Attention (DA): Correct Vigilance, Omission Vigilance, Commissions
- Vigilance, Reaction Vigilance, Deviation Vigilance

After completing the driving scenario, drivers will be administered a Visual Analog Scale (VAS) to assess motivation and self-appraisal of their driving performance.

## Discussion and Conclusions

### *General Study Design*

**The monotonous driving scenario and other proposed tests are acceptable for characterizing the effect of flibanserin on alertness/arousal, the main concern from this drug for driving safety. Patient self-perception of sleepiness will be measured before the driving test using the KSS, but DNP recommends additionally asking subjects to predict their ability to drive before the driving test, as this may be informative about patient ability to self-identify impairment.**

**The proposed design includes a positive control for assay sensitivity, but only in the first study period, which is not acceptable for a pharmacodynamic study that is expected to have large effects from learning/learning and subject effort. A positive control should be included in all test periods.**

**The sponsor (b) (4) as the positive control, but acknowledges that this has not been used before in driving tests similar to that proposed. (b) (4)**

(b) (4)

(b) (4) but DNP concludes that the level of impairment will be too great to demonstrate that the study is sensitive to the lesser but clinically meaningful degrees of impairment that are of primary interest, e.g. an SDLP increase of about 2- to 3 cm. Driving studies similar to that proposed often use zopiclone 7.5 mg as a positive control. Zopiclone is a non-benzodiazepine hypnotic that is the most commonly prescribed drug for insomnia in Europe and that is similar to eszopiclone (Lunesta) that is approved in the US.

A full 3-way, 3-treatment period crossover design with the arms below is recommended by DNP. Each treatment period is 1 week in duration, with a one week washout period in between. Subjects should be randomized equally (1:1:1:1:1:1) to the 6 possible sequences of the 3 treatments. Testing after acute dosing is conducted on day 1 (after HS dosing), and drug is then taken for the remainder of the week, with testing after chronic exposure the morning after the seventh dose:

- Treatment A: Flibanserin 100 mg + zopiclone placebo, night 1 and 7; flibanserin only on night 2-6
- Treatment B: zopiclone 7.5 mg + flibanserin placebo, night 1 and 7; flibanserin placebo only on night 2-6
- Treatment C: zopiclone placebo + flibanserin placebo, night 1 and 7; flibanserin placebo only on night 2-6

Dr. Tristan Massie from the Office of Biostatistics estimated study power based on data from previous driving studies, and concludes that a sample size of 54 or 60 would be adequate (sample size should be a multiple of 6 for the DNP-proposed design).

#### *Flibanserin Exposure*

Studies of driving impairment should be designed to characterize drug effects at the high end of exposures expected to be encountered with use as directed, because such exposures are expected to be associated with the largest impairment. This should include exposures experienced by patients taking concomitant medications according to labelling. The following are some of the factors identified by clinical pharmacology as increasing flibanserin exposure:

- Food effect: compared to the fasted condition, exposure to flibanserin is increased 53% after a high fat/calorie breakfast, but only 17% after a light breakfast.
- Oral contraceptives: The adjusted geometric ratio of AUC of flibanserin was 1.42 following a single dose in patients using oral contraceptive, and CNS adverse effects such as dizziness and fatigue were more pronounced with concomitant administration of flibanserin and hormonal contraceptives.
- Fluconazole, a moderate CYP3A4 inhibitor, increased AUC of flibanserin 7-fold. CYP2C9 and CYP2C19 may also be involved.

Adequate characterization of risk associated with common blood levels might be possible by enrolling subjects on concomitant oral contraceptives, and dosing under high fat fed conditions. Alternatively, studying a cohort dosed at 150 or 200 mg flibanserin would provide data about impairment from exposures at the high end of what is expected from the 100 mg recommended dose.

### ***Endpoints and Statistical Analysis***

The proposed safety endpoints are reasonable. However, as a descriptive safety study, there is less distinction between primary and secondary endpoints. In particular, lane exceedences, particularly if large or prolonged, appear to have considerable face-validity as indicators of risk. The specific pre-specified analyses and cutoffs for secondary endpoints should be described in detail in the final protocol.

The sponsor has proposed studying the *average* effects of the 100 mg recommended dose on measures of driving impairment, but such an approach does not allow determination of the degree of impairment of patients at the higher end of exposure, and may yield negative findings even if a meaningful proportion of patients are significantly impaired. Some of the shortcomings of an endpoint based on average effects can be addressed by a responder analysis that assesses the *proportion* of patients on drug vs. placebo that exceed the 2.4 cm increase in SDLP commonly used as a threshold for clinically meaningful impairment, or other thresholds, larger and smaller, that are of interest in understanding the degree of impairment. The statistical test used for such an analysis has been called a 'symmetry analysis' because it tests if the distribution of changes (drug minus placebo) in SDLP above the threshold and below the threshold is symmetric around zero.

### **Sponsor Meeting Question and Draft Response:**

1. Does the Agency agree that the design of this study is adequate to address the Agency's concerns regarding next-day impairment of mental alertness?

The monotonous driving scenario and other proposed tests are generally acceptable for characterizing the effect of flibanserin on alertness/arousal, although you should add a question about patient self-perception of ability to drive for both pre- and post- testing.

You propose to use (b) (4) as the positive control, but have acknowledged that it has not been used before in similar driving studies. We recommend use of zopiclone 7.5 mg as a positive control, as it has been used in many similar studies.

The positive control should be included in all test periods. We recommend a full 3-way, 3-treatment period crossover design with the arms as follows:

- Treatment A: Flibanserin 100 mg + zopiclone placebo, night 1 and 7; flibanserin only on night 2-6
- Treatment B: zopiclone 7.5 mg + flibanserin placebo, night 1 and 7; flibanserin placebo only on night 2-6
- Treatment C: zopiclone placebo + flibanserin placebo, night 1 and 7; flibanserin placebo only on night 2-6

Each treatment period should be approximately 1 week in duration, with a washout period in between periods. Subjects should be randomized equally (1:1:1:1:1:1) to the 6 possible

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sequences of the 3 treatments. Testing after acute dosing is conducted on day 1 (after HS dosing), and drug is then taken for the remainder of the week, with testing after chronic exposure the morning after the final dose.

Studies of driving impairment should be designed to have the ability to characterize drug effects at the higher end of exposures expected to be encountered commonly with use as directed. We recommend that you enroll patients on concurrent oral contraceptives, and dose after a high-fat snack, because flibanserin exposure is higher in these conditions.

The proposed safety endpoints are generally reasonable. However, as a descriptive safety study, there is less distinction between primary and secondary endpoints. The specific pre-specified analyses and cutoffs for secondary endpoints should be described in detail in the final protocol.

You have proposed studying *average* effects of flibanserin on safety endpoints, but such an approach does not allow determination of the degree of impairment of patients at the higher end of exposure, and may yield negative findings even if a meaningful proportion of patients are significantly impaired. You should also conduct a responder analysis that assesses the *proportion* of patients on drug vs. placebo that exceed the 2.4 cm increase in SDLP commonly used as a threshold for clinically meaningful impairment, and other thresholds, larger and smaller, that are of interest in understanding the degree of impairment, similar to as described by Laska et al.<sup>2</sup>

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<sup>2</sup> Laska E, Meisner M, Wanderling J. A maximally selected test of symmetry about zero. Stat Med 2012;31:3178-91.

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AARON SHERMAN  
05/15/2014

RONALD H FARKAS  
05/15/2014

WILLIAM H Dunn  
05/15/2014



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF NEUROLOGY PRODUCTS**

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**CONSULT M E M O R A N D U M**

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DATE: April 4, 2014  
TO: Jennifer Mercier, Bone, Reproductive and Urologic Products  
THROUGH: Billy Dunn, MD, Acting Director, Division of Neurology Products  
FROM: Ronald Farkas, MD, PhD, Clinical Team Leader, Division of Neurology Products  
RE: Flibanserin, NDA 22526

## **1. Background**

The Division of Bone, Reproductive and Urologic Products (DBRUP) is consulting the Division of Neurology Products (DNP) to assess revisions made to a driving impairment study for flibanserin. DBRUP previously consulted DNP to evaluate the original driving protocol. A type A meeting was held on March 12, 2014, between DBRUP and the sponsor at which various potential design changes to their study were discussed.

## **2. Revised Driving Study Protocol**

The revised study SPR-14-01 is titled '*A Phase I, Randomized, Double-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Next-Day Residual Effects of Flibanserin on Simulated Driving Performance in Normal Premenopausal Female Volunteers.*'

The sponsor provided the following summary of changes to the previous version of the protocol:

1. Addition of self-perception question: "right now do you feel safe to drive".
2. Change in active control. The sponsor incorporated zopiclone 7.5 mg as the positive control, as suggested by the Agency at the March 12 meeting.
3. Change to 4-way, 4-treatment period cross-over design including higher 200 mg dose arm, instead of enrolling patients with higher exposure due to drug-drug interaction with oral contraceptives.

The study will examine the acute (next day after first night's dose) effects of 100 mg flibanserin, as previously proposed, but has been revised to examine the effect of a 200 mg flibanserin on night 7 to gain safety information about higher exposures. The study also examines the effects of placebo and positive control. As requested by FDA, subjects will be randomized in a Latin square design such that all patients will be exposed to all treatment arms in a randomized fashion.

A total of 68 subjects will be enrolled, 17 for each of 4 treatment sequences, randomized 1:1:1:1. The washout period between treatment periods will be about one week.

The four treatment arms are as follows:

- Treatment A: flibanserin 100 mg + zopiclone placebo, night 1; flibanserin only on nights 2 – 6; flibanserin 100mg + flibanserin placebo + zopiclone placebo on night 7
- Treatment B: zopiclone 7.5 mg + flibanserin placebo, night 1; flibanserin placebo only on nights 2 – 6; flibanserin placebo (2) + zopiclone 7.5mg on night 7
- Treatment C: zopiclone placebo + flibanserin placebo, night 1; flibanserin placebo only on nights 2 – 6; flibanserin placebo (2) + zopiclone placebo on night 7
- Treatment D: flibanserin 100 mg + zopiclone placebo, night 1; flibanserin only on nights 2 – 6; flibanserin 100 mg (2) + zopiclone placebo on night 7

The randomization schedule is as follows:

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1	A	D	B	C
2	B	A	C	D
3	C	B	D	A
4	D	C	A	B

4. Additional analyses: As suggested by FDA, the sponsor revised the protocol to include the symmetry analysis for Standard Deviation of Lateral Position (SDLP). The sponsor indicates that they will test with this analysis at the SDLP difference attributed to a blood alcohol level of 0.05%

### **3. DNP Discussion and Conclusions**

The sponsor proposes to use the 200 mg dose of flibanserin at night 7, but the night 1 through 6 dose is 100 mg. The sponsor declined FDA's suggestion to enroll patients on oral contraceptives to achieve higher flibanserin exposures. This will decrease the statistical power of the study to detect clinically meaningful impairment in patients with above-average exposures from the 100 mg dose. However, the revised study will enroll 68 patients, vs. 54 in the original protocol, such that the study may still have adequate power to detect impairment. Per FDA recommendations, the sponsor has also added a symmetry analysis, which will decrease the risk of failing to detect impairment that occurs in only a minority of patients.

The sponsor's proposal to study 200 mg only at night 7, instead of at night 1, should still provide useful information about risk at higher drug exposures. Dosing 200 mg on night 1 appears impractical because of the poor tolerability documented previously (e.g. SPR-12-04; adverse events included dose-related dizziness, somnolence and nausea). The very fact that dosing in driving safety studies is less than ideally high due to poor drug tolerability may suggest that warnings against driving for the first few days after starting the drug may be warranted.

The other changes to the protocol are acceptable.

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AARON SHERMAN  
05/15/2014

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05/15/2014

WILLIAM H Dunn  
05/15/2014

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2013-147
APPLICATION NUMBER	<b>NDA 22526</b>
LETTER DATE/SUBMISSION NUMBER	<b>October 1, 2013</b>
PDUFA GOAL DATE	N/A
DATE OF CONSULT REQUEST	October 2, 2013
REVIEW DIVISION	DBRUP
MEDICAL REVIEWER	<b>Daniel Davis</b>
REVIEW DIVISION PM	Charlene Williamson
SEALD REVIEWER(S)	<b>Ashley F. Slagle</b>
REVIEW COMPLETION DATE	<b>Nov 7, 2013</b>
ESTABLISHED NAME	Flibanserin
TRADE NAME	Addyi
APPLICANT	Sprout Pharmaceuticals
ENDPOINT(S) CONCEPT(S)	<b>Sexual desire</b>
MEASURE(S)	FSFI; DSDD
CLINICAL OUTCOME ASSESSMENT TYPE	<b>PRO</b>
INDICATION	Hypoactive sexual desire disorder (HSDD)
INTENDED POPULATION(S)	Pre-menopausal women in the United States

## **A. EXECUTIVE SUMMARY**

This Study Endpoints and Labeling Development (SEALD) abbreviated review is provided as a response to a request for consultation by the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding NDA 22526. The sponsor has used the evaluation of satisfying sexual events (SSEs) and the Female Sexual Function Index (FSFI) (items 1 and 2) for the measurement of desire to support primary endpoints in clinical trials of patients with Hypoactive Sexual Desire Disorder (HSDD), who are premenopausal women in the United States described in their NDA submission earlier this year.

On September 27, 2013 the NDA received a CR letter due to both safety and efficacy deficiencies. The applicant has requested a Type A meeting to discuss the complete response letter (CRL). This review is intended to support discussion at the Type A meeting.

This abbreviated SEALD review does not re-review the FSFI, as details of that review are available in consult AT-2013-60. Instead, this review focuses on responding to specific questions and evidence provided by the sponsor in the briefing package (dated October 21, 2013). The consult request also requests consultation on the Decreased Sexual Desire Screener (DSDS), also referred to as the Brief Diagnostic Procedure (BDP); however, the DSDS/BDP was not identified as a primary or secondary endpoint, but rather for use as diagnostic criteria. As SEALD reviews are limited to those instruments that are proposed to support only primary or secondary endpoints, and no question related to the DSDS/BDP was identified in the briefing package, this diagnostic assessment was not reviewed.

The review concludes that the evidence submitted by the sponsor is still inadequate to demonstrate the content validity of the FSFI sexual desire domain (items 1-2) or FSFI total score to assess sexual desire in the stated context of use. Concerns exist that the two items in the FSFI desire domain do not comprehensively and specifically assess the relevant components of desire, in order to adequately understand what any change in score in this domain represents. Other items in the total score of the FSFI raise content validity concerns. For example, it is not clear that items asking about satisfaction (e.g., with overall sexual life) accurately and specifically represent desire. In addition, the materials submitted by the sponsor do not adequately support the selection of a 28-day recall period for the assessment of desire in this context of use. However, while concerns exist about the content validity of the FSFI total score and desire domain, we note that the lack of sufficient content validity is not the primary reason for the CRL, and may not prevent the approval of a product if a large treatment effect is detected and the benefit of treatment is deemed to outweigh safety risks.

## **B. SUGGESTED RESPONSES TO SPONSOR QUESTIONS**

### **Efficacy Question 2: Do the Office and Division agree that the demonstrated differences are clinically meaningful to premenopausal women with HSDD as demonstrated by the FDA recommended approach?**

The documentation in the briefing book helps to support what amount of change on SSEs may be clinically meaningful. The sponsor has described an anchor based approach using a patient global impression of improvement, as well as a summary of evidence from a survey in women with low sexual desire indicating that most women (95%) report that an increase of 1-2 SSEs per month is meaningful to them. Combining the PGI anchor based approach with qualitative results from the survey seem to point to a clinically meaningful amount of change on SSEs as being between 1-2 events/month, likely closer to 2 events/ month. However, the details of this survey have not been found in the submission for review to ensure agreement with the sponsor's methods and conclusions. It is also a review issue whether a difference in percent of responders based on these conclusions between treatment and placebo groups of 10-12% is sufficient to outweigh safety concerns.

### **Efficacy Question 3: Does the Division agree that the FSFI is a valid and reliable tool to assess sexual desire?**

We do not agree that the FSFI has been documented to be a well-defined and reliable tool to assess sexual desire. While the sponsor has provided some findings from qualitative research, we do not agree that the FSFI desire domain or total score has sufficient documented content validity. However, while we encourage the development of better assessments, we note that other, better assessments have not yet been identified for use in this context. In this case, in order to avoid holding up drug development, we acknowledge that the FSFI desire domain may be a useful assessment for use in the interim. The concerns with the FSFI will likely make it more difficult for a sponsor to detect a treatment benefit. If an improvement is detected using the FSFI desire domain, we will need to interpret the findings cautiously, and in the case of approved products, determine the best way to describe the treatment benefit in labeling in a way that is not misleading.

The sponsor's briefing materials indicate that "the 2013 CRL incorrectly notes that open-ended concept elicitation interviews were not performed to determine if there are additional components of sexual desire that should be included as separate items in an assessment of sexual desire. Revicki et al., 2011 describe their qualitative interviews as follows: 'The interviews began with open, non-leading global questions about the woman's experiences... The women then completed the FSFI.'" This quotation from the Revicki et al publication is contrary to the methods described in Study 511.144 that indicates "After providing written informed consent, participants completed the FSFI. A (b) (4) scientific staff member then conducted a one-on-one

interview...” (page 8 of (b) (4) Study Report “Assessing the content validity of the female sexual function index (FSFI) in pre-menopausal women with HSDD”). Upon further review of the individual transcripts, it appears that a few open ended questions were asked at the beginning of the cognitive debriefing interviews, prior to instrument administration, consistent with the summary in Revicki et al., 2011. However, the primary focus of the interviews was to cognitively debrief the FSFI, and adequate exploration of the experience of desire in an open-ended way was not achieved using these limited initial global questions.

The interview questions used do not sufficiently explore the meaning of the term desire in order to select or develop the appropriate items to comprehensively assess desire. For example, after reviewing several transcripts, it appears women include multiple components in their definition of desire, including: interest in sex, becoming aroused (this should have been explored further – is this physiological arousal, or the same thing as interest?), being receptive to a partner’s initiation of sex, enjoying sex, being able to achieve orgasm, drive to have or initiate sex, etc. Also, women describe both mental and physical components of desire. However, these multiple components were not fully explored in concept elicitation interviews, and there is not sufficient documentation that the multicomponent features are captured comprehensively and specifically using Q1 and Q2 of the FSFI instrument.

While many of the experiences and descriptions of desire may be covered by the FSFI instrument (total score), saturation tables, summary tables of concept findings and rationale for inclusion of specific items in the FSFI, based on the qualitative findings, have not been identified for review to determine whether sufficient documentation exists for the content validity of the overall FSFI total score to assess desire in premenopausal patients with HSDD. Some of the items in the FSFI raise concerns in that they are asking about satisfaction with varying components of a woman’s life that do not appear, and have not been documented, to be directly related to the condition or the treatment. For example, it is not clear that the items asking about *satisfaction* with overall sexual experiences or emotional closeness during sexual intercourse are relevant and related to treatment, as satisfaction may be impacted by many other factors. This makes it challenging to ensure that an increased score detected on the FSFI is in fact related to the treatment under study and represents an improvement in desire in the clinical trial.

There is also no exploration within these interviews of the experience of desire over time. Do women conceptualize this as a steady state with little to no change over a period of weeks or months, or does it change from day to day? This experience of desire and how it changes over time is important information to consider when assessing appropriate recall periods. Asking women what is their preferred recall period is not sufficient for selecting a recall period. While we have concerns about the 28-day recall period, its likely impact is to increase noise making it more difficult to detect a treatment effect if one exists, and is not the primary reason for the CRL. Future studies may be improved using a shorter recall period.

While we do not agree that the FSFI desire domain or total score has sufficient content validity, this is not the primary reason for the CRL. Although we recommend that the future selection or

development of instruments be based upon the good principles of instrument development (outlined in the PRO Guidance) addressing the concerns noted here, we acknowledge that if a very large treatment effect is shown using an instrument such as the FSFI desire domain, the lack of content validity may not prevent the approval of a drug product. It then becomes a review issue to evaluate the amount of change that is clinically meaningful and then to weigh benefits with safety risks.

## 1 CONCEPTUAL FRAMEWORK

The FSFI conceptual framework:

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

## C. APPENDICES

### FSFI Instrument

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

In answering these questions the following definitions apply:

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

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

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

**CHECK ONLY ONE BOX PER QUESTION.**

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

1. Over the past 4 weeks, how often did you feel sexual desire or interest?
  - 5  = Almost always or always
  - 4  = Most times (more than half the time)
  - 3  = Sometimes (about half the time)
  - 2  = A few times (less than half the time)
  - 1  = Almost never or never
  
2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?
  - 5  = Very high
  - 4  = High
  - 3  = Moderate
  - 2  = Low
  - 1  = Very low or none at all

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Thank you for completing this questionnaire**

e-Diary for SSEs

10.11 ELECTRONIC DIARY (E-DIARY FOR HSDD TRIALS)

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

1. Did you have sex. . .

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

NO

YES

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

*The following questions are asked only if the patient answers "yes" to the previous question.*

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

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

<Number spinner to increase by increments of 1>

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

3. Select the day of your sexual activity.

3a. Was the sex satisfying for you? <sup>1</sup>

NO

YES

3b. Did you have an orgasm?

NO

YES

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

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ASHLEY F SLAGLE  
11/07/2013

ELEKTRA J PAPADOPOULOS  
11/07/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** October 4, 2013

**To:** Charlene Williamson, RPM  
Division of Bone, Reproductive, and Urologic Products (DBRUP)

**From:** Lynn Panholzer, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** Flibanserin Tablets 100mg  
NDA 022526

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We acknowledge your May 17, 2013, consult request for OPDP's review of the proposed product labeling (Package Insert, Patient Package Insert, Carton/Container labeling) for Flibanserin Tablets 100mg. OPDP notes that the application received a Complete Response (CR) on September 27, 2013. Therefore, OPDP defers comment on the labeling at this time. A review will be performed when the applicant submits a complete response to the CR letter. OPDP requests that DBRUP submit a new consult request at that time.

Thank you for the opportunity to comment on these proposed materials. If you have any questions, please contact Lynn Panholzer at 301-796-0616 or [Lynn.Panholzer@fda.hhs.gov](mailto:Lynn.Panholzer@fda.hhs.gov).

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/s/  
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LYNN M PANHOLZER  
10/04/2013



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

**Date:** September 26, 2013

**To:** Hylton Joffe, M.D., Director  
Division of Bone, Reproductive and Urologic Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** Evaluation of Human Abuse Potential Study  
Flibanserin (Girosa)  
NDA 22-526 (resubmission)  
Indication: Treatment of Hyposexual Desire Disorder in  
Premenopausal Women (100 mg/day)  
Sponsor: Boehringer Ingelheim Pharma GmbH and Co.  
PDUFA Goal Date: September 27, 2013

**Materials reviewed:** General Advice Letter to Sponsor (August 30, 2013); Sponsor  
response to General Advice Letter (September 12, 2013)

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## **1. Background**

This memorandum is an amendment to the August 23, 2013 CSS review of the abuse potential data contained in the resubmitted NDA 22-526 for flibanserin. This amendment includes additional information based on discussions with the Division, as well as a CSS evaluation of the safety review by the Medical Officer team regarding the abuse-related adverse events associated with flibanserin administration.

On August 30, 2013, a General Advice Letter (GAL) was sent from FDA to the Sponsor which contained the CSS Conclusions and Recommendation in our August 23, 2013 consult review. The Sponsor responded to these concerns on September 12, 2013. The information below is responsive to the issues raised by the Division during discussions with CSS (see Section 2, Conclusions for Division) as well as issues raised by the Sponsor in their response to the GAL (see Sections 3 (Conclusions for Sponsor, at the Division's discretion) and Section 4 (Recommendation). CSS consulted with Dr. Ling Chen and Dr. Yi Tsong in the Office of Biostatistics in preparing our responses.

## **2. Conclusions (for Division only, do not convey to Sponsor)**

During discussions with the Division, clarifying questions were raised regarding how abuse-related assessments are made by CSS. The Division issues are summarized below, followed by CSS responses.

### Division Question #1

*All three tested doses of flibanserin produced significantly less At-the-Moment Drug Liking (the primary endpoint) than the higher dose of the positive control, zolpidem 30 mg. CSS had concerns that more than 25% of zolpidem-treated patients had neutral responses on this scale. Why should we not interpret these results as showing that flibanserin is different from zolpidem? If zolpidem had performed as expected, would there be an even larger difference between flibanserin and zolpidem 30 mg? Is the issue that the 30 mg dose is too suprathreshold and we don't know what would happen with the 15 mg dose? Should they be comparing flibanserin to the maximum recommended zolpidem dose?*

### CSS Response

Although there was a statistical difference between zolpidem and flibanserin, we do not consider this finding to be valid, since 26-32% of subjects who received zolpidem responded to the positive control as if they had received placebo. This suggests that up to one-third of subjects cannot distinguish between the positive control and placebo. Thus, these subjects may be similarly unable to distinguish between any test drug (including flibanserin) and placebo. We elaborate upon these issues in point #2a (below, in Conclusions for Sponsor).

As we noted in our NDA review (August 23, 2013), the 15 and 30 mg doses of zolpidem are standard for human abuse potential studies when zolpidem is used as the positive control. The doses were selected because they are suprathreshold and expected to produce increases in positive subjective responses, in a dose-dependent manner (where both produce increases in the variable analog scale (VAS) for Drug Liking, High, and Good Drug Effects, but the higher dose produces larger responses). The standard statistical analysis compares a test drug at each dose to the positive control drug at each dose.

### Division Question #2

*Given that there are issues with large placebo responses for many of the secondary measures, did these large responses lead to flibanserin not being statistically different to placebo on these secondary endpoints? If yes, how critical are these secondary endpoints given that the Sponsor was able to show that flibanserin is statistically significantly different from placebo on the primary endpoint?*

### CSS Response

The human abuse potential study is a safety study that investigates the occurrence of signals indicating that the test drug may have abuse potential. Thus, secondary measures such as VAS Good Drug Effects, VAS High, VAS Overall Drug Liking, and VAS Take Drug Again have some value in providing information about positive subjective responses beyond the primary measure of VAS Drug Liking. However, the weight of each metric should be asserted prospectively.

If all subjects in the present human abuse potential study had been properly selected, the result from the comparison between zolpidem 30 mg and flibanserin would be valid (e.g., that flibanserin produced positive subjective responses that were statistically less than those produced by zolpidem). However, because of the inability of one-third of the subjects to distinguish between the positive control, zolpidem, and placebo (as explained above in Question #1), the result that there is no significant difference between flibanserin and zolpidem might be skewed by these poor-performing subjects. In other words, those subjects who did not respond appropriately to zolpidem might contribute to the apparent “not significant” result of the comparison between flibanserin and zolpidem.

### Division Question #3

*Prior to the initiation of the human abuse potential study, FDA provided feedback to the Sponsor regarding their study design. It appears we told them not to serve breakfast two hours after study drug administration and that we told them not to use alcohol as a “sedative drug” for purposes of an acceptable drug history. Do we know why they did not adhere to our recommendations?*

### CSS Response

We informed the Sponsor about our issues with the timing of breakfast and using a history with alcohol as an acceptable history with sedative drugs in our consults on January 30, 2013 and August 3, 2012. We cannot speculate why the Sponsor did not follow our recommendations, but we were very clear that we wanted the protocol changed. In the Sponsor response to the General Advice Letter (GAL) on these issues, they acknowledge that the protocol was conducted in a manner contrary to our recommendations. Thus, their responses do not negate any of our issues about protocol design that were delineated in the GAL.

### Division Question #4

*In the Sponsor's response to the GAL, they state that, "No subjects entered the Qualification Phase having used only alcohol and THC (marijuana)." Does this address your issue of the use of alcohol being used to qualify subjects for this study?*

### CSS Response

The issue we raised in the GAL is not whether subjects had experience with alcohol. The issue is whether they had adequate experience with sedatives (benzodiazepines and barbiturates) to be able to give appropriate information about the study drugs.

We were very clear that they should not consider alcohol as a sedative when qualifying subjects as sedative abusers, based on lifetime (not recent) sedative use. This is because alcohol is not a scheduled drug under the Controlled Substances Act. However, the Sponsor did not change their protocol (e.g., they allowed alcohol to be one of the sedatives an individual could use when qualifying as a sedative abuser, when we told them it should only be based on lifetime use of benzodiazepines and barbiturates).

By the Sponsor's own demographic data provided in the GAL, only 69% of subjects had experience with benzodiazepines, barbiturates, sedative drugs or hypnotics. This means that 31% of subjects did not have experience with an acceptable sedative and yet they qualified as a sedative abuser. According to the protocol, nearly one third of the subjects qualified as a sedative abuser based on alcohol experience.

The subjects who participated had experience with many different classes of drugs. So when the Sponsor states that no one qualified solely on the basis of recent use of alcohol or THC, this suggests that the subjects had also used additional classes of drugs other than sedatives. However, their statement does not refute that a large percent of the subjects had no experience with benzodiazepines or barbiturates.

### Division Question #5

*Since the human abuse potential study is inconclusive, why have you concluded that a new human abuse potential study will not be needed? Is this because abuse-related signals in the original NDA were not present in the data included in the Complete Response submission? Did any of the counterarguments provided by the Sponsor in the GAL influence your decision?*

### CSS Response

CSS has determined that a new human abuse potential study will not be needed, based on the totality of preclinical and clinical data contained in the resubmitted NDA (see elaboration of this issue in our comments in Recommendation, below). This determination was based in large part on the lack of abuse-related adverse events in any Phase 1, 2 or 3 clinical studies conducted to date with flibanserin, especially when newly submitted data were considered. Thus, the determination that a new human abuse potential study will not be needed is not based on any information provided or arguments made by the Sponsor in their response to the GAL.

CSS has made some clarifying revisions to our Conclusions for Sponsor (below), including a direct response in point #5 to their primary arguments in the GAL. I do not believe that their arguments are valid and they did not change my conclusions that the human abuse potential study is not valid.

### **3. Conclusions (to be conveyed to Sponsor at the Division's discretion)**

*[Note to Division: The following Conclusions are a revision of the Conclusions found in the August 23, 2013, NDA review by CSS. These revisions are clarifications of the issues raised in each point, based on CSS discussions with the Division and the statisticians in the Office of Biostatistics (Dr. Ling Chen and Dr. Yi Tsong).]*

- 1) The human abuse potential study conducted with flibanserin provided in the resubmitted NDA does not fulfill the 2010 Complete Response requirement for the submission of a valid human abuse potential study.
- 2) The human abuse potential study conducted with flibanserin is invalid and inconclusive based on the evaluation of the statistical analysis of the study. Specifically, the study data were deemed uninterpretable because of the problems detailed below. Since these issues were conveyed to you in the General Advice Letter (GAL) on August 30, 2013, refer to item #5 for responses to your comments. The problems with the human abuse potential study include:
  - a) On the primary subjective measure of Drug Liking visual analog scale (VAS), the positive control, zolpidem, did not produce an appropriate positive subjective response in a large percent of subjects. Even though on the primary subjective

measure of Drug Liking visual analog scale (VAS) the validation tests (compared zolpidem 15 mg and 30 mg to placebo) were statistically significant ( $p < 0.0001$ ), it was found that more than 25% of subjects did not respond to the positive control appropriately. Specifically, 32% of subjects who received 15 mg zolpidem and 26% of subjects who received 30 mg zolpidem had an Emax response that was in the neutral range (40-60 on the bipolar scale of 0 to 100, where 50 is neutral). When the Emax values from these subjects were evaluated, they were found to be between 48 and 53 in response to zolpidem 15 mg, and between 50 and 57 in response to zolpidem 30 mg. These neutral responses from zolpidem are similar to the response expected from placebo. Since more than 26% of subjects could not distinguish the positive control from placebo, it is possible that the responses from these subjects could skew the results of this study and that the subjects would be similarly unable to distinguish any test drug from placebo.

b) Inappropriately large placebo responses were observed for secondary subjective measures in the study. These secondary measures use unipolar scales ranging from 0-100, with an acceptable neutral response of 0-20. For example:

- For Good Drug Effects VAS, 18 of 34 subjects (53%) had Emax values in response to placebo that were  $\geq 20$  on the unipolar scale.
- For High VAS, 11 of 34 subjects (32%) had Emax values in response to placebo that were  $\geq 20$  on the unipolar scale.

Given that there was a large percent of subjects who had a response to placebo outside the acceptable neutral response range, the study results with the positive control drug, zolpidem, and flibanserin are uninteruptable. In this study, each subject served as his/her own control, such that the data analysis is based in part on the difference in Emax values between placebo and one of the drug treatments. A large placebo response can change the possible range in differences in Emax values between a drug treatment and placebo.

c) On the secondary subjective measure of High VAS, predose responses were collected in each treatment period before dosing for each subject. However, these predose responses were not utilized in the study analysis. Instead, you inappropriately used baseline responses (defined as predose responses for each subject in Period 1 on Day 1) in calculating the response for each subject for each of the treatments for each of the subjective measures. The baseline responses were also used for the covariate in the statistical analysis.

d) Inappropriately large predose responses were observed in the study. For example, for the subjective measure of High VAS (a unipolar measure ranging from 0 to 100, with an acceptable neutral predose response range between 0 to 20), 32 of 34 subjects (94%) had a predose response of 46 to 51. Given the problems with placebo and predose responses detailed in (b) and (c), conducting a re-analysis of the data using predose responses would not give meaningful results.

- e) On two subjective measures that assess retrospective (next-day) positive responses to a drug treatment, a very large number of subjects did not identify the positive control, zolpidem, as producing positive responses. For Overall Drug Liking VAS (a bipolar scale of 0 to 100, with an acceptable neutral score ranging from 40 to 60), 25 of 34 subjects (74%) and 24 of 34 subjects (71%) had an Emax response to the positive control, zolpidem at 15 mg and 30 mg (respectively), of < 55 (within the neutral or drug disliking response range). Similarly, for Take Drug Again VAS (a bipolar scale), 22 of 34 subjects (65%) and 21 of 34 subjects (62%) had an Emax response to the positive control, zolpidem at 15 mg and 30 mg (respectively), of < 55 (within the neutral or drug disliking response range). The response to a positive control drug like zolpidem on these scales should have been > 60, which indicates drug liking.
- 3) The uninterpretable data described above suggest that the study design may be flawed and unacceptable. These issues were communicated to you prior to study initiation and include the following:
- a) The inclusionary criteria allow for the use of alcohol as a “sedative drug” for purposes of an acceptable drug history. You were previously informed that an acceptable history of sedative abuse should be based only on the use of benzodiazepines and barbiturates, and should not be based on alcohol use. Thus, it is possible that the poor responses observed in the study to the positive control, zolpidem, were based on subjects qualifying for the study solely on the basis of use of alcohol rather than other acceptable sedatives (see item #5c below for further explanation).
  - b) The final study report does not provide a definition for an “acceptable placebo response” in the Qualification Phase. An acceptable response to the positive control was deemed to be at least a 10 point increase compared to placebo. However, if the placebo response was outside the acceptable neutral range, then this would invalidate the qualification criterion. Thus, it is possible that the inappropriate placebo responses observed in the study simply paralleled inappropriate placebo responses during the Qualification Phase.
  - c) Subjects were served breakfast two hours after drug administration. Thus, it is possible that being served food or consuming food may have interfered with data collection, disrupted a subject’s concentration for responding to subjective measures, or altered the emotional state of the subject while answering questions about positive subjective responses to the drug treatment.
- 4) The data described above suggest that study subjects were not appropriately trained in the study procedures, including the differences in responding using both unipolar and bipolar scales. This may account for the apparent inability of many subjects to provide:

- a) An appropriate neutral (predose or placebo) response on a unipolar scale (< 20 on a scale of 0 to 100) after having immediately responded on a bipolar scale (where 40-60 is an appropriate neutral response on a scale of 0 to 100).
  - b) An apparent inability of many subjects to provide an appropriate positive response to the positive control drug, zolpidem, when answering on bipolar and unipolar scales.
- 5) An earlier version of the problems described above was conveyed to you in a General Advice letter (GAL) on August 30, 2013. In your response to the GAL on September 12, 2013, you addressed concerns regarding the following abuse-related:

a) *Appropriate placebo or neutral response range.*

From a regulatory perspective, a human abuse potential study examines drug discrimination, in that subjects must be able to adequately distinguish between placebo and a positive control in order for the study to be valid. In a human abuse potential study where the positive subjective response to a drug ranges from 0 to 100, an acceptable placebo response ranges from 0-20 for a unipolar scale or 40-60 for a bipolar scale. Individuals that are unable to meet this criterion and maintain this level of responding are deemed to be unreliable subjects for providing information about whether a test drug is similar to the positive control. Thus, evaluating individual responses are an important way of determining if a particular subject can provide reliable data in a human abuse potential study.

During protocol development for the human abuse potential study, you were informed two times that you needed to provide a definition of an “acceptable placebo response.” However, you did not provide this information in the final study report, and you did not provide it in your response to the GAL.

b) *Subject responses on bipolar vs. unipolar scales.*

In the GAL, we expressed concern that subjects were not adequately trained to respond appropriately using both unipolar and bipolar scales, leading to inappropriate predose responses. In your response to the GAL, you state that subjects “misunderstood” the scales and that staff had “incorrectly” instructed subjects. Both of these statements affirm that subjects did not understand how to respond using these instruments, especially with regard to switching between the two. The inability of subjects to utilize the scales properly contributes to the invalidity of the responses by these subjects.

c) *Qualification as a Sedative Abuser*

In order for the study to be valid, the study subjects must be shown to have the appropriate drug history. Since flibanserin has CNS depressant properties, subjects in this study were required to have a lifetime history of sedative abuse. During protocol development for the human abuse potential study, you were informed that you needed to revise the protocol so that a history of the use of alcohol (a substance that is not scheduled under the Controlled Substances Act)

could not be used to qualify a subject as having a lifetime history of CNS depressant abuse. However, in your response to the GAL, you quote from the final protocol, which states that a subject qualifies for the study on the basis of having a history with sedative drugs, including alcohol. This demonstrates that you did not appropriately revise your protocol based on our feedback. In your response to the GAL, you also provide data demonstrating that 31% of subjects did not have a history of using benzodiazepines, barbiturates, sedative drugs or hypnotics. This strongly suggests that some subjects inappropriately qualified as abusers of CNS depressants by having a lifetime history of alcohol use, rather than by having a lifetime history of benzodiazepine or barbiturate use. Although subjects who participated in the study may have had experience with drugs other than alcohol, it is the lack of experience with CNS depressants (benzodiazepines or barbiturates) in nearly one-third of the subjects that may have contributed to the responses delineated in #2 (above).

#### **4. Recommendation**

Based on the totality of preclinical and clinical data contained in the resubmitted NDA for flibanserin, there does not appear to be any significant new abuse-related signals.

Assessment of the abuse potential of a drug is based upon the comprehensive evaluation of the chemical, pharmacological, and pharmacokinetic characteristics of the drug, as well as clinical data (human abuse studies, abuse-related adverse event data from clinical studies), and epidemiological data if available. There is no single study alone that will determine the abuse potential of a drug.

In the previous NDA submission, there was a high rate of adverse events that are often associated with abuse potential, including sedative-like effects (fatigue (up to 31.0%), somnolence (up to 22%), sedation (up to 13%)), as well as a low rate of disturbance in attention (up to 2%). To fully characterize whether flibanserin has abuse potential, a human abuse potential study was requested and submitted as part of the Sponsor's Complete Response to NDA 22-526. Although the human abuse potential study did not provide conclusive data regarding the abuse potential of flibanserin, re-analysis of the adverse event profile from all Phase 1, 2 and 3 clinical studies showed that no novel adverse events were identified that are suggestive of abuse potential. The lack of an abuse potential signal in preclinical and clinical studies mitigates my prior concerns regarding the abuse potential of flibanserin. Thus, a new human abuse potential study is not necessary.

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/s/  
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KATHERINE R BONSON  
09/26/2013

SILVIA N CALDERON  
09/26/2013

MICHAEL KLEIN  
09/26/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**REVIEW DEFERRAL MEMORANDUM**

Date: September 16, 2013

To: Hylton Joffe, MD  
Director  
**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review Deferred: Patient Package Insert (PPI)

Drug Name (established name): Addyi (flibanserin)

Dosage Form and Route: tablets

Application Type/Number: NDA 22-526

Applicant: Sprout Pharmaceuticals, Inc.

## **1 INTRODUCTION**

On March 28, 2013, Sprout Pharmaceuticals, Inc. submitted for the Agency's review a complete response to the Agency's August 27, 2010, Complete Response letter for New Drug Application (NDA) for Addyi (flibanserin) tablets, indicated for the treatment of Hypoactive Sexual Desire Disorder (HSDD). On May 17, 2013, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Addyi (flibanserin) tablets.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) for Addyi (flibanserin) tablets.

## **2 CONCLUSIONS**

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/  
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ROBIN E DUER  
09/16/2013

MELISSA I HULETT  
09/16/2013

LASHAWN M GRIFFITHS  
09/16/2013

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

**DATE:** August 28, 2013

**TO:** Charlene Williamson, Regulatory Project Manager  
Daniel Davis, M.D., Medical Officer  
Christina Chang, M.D., Medical Team Leader  
Division of Bone, Reproductive, and Urologic Products

**FROM:** Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Susan D. Thompson, M.D.  
(covering for Kassa Ayalew, M.D., M.P.H.)  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22526

**APPLICANT:** Sprout Pharmaceuticals, Inc.

**DRUG:** Flibanserin

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** Treatment of premenopausal women with primary generalized, acquired Hypoactive Sexual Desire Disorder (HSDD)

CONSULTATION REQUEST DATE: May 10, 2013  
 CLINICAL INSPECTION SUMMARY DATE: August 30, 2013  
 DIVISION ACTION GOAL DATE: September 27, 2013  
 PDUFA DATE: September 29, 2013

**I. BACKGROUND:**

The Applicant submitted this NDA to support the use of flibanserin for the treatment of premenopausal women with primary generalized, acquired Hypoactive Sexual Desire Disorder (HSDD).

The pivotal study, Protocol 511.147 entitled “A Twenty-four Week, Randomized, Double-blind, Placebo-controlled, Safety and Efficacy Trial of Flibanserin (100 milligrams) Administered Orally Once Daily in Premenopausal Women with Hypoactive Sexual Desire Disorder in the United States” was inspected in support of the indication.

Protocol 511.147 was a 24-week, randomized, double-blind, placebo-controlled, parallel-group study consisting of a four-week screening period without any study medication followed by a 24-week double-blind treatment period with study medication, and a one-week follow-up period after discontinuation of study medication. The primary endpoints were the change from baseline to Week 24 in the score of the Female Sexual Function Index (FSFI<sup>®</sup>) desire domain and the change from baseline in the number of satisfying sexual events (SSE) as measured by the eDiary standardized to a 28-day period (see Amendment 4 for the revision of the definition of the primary endpoints).

The clinical sites of Drs. Lee, Ackerman, and Katz were selected for inspection because Dr. Lee’s site had a large treatment effect observed for both primary endpoints; Dr. Ackerman had the highest enrollment; and Dr. Katz’s site had not been inspected recently. Furthermore, the clinical sites of both Drs. Lee and Katz had relatively large subject enrollments.

**II. RESULTS (by Site):**

Name of CI, Location	Protocol #/ Site #/ # of Subjects (mITT)	Inspection Dates	Final Classification
Elly Lee, M.D. 16263 Laguna Canyon Road, Suite 150 Irvine, CA 92618	511.147/ 1037/ 28	Jul 2013	VAI. Pending final classification.
Ronald Ackerman, M.D. 603 Village Blvd., Suite 201-B West Palm Beach, FL 33409	511.147/ 1001/ 50	Aug 2013	NAI. Pending final classification.
Molly Katz, M.D. 71 E. Hollister Street Cincinnati, OH 45219	511.147/ 1033/ 39	31 Jul – 5 Aug 2013	NAI. Pending final classification.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Elly Lee, M.D.

16263 Laguna Canyon Road, Suite 150  
Irvine, CA 92618

- a. What was inspected:** At this site for Protocol 511.147, 39 subjects were screened, 28 subjects were enrolled, and 20 subjects completed the study. Signed informed consent forms were present for all subjects. An audit of the study records of 15 subjects was conducted in-depth, and another 13 files were reviewed for adverse event and primary efficacy endpoint reporting. Other records reviewed included inclusion/exclusion criteria, case report forms (CRFs), medical records, and concomitant medications.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included the enrollment of Subject 42884 (flibanserin treatment group (tg)) despite an exclusionary history of melanoma; the lack of the completion of the BDI-II questionnaire by Subjects 42908 (placebo tg), 42911 (placebo tg), 42914 (flibanserin tg), and 42917 (flibanserin tg); the completion of incorrect diaries at Visits 8 and/or 9 by Subjects 42911 and 42914; and several transcription errors between source documents and electronic case report forms with regards to adverse event reporting including the presence of dental caries, moderate anxiety, and a cold in Subjects 42900 (placebo tg), 42901 (placebo tg), and 42911, respectively. The Female Sexual Distress Scale-Revised questionnaire for Visit 9 for Subject 42911 had several responses transcribed incorrectly to the eCRF, including Question 5 which was “3” on the source document and “1” on the eCRF, Question 6 which was “1” on the source document and “2” on the eCRF; Question 8 which was “2” on the source document and 1 on the eCRF, Question 10 which was “1” on the source document and “3” on the eCRF, and Question 11 which was 3 on the source document but without a corresponding response on the eCRF.

Dr. Lee’s written response dated August 9, 2013, noted that the enrollment of Subject 42884 despite a disqualifying history of melanoma was reported as a protocol violation to the sponsor and the IRB. As the subject was cleared of any malignancy as of 2004, the medical monitor allowed the retention of the subject in the study. For Subjects 42908, 42911, 42914, and 42917, Dr. Lee says that they were not experiencing depression or suicidality as assessed at their respective visits by the Columbia Suicide Severity Rating Scale; however, the Beck Depression Inventory® II (BDI-II) forms were inadvertently not provided to these subjects. Dr. Lee says this protocol violation was reported to the sponsor and the IRB. Subject 42911 completed the incorrect questionnaire because of timing issues related to the implementation of Amendment 4. Subject 42914 was inadvertently provided the wrong questionnaire. The correct questionnaire was completed by this subject at the next visit. Failure to fully document adverse events was attributed to data entry errors. Incorrect questionnaire responses for Subject 42911 were attributed by Dr. Lee to a skipped line in the log resulting in incorrect responses for Questions 5 through 11.

Dr. Lee states that study staff has been re-educated on the need for contemporaneous and accurate capture of data on both source documentation and eCRF records.

**c. Assessment of data integrity:** Most of the observations listed on the Form FDA 483 appear to be isolated, sporadic, and randomly distributed across treatment groups and unlikely to affect critical efficacy or safety parameters. The failure to distribute and collect responses to the BDI-II questionnaire from four subjects is also expected to have minimal impact on safety parameters since this requirement was instituted approximately 11 months into the study (Protocol Amendment 4, September 16, 2010) to help differentiate AE symptoms related to depression from non-specific AEs such as sleeplessness. Notwithstanding these observations, the study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

2. Ronald Ackerman, M.D.  
603 Village Blvd., Suite 201-B  
West Palm Beach, FL 33409

**a. What was inspected:** At this site for Protocol 511.147, 81 subjects were screened, 50 subjects were enrolled, and 33 subjects completed the study. Signed informed consent forms were present for all subjects. The records of all 50 enrolled subjects were audited with respect to adverse event reporting. The records of 23 subjects were audited in-depth and verified against line listings.

**b. General observations/commentary:** FSFI scores and electronic diary entries corresponded with line listings. All subjects met appropriate inclusion/exclusion criteria, all adverse events were reported appropriately, subjects and study personnel were appropriately blinded, and protocol deviations were reported. A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

**c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Molly Katz, M.D.  
71 E. Hollister Street  
Cincinnati, OH 45219

**a. What was inspected:** At this site for Protocol 511.147, the study records of 20 of the 39 subjects completing the study were reviewed for adherence to protocol with respect to informed consent, source documentation, inclusion/exclusion criteria, concomitant medications, test article accountability, the primary efficacy endpoint, monitoring communications, electronic diary compliance, and blinding and randomization procedures.

**b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

**c. Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Lee, Ackerman, and Katz were inspected in support of this NDA. Dr. Lee was issued a Form FDA 483 citing several observations including the enrollment of a subject with an exclusionary medical history, the lack of completion or the incorrect completion of specific questionnaires by four subjects, a lack of documentation of some adverse events, and several data entry errors (for one subject). Dr. Lee acknowledged these observations in her written response and indicated that her staff had been re-educated regarding the importance of correct data capture. Most of the observations listed on the Form FDA 483 appear to be isolated, sporadic, and randomly distributed across treatment groups and unlikely to affect critical efficacy or safety parameters. This inspection is preliminarily classified as Voluntary Action Indicated (VAI). Notwithstanding the cited observations, the data generated by this site and submitted by the sponsor appear adequate in support of the respective indication.

Drs. Ackerman and Katz were not issued Form FDA 483s. These inspections are preliminarily classified as No Action Indicated (NAI). The data generated by these two clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

**Note:** The preliminary classifications of the inspections of Drs. Lee, Ackerman, and Katz are based on preliminary communications with the field. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Reports (EIRs).

*{See appended electronic signature page}*

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/s/  
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ROY A BLAY  
08/29/2013

JANICE K POHLMAN  
08/29/2013

SUSAN D THOMPSON  
08/29/2013



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

**Date:** August 23, 2013

**To:** Hylton Joffe, M.D., Director  
Division of Bone, Reproductive and Urologic Products

**Through:** Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** Evaluation of Human Abuse Potential Study  
Flibanserin (Girosa)  
NDA 22-526 (resubmission)  
Indication: Treatment of Hyposexual Desire Disorder in  
Premenopausal Women (100 mg/day)  
Sponsor: Boehringer Ingelheim Pharma GmbH and Co.  
PDUFA Goal Date: September 27, 2013

**Materials reviewed:** Sponsor-submitted human abuse potential study report,  
“A Single-Dose, Randomized, Double-Blind, Placebo- and  
Active-Controlled Crossover Study to Evaluate the Relative  
Abuse Potential of Flibanserin in Healthy Recreational Poly-  
Drug Users” (Study #SPR-12-05, 3/29/13); FDA Statistical  
Review and Evaluation of Flibanserin (Dr. Ling Chen,  
DARRTS NDA 22-526, 8/21/13)

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## **1. Background**

This memorandum responds to a consult request by the Division of Reproductive and Urology Products to evaluate the study report for a human abuse potential study conducted with flibanserin. This report was provided as part of the resubmitted NDA, in response to a Complete Response letter (August 27, 2010) in which the Sponsor was informed that it was not possible to determine the abuse potential of flibanserin in the absence of a human abuse potential study. No other new abuse-related data were submitted in the revised NDA. CSS previously provided feedback to the Sponsor regarding the protocol design for the human abuse potential study on August 3, 2012 and on January 20, 2013.

Flibanserin is a new molecular entity with 5-HT<sub>1A</sub> agonist/5-HT<sub>2A</sub> antagonist properties. It is also a ligand at 5HT<sub>2B</sub>, 5HT<sub>2C</sub> and dopamine D4 receptors, although no information has been provided to determine functionality at these sites. The Sponsor for this drug is Sprout Pharmaceuticals, Inc., which licensed flibanserin from Boehringer-Ingelheim for the indication of hypoactive sexual desire disorder in premenopausal women. Flibanserin is not currently marketed in any country.

## **2. Conclusions**

- 1) The human abuse potential study conducted with flibanserin provided in the resubmitted NDA does not fulfill the 2010 Complete Response requirement for the submission of a valid human abuse potential study. Thus, it is still not possible to fully assess the abuse potential of flibanserin.
- 2) CSS has determined that the human abuse potential study conducted with flibanserin is invalid and inconclusive based on the evaluation of the statistical analysis of the study conducted by Dr. Ling Chen in the Office of Biostatistics at FDA. Specifically, the study data were deemed uninterpretable because of the following problems identified by Dr. Chen:
  - a) On the primary subjective measure of Drug Liking visual analog scale (VAS), the positive control, zolpidem, did not produce an appropriate positive subjective response in a large percent of subjects. Specifically, 33% of subjects who received 15 mg zolpidem and 27% of subjects who received 30 mg zolpidem had an Emax response that was in the neutral range (40-60 on the bipolar scale of 0 to 100). This neutral response is similar to the response expected from placebo. The response to a positive control drug like zolpidem should have been > 60, which indicates drug liking.
  - b) Inappropriately large placebo responses were observed for secondary subjective measures in the study. These secondary measures use unipolar scales ranging from 0-100, with an acceptable neutral response of 0-20. For example:

- For Good Drug Effects VAS, 18 of 34 subjects (53%) had Emax values in response to placebo that were  $\geq 20$  on the unipolar scale.
- For High VAS, 11 of 34 subjects (32%) had Emax values in response to placebo that were  $\geq 20$  on the unipolar scale.

c) On the secondary subjective measure of High VAS, predose responses were collected in each treatment period before dosing for each subject. However, these predose responses were not utilized in the study analysis. Instead, the Sponsor inappropriately used baseline responses (defined as predose responses for each subject in Period 1 on Day 1) in calculating the response for each subject for each of the treatments for each of the subjective measures. The baseline responses were also used for the covariate in the statistical analysis.

d) Inappropriately large predose responses were observed in the study. For example, for the subjective measure of High VAS (a unipolar measure ranging from 0 to 100, with an acceptable neutral predose response between 0 to 20), 32 of 34 subjects (94%) had a predose response of 46 to 51.

e) On two subjective measures that assess retrospective (next-day) positive responses to a drug treatment, a very large number of subjects did not identify the positive control, zolpidem, as producing positive responses. For Overall Drug Liking VAS (a bipolar scale of 0 to 100, with an acceptable neutral score ranging from 40 to 60), 25 of 34 subjects (74%) and 24 of 34 subjects (71%) had an Emax response to the positive control, zolpidem at 15 mg and 30 mg (respectively), of  $< 55$  (within the neutral or drug disliking response range). Similarly, for Take Drug Again VAS (a bipolar scale), 22 of 34 subjects (65%) and 21 of 34 subjects (62%) had an Emax response to the positive control, zolpidem at 15 mg and 30 mg (respectively), of  $< 55$  (within the neutral or drug disliking response range). The response to a positive control drug like zolpidem on these scales should have been  $> 60$ , which indicates drug liking.

3) The uninterpretable data described above suggest that there may have been study design issues. An examination by CSS of the study protocol reveals design flaws that are unacceptable. These issues were communicated to the Sponsor prior to study initiation and include the following:

a) The inclusionary criteria allows for the use of alcohol as a “sedative drug” for purposes of an acceptable drug history. CSS previously informed the Sponsor that an acceptable history of sedative abuse should be based only on the use of benzodiazepines and barbiturates, and should not be based on alcohol use. Thus, it is possible that the poor responses observed in the study to the positive control, zolpidem, were based on subjects qualifying for the study solely on the basis of use of alcohol rather than other acceptable sedatives.

- b) The final study report does not provide a definition for an “acceptable placebo response” in the Qualification Phase. An acceptable response to the positive control was deemed to be at least a 10 point increase compared to placebo. However, if the placebo response was outside the acceptable neutral range, then this would invalidate the qualification criterion. Thus, it is possible that the inappropriate placebo responses observed in the study simply paralleled inappropriate placebo responses during the Qualification Phase.
- c) Subjects were served breakfast two hours after drug administration. Thus, it is possible that being served food or consuming food may have interfered with data collection, disrupted a subject’s concentration for responding to subjective measures, or altered the emotional state of the subject while answering questions about positive subjective responses to the drug treatment.
- 4) The data described above suggest that study subjects were not appropriately trained in the study procedures, including the differences in responding using both unipolar and bipolar scales. This may account for the apparent inability of many subjects to provide:
- a) An appropriate neutral (predose or placebo) response on a unipolar scale (< 20 on a scale of 0 to 100) after having immediately responded on a bipolar scale (where 40-60 is an appropriate neutral response on a scale of 0 to 100).
- b) An apparent inability of many subjects to provide an appropriate positive response to the positive control drug, zolpidem, when answering on bipolar and unipolar scales.

### **3. Recommendation**

The Sponsor must conduct a valid human abuse potential study in well-trained individuals with a history of sedative abuse in order to fully assess the abuse potential of flibanserin.

## **4. Discussion**

### **4.1 Clinical Studies**

#### **4.1.1. Outline of Human Abuse Potential Study Conducted with Flibanserin**

**Study Title:** A Single-Dose, Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Relative Abuse Potential of Flibanserin in Healthy Recreational Poly-Drug Users (Study #SPR-12-05)

**Investigators:** Bradley D. Vince, Vince and Associates Clinical Research, Overland Park, Kansas

**Objectives:** The primary objectives of this study were:

- 1) to evaluate the abuse potential of flibanserin compared to placebo
- 2) to evaluate the abuse potential of flibanserin compared to zolpidem, and
- 3) to evaluate the abuse potential of zolpidem compared to placebo

The secondary objective was to evaluate the safety and tolerability of flibanserin.

**Study Site:** All study sessions were conducted in a clinical research unit, with access to emergency responders for medical and psychiatric adverse events.

**Methodology:**

- This is a double-blind, placebo-controlled, randomized 6-way crossover study evaluating the effects of acute oral doses of flibanserin, zolpidem, and placebo on subjective measures and physiological measures.
- The study included a screening visit, a Qualification Phase, a Treatment Phase, and a post-treatment follow-up/end of study visit (5 to 14 day).

*Subjects:*

- Adults (age 18-55) with a body mass index (BMI) ranging from 18-32 and a minimum weight of 50 kg
- Subjects must have recreationally used at least two classes of abusable drugs (“e.g., THC, opiates”) at least twice in the past 3 months. Subjects must have at least 10 lifetime experiences with sedative drugs (defined as benzodiazepines, barbiturates and alcohol).
- Exclusionary criteria are standard. Notably, subjects were excluded if they have a self-reported history of drug or alcohol dependence, but an exception is made for caffeine dependence and for participation in smoking cessation programs, as long as individuals do not smoke more than 20 cigarettes or 2 cigars a day and have not used a tobacco cessation product within the past month.
- A total of 106 subjects entered the Qualification Phase. Of these subjects, 36 (26 men, 10 women) entered the Treatment Phase, with 34 study completers.

*Qualification Phase*

- Test conditions were 20 mg oral zolpidem or placebo in a randomized, 4-day, 2-session series of testing with a washout period of at least 24 hours.
- In order to qualify for the Treatment Phase, subjects had to:
  - Tolerate flibanserin
  - Discriminate zolpidem from placebo (at least 10 point difference in Emax on VAS Momentary Drug Liking)

*Zolpidem is justified as the positive control on the basis of its ability to produce sedation, which has been previously observed in clinical studies with flibanserin. The dose is inbetween the doses used in the Treatment Phase (15 and 30 mg).*
  - Show “an acceptable placebo and temporal response”
  - Have “appropriate temporal response patterns” to both drugs

- Show responses on other subjective measures “consistent with those seen on the VAS Drug Liking”
- Exhibit appropriate study participation behavior.

#### *Treatment Phase*

- Sessions occurred on Days 1, 4, 7, 10, and 13. The washout period between sessions was at least 48 hours. Given that the half-life of flibanserin is 7 hours, the 48-hour period represents ~7-elimination half-lives. The half-life of zolpidem is only 3 hours, so this is 16 elimination half lives for this drug.
- Drugs (all drugs were overencapsulated):
  - Flibanserin (100, 200 and 250 mg, p.o.)  
*The 100 mg dose is the proposed therapeutic dose. The 250 mg dose is the maximum tolerated dose tested to date.*
  - Zolpidem (15 and 30 mg, p.o.)  
*Zolpidem is justified as the positive control on the basis of its ability to produce sedation, which has been previously observed in clinical studies with flibanserin. The doses are standard for human abuse potential studies.*
  - Placebo (p.o.)
- Subjects were fasted for at least 8 hours prior to drug administration and fasted for 2 hours following drug administration. This suggests that subjects received breakfast during the active collection of subjective data, although the protocol does not state this definitively.
- A follow-up visit was conducted within 5-14 days after the last test session.

#### *Outcome Measures for Qualification and Treatment Phases*

- *Subjective Measures:*
  - The primary endpoint was visual analog scale (VAS) for At the Moment Drug Liking (Emax, bipolar scale).
  - Secondary endpoints included VAS for:
    - Momentary Drug Liking (Emin, bipolar scale),
    - Overall Drug Liking (Emax and Emin at 12 hour and 24 hour scores),
    - High (Emax and Emin),
    - Good Drug Effects (Emax and Emin),
    - Bad Drug Effects (Emax and Emin),
    - Alert/Drowsiness scale (Emax, Emin, bipolar scale) and
    - Any Drug Effects (Emax and Emin)
  - Secondary endpoints also included Addiction Research Center Inventory (ARCI) for:
    - MBG scale (Euphoria) (Emax and Emin),
    - LSD scale (Dysphoria) (Emax and Emin),
    - PCAG scale (Sedation) (Emax v),
    - Amphetamine scale (Emax and Emin).
  - Secondary endpoints also included VAS for:
    - Drug Similarity (arithmetic mean at 12 hours),

- Take Drug Again (Emax and Emin at 12 and 24 hour scores),
    - Subjective Drug Value (Emax and Emin at 12 and 24 hour scores).
  - All measures were taken at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after drug treatment administration, with the following exceptions:
    - No baseline evaluations for VAS Momentary Drug Liking, Good Drug Effects, Bad Drug Effects, and Any Drug Effects
    - VAS for Subjective Drug Value and Take Drug Again were taken at 12 and 24 hours
    - The Drug Similarity Questionnaire were taken at 12 hours
    - 24 hour assessments did not occur in the Qualification Phase
- *Physiological Measures:*
  - Adverse events were monitored from the first drug session until the follow-up visit.
  - Vital signs were monitored at screening, upon admission to the study ward and at hours 1, 3, 8, 12 and 24 after drug administration.
  - Single EEG was recorded at screening and at follow-up.
  - Blood and urine were collected at screening, on the day before study procedures begin and at follow-up for purposes of assessing hematology and urinalysis. Blood collected for pharmacokinetic purposes was drawn at the time of each subjective measure collection.

#### **4.1.1.2 Findings and Interpretations**

CSS has evaluated the statistical analysis conducted by FDA Statistician Dr. Ling Chen (DARRTS, NDA 22-526, 8/21/13) regarding the human abuse potential study conducted by the Sponsor with flibanserin.

In the report for this study, the Sponsor concluded that, “The findings that all 3 doses of flibanserin were associated with significantly less ‘at the moment’ drug liking than the 30-mg dose of zolpidem, coupled with its sedative effects and the fact that flibanserin was generally associated with fewer positive effects than the 30-mg dose of zolpidem and the ‘subjective drug value’ for flibanserin was generally less than for zolpidem, indicate that flibanserin, even at a dose of 250 mg (2.5 times the proposed therapeutic dose), is less preferred than a 30-mg dose of zolpidem. Single doses of 100, 200, and 250 mg of flibanserin and single doses of 15 and 30 mg of zolpidem were well tolerated in this population of recreational polydrug users, with no new safety concerns identified.”

However, as described below, analyses of both the primary measure and the secondary measures in this study have identified significant problems associated with the data resulting from these measures. Thus, the conclusions drawn by the Sponsor are not accurate and the study cannot be used to satisfy the requirement for a valid human abuse potential study.

Throughout this section, the six treatments tested in the study will be abbreviated as follows: flibanserin 100, 200 and 250 mg (F100, F200, F250), zolpidem 15 and 30 mg (Z15 and Z30), and placebo (P).

*Primary Analysis:*

In order for the study to be considered valid, the positive control, zolpidem, at either the 15 or 30 mg dose, must statistically differentiate based on Emax from placebo on the primary measure of Drug Liking VAS. The Drug Liking VAS measure is a bipolar scale ranging from 0 to 100, with a neutral response being 50. An acceptable neutral response ranges from 40-60. Emax scores of 0 to 49 indicate drug disliking, while Emax scores of 51 to 100 indicate drug liking.

Table 1 (below) summarizes the mean, standard error, minimum, the first quartile (Q<sub>1</sub>), median, the third quartile (Q<sub>3</sub>), and maximum for six treatments in the study and for the treatment differences between flibanserin and zolpidem or placebo, as well as among doses of each drug for Emax of Drug Liking VAS. Table 2 (below) summarizes the statistical analyses conducted on the treatments.

Table 1: Summary Statistics for Emax on Drug Liking VAS (n = 34) (table reproduced from Dr. Chen's review, DARRTS, NDA 22-526, 8/21/2013)

Treatment or Comparison	Mean	Std Error	Min	Q1	Med	Q3	Max
F100	61.12	2.25	47	51.0	55.0	68.5	96
F200	66.68	2.78	46	51.0	69.5	76.3	99
F250	66.32	2.62	47	53.0	66.5	77.3	98
P	53.82	1.03	48	51.0	52.0	53.3	70
Z15	68.53	2.51	48	52.8	70.0	79.3	100
Z30	74.06	2.88	50	56.8	74.0	87.3	100
Z15-P	14.71	2.67	-18	0.8	12.5	27.5	48
Z30-P	20.24	3.11	-20	2.8	20.5	35.0	51
F100-P	7.29	2.39	-17	-0.3	2.0	14.0	46
F100-Z15	-7.41	2.39	-41	-14.8	-4.0	1.0	19
F100-Z30	-12.94	2.51	-49	-20.8	-12.0	-1.0	6
F200-P	12.85	3.02	-17	0.0	3.5	26.3	48
F200-Z15	-1.85	2.24	-41	-5.5	-0.5	6.0	21
F200-Z30	-7.38	2.70	-49	-14.0	-6.0	-0.8	42
F250-P	12.50	2.83	-16	0.0	4.5	26.3	48
F250-Z15	-2.21	2.05	-44	-6.5	-2.0	4.5	18
F250-Z30	-7.74	3.10	-52	-16.0	-7.5	-0.5	41
Z30-Z15	5.53	2.61	-43	1.8	4.5	15.0	37
F200-F100	5.56	2.03	-16	-1.3	2.0	13.5	36
F250-F100	5.21	2.18	-18	-0.3	3.0	14.3	35
F250-F200	-0.35	1.86	-26	-3.0	0.0	2.3	33

Table 2: Statistical Analysis Results for Drug Liking VAS (table reproduced from Dr. Chen's review, DARRTS, NDA 22-526, 8/21/2013)

Measure	Treatment	F100	F200	F250	Z15	Z30	P
	N	34	34	34	34	34	34
Drug Liking VAS	LSmean	61.37	66.78	66.36	68.79	74.16	53.86
	95% CI	(56.50, 66.25)	(61.91, 71.65)	(61.49, 71.23)	(63.91, 73.66)	(69.29, 79.04)	(48.99, 58.73)
	Diff vs Z15/ pval	-7.41 / 0.0423	-2.00/ 0.9678	-2.43/ 0.9284			
	Diff vs Z30/ pval	-12.79/ <.0001	-7.38/ 0.0437	-7.81/ 0.0272			
	Diff vs P/ pval	7.52/ 0.0379	12.92/ <.0001	12.50/ <.0001	14.93/ <.0001	20.31/ <.0001	

Note: pval denotes p-value. All p-values were from the two-sided t test, and adjusted by Tukey - Kramer's method for unequal variances.

Table 2 shows that the responses to Drug Liking VAS for both doses of the positive control, Z15 and Z30, are statistically significantly different from placebo (p values < 0.001 for both conditions). This statistical test validates the study.

Notably, though, as seen in Table 1, the first quartiles of Z15 and Z30 are 52.8 and 56.8 (respectively). These values are within the range of neutral response (~40 to 60) for a bipolar scale such as Drug Liking VAS. This suggests that it is possible that zolpidem, the positive control, did not produce a response that differentiated from placebo in at least 25% of subjects. This possibility is validated through an analysis of individual responses, as described below.

For each dose of flibanserin (F100, F200 and F250), there was a statistically significant increase in response on Drug Liking VAS compared to placebo (p = 0.04, < 0.0001 and < 0.0001, respectively). On the average, there was no significant difference in responses between the two high doses of flibanserin (F200 and F250) and Z15 on Drug Liking VAS (p > 0.10). These data suggest that, on average, the higher doses of flibanserin produce positive subjective responses that are statistically greater than placebo and possibly similar to zolpidem, a Schedule IV drug.

However, the foundation of this analysis may not be accurate, since, as noted above, more than 25% of subjects did not respond appropriately to the positive control, zolpidem. This suggests that the subjects were either not selected properly or were not trained properly. If, instead, every subject in this study had shown an appropriate response to zolpidem (e.g., responded with a score greater than 60 out of 100), there would be an increase in the mean response for each dose of zolpidem that was tested, compared to the current results. If the mean responses to zolpidem increased, then the comparison to flibanserin responses would also likely change.

An analysis of individual responses shows that 5 of 34 subjects (14.7%) have placebo responses greater than 60 on Drug Liking VAS, which is outside the acceptable neutral response for placebo that ranges from 40-60. In contrast, the positive control, zolpidem, produced an inappropriate response in the neutral range of 40-60 for 11 of 34 subjects

(32.6%) who received Z15 and for 9 of 34 subjects (26.5%) who received Z30. These data demonstrate that a large percent of subjects did not respond to the positive control with positive responses greater than placebo, as predicted by using the first quartile in Table 1 (above).

### *Secondary Analyses*

As described above in Methods, the secondary subjective measures for this study included VAS for: Overall Drug Liking, High, Good Drug Effects, Bad Drug Effects, Alert/Drowsiness, Any Drug Effects, Drug Similarity, Take Drug Again, Subjective Drug Value. All of these scales were unipolar, with the exception of Alert/Drowsiness, Overall Drug Liking and Take Drug Again, which are bipolar. For unipolar scales (0-100), neutral is 0 with an acceptable neutral response being 0 to 20. For bipolar scales (0-100), neutral is 50 with an acceptable neutral response being 40-60.

During the statistical analysis by Dr. Chen, the following problems were identified for the secondary measures:

1) Large placebo responses were observed in the study for two secondary measures that evaluate positive subjective responses. As noted above, an acceptable neutral response on a unipolar visual analog scale is 0-20.

- For Good Drug Effects VAS, 18 of 34 subjects (53%) had Emax values in response to placebo that were  $\geq 20$  on the unipolar scale ranging from 0 to 100.
- For High VAS, 11 of 34 subjects (32%) had Emax values in response to placebo that were  $\geq 20$  on the unipolar scale ranging from 0 to 100.

2) On the secondary subjective measures of High VAS, predose responses were collected in each treatment period before dosing for each subject in the study. However, these predose responses were not utilized in the statistical analysis. Instead, the Sponsor inappropriately used baseline responses (defined as predose responses for each subject in Period 1 on Day 1) in calculating the response variable and the covariate in the statistical model for the analysis.

3) Inappropriately large predose responses were observed in the study. For example, for the subjective measure of High VAS (a unipolar measure ranging from 0 to 100), 32 of 34 subjects (94%) had a predose response of 46 to 51 in the first treatment period. On a unipolar scale, an acceptable neutral predose response is between 0 to 20. However, on a bipolar scale (such as the primary measure, Drug Liking VAS, where 50 is neutral), an acceptable neutral predose response is between 40 to 60 on a scale ranging from 0 to 100. Thus, it is possible that subjects were not appropriately able to register neutral responses when asked to switch between bipolar and unipolar scales.

4) On the subjective measure Overall Drug Liking VAS (a bipolar scale of 0 to 100, with an acceptable neutral score ranging from 40 to 60), 25 of 34 subjects (74%) and 24 of 34

subjects (71%) had an Emax response to the positive control, zolpidem at 15 mg and 30 mg (respectively), of < 55. Similarly, for the subjective measure Take Drug Again VAS (a bipolar scale), 22 of 34 subjects (65%) and 21 of 34 subjects (62%) had an Emax response to the positive control, zolpidem at 15 mg and 30 mg (respectively), of < 55.

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/s/  
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KATHERINE R BONSON  
08/23/2013

SILVIA N CALDERON  
08/23/2013

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2013-060
APPLICATION NUMBER	<b>NDA 22526</b>
LETTER DATE/SUBMISSION NUMBER	<b>March 29, 2013</b>
PDUFA GOAL DATE	September 29, 2013
DATE OF CONSULT REQUEST	May 2, 2013
REVIEW DIVISION	DBRUP
MEDICAL REVIEWER	<b>Daniel Davis</b>
REVIEW DIVISION PM	Charlene Williamson
SEALD REVIEWER(S)	<b>Ashley F. Slagle</b>
REVIEW COMPLETION DATE	<b>August 14, 2013</b>
ESTABLISHED NAME	Flibanserin
TRADE NAME	Currently under review
APPLICANT	Sprout Pharmaceuticals
ENDPOINT(S) CONCEPT(S)	<b>Sexual desire</b>
MEASURE(S)	FSFI
CLINICAL OUTCOME ASSESSMENT TYPE	<b>PRO</b>
INDICATION	Hypoactive sexual desire disorder (HSDD)
INTENDED POPULATION(S)	Pre-menopausal women in the United States

## **A. EXECUTIVE SUMMARY**

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding NDA 22526. The sponsor has used the Female Sexual Function Index (FSFI) (items 1 and 2) for the measurement of desire to support a primary endpoint in a clinical trial of patients with Hypoactive Sexual Desire Disorder (HSDD), who are premenopausal women in the United States.

While multiple other PRO endpoints were used in the clinical trials, this SEALD review focuses only on FSFI Items 1 and 2 for the measurement of sexual desire. The consult request also requests consultation on the Sexual Interest and Desire Inventory (SIDI); however, the SIDI was not identified as a primary or secondary endpoint. As SEALD reviews are limited to those instruments that are proposed to support only primary or secondary endpoints, the SIDI was not reviewed.

The review concludes that the evidence submitted by the sponsor is inadequate to demonstrate the content validity of the FSFI sexual desire domain (items 1-2) in the stated context of use. We agree that the studies 511.144 and 511.151, in addition to the original instrument development work, provide sufficient evidence that the items in the FSFI use words and phrases that are understood by patients and are relevant to their condition. However, we do not agree that these studies provide sufficient evidence that the two items in the sexual desire domain comprehensively and appropriately capture the relevant experiences of patients diagnosed with HSDD in order to show and describe treatment benefit. Sexual desire is a complex, multi-domain experience with cognitive, affective, and motivational elements, having factors associated with both psychological and physiological elements, as well as social, situational, relationship, and other factors. A complex, multi-domain claim cannot be substantiated by instruments that do not adequately measure the individual component domain concepts adequately.

Based on the instrument's definition of sexual desire, here are at least three distinct sub-concepts of sexual desire (i.e., wanting to have sexual experience, feeling receptive to a partner's initiation, and thinking or fantasizing about having sex). However, because these components (and potentially others that are being considered implicitly by the patients) are considered together in single items, a change in score of these items does not provide an understanding of what the instrument is really assessing and what the treatment benefit is.

Published evidence (Rosen et al., 2000) of the FSFI indicates it was not developed for patients with HSDD, nor was it developed in line with the PRO Guidance. The conceptual framework is statistically developed, and it is not clear that the items in the sexual desire domain actually represent sexual desire to patients. The current FSFI desire items are more similar to a global type question as sexual desire is multidimensional and the FSFI does not individually assess each

component of sexual desire. Granting an approval or labeling claim based on the findings from the FSFI sexual desire domain will be a review issue, noting that concerns exist with claiming an improvement in sexual desire using the FSFI when we do not know exactly what elements comprise desire to patients or that the FSFI comprehensively captures those elements, and could prove misleading. We have previously recommended qualitative research be performed to establish content validity of the FSFI and its domains, with potential instrument modifications needed. None of the studies submitted by the sponsor adequately support content validity of the FSFI sexual desire domain.

This reviewer is also concerned about the use of Satisfactory Sexual Events (SSEs) as a primary endpoint based on a single, dichotomous item assessing satisfaction. SSE is a broad, multidimensional concept that relies on multiple factors, much like the concept of sexual desire (e.g., psychological, physiological, social, situational, relationship factors), and cannot be validly and reliably measured using one item.

We acknowledge that previous advice to the sponsor and other sponsors seeking HSDD indications has included the recommendation to include SSEs and sexual desire as primary endpoints. Therefore, this review focused primarily on the FSFI and its ability to adequately and appropriately assess sexual desire in the HSDD context of use.

We do not agree that a 28-day recall is appropriate for the FSFI sexual desire domain in this context of use. While it shows similar reliability and consistency with a 7-day version in a nested crossover study, we do not have data to compare it to the preferred 24-hour recall or event-based recall period. We cannot conclude that a 28-day measure validly assesses sexual desire in this context.

If DBRUP determines the study findings based on the FSFI are sufficient to support an approval of flibanserin in the treatment of HSDD, we offer specific recommendations for describing the efficacy findings in the clinical studies section of labeling. These recommendations include: we recommend avoiding the use of the instrument names in labeling; (b) (4)  
), with the recall period clearly noted.

## **B. SUGGESTED RESPONSES TO SPONSOR QUESTIONS**

There are no specific questions from the Sponsor. The division has requested this SEALD consult to evaluate the instruments, particularly the FSFI, used in this NDA resubmission for flibanserin. Responses to the division questions are provided here:

### **Questions:**

- 1. Please review the 7 validation studies and provide an assessment on whether they support the conclusions on efficacy drawn by the sponsor.**

Our review of the 7 validation studies (511.121, 511.74, 511.144, 511.151, 511.73, 511.85, and 511.106) concludes that content validity has not been established for the FSFI sexual desire domain, and therefore cannot support an assessment of efficacy based on improvement of sexual desire.

We have the following concerns:

- Sexual desire is a multidimensional concept and the FSFI does not individually assess each component of sexual desire.
- Claiming an improvement in sexual desire could be misleading when we do not know exactly what elements comprise sexual desire to patients or that the FSFI comprehensively captures those elements.

**2. This resubmission includes a new phase 3 trial, Study 511.147. Please comment on whether you agree with the methods and instruments used in Study 511.147. In particular, we appreciate your comments on two key issues in this trial: 1) the use of two items in the FSFI sexual desire domain as the endpoint measure for change in sexual desire with treatment, and 2) the recall period of 7 versus 28 days.**

We do not agree that the two items in the FSFI sexual desire domain constitute a valid and reliable endpoint for use in HSDD to assess sexual desire. Our particular concerns relate to the content validity of this domain (for details, please see below: Section 5. Content Validity).

While the 28-day recall shows similar reliability and consistency with a 7-day version in a nested crossover study, we do not have data to compare either the 28-day or 7-day recall to a preferred 24-hour recall or event-based recall period. We do not agree that the results provide adequate documentation that a 7-day or 28-day recall period provide a valid assessment of the concept of sexual desire as experienced by patients. It is true that the cognitive debriefing study participants did not have a clear preference for a shorter recall period, however, patients generally do not understand the rigorous needs of clinical trial data collection. Patient preference on recall period is only one small piece of the information needed to identify an appropriate recall period. In addition, one needs to understand the nature of the experience – does it wax and wane over time, is the feeling persistent for long periods of time or are there discrete events, and if so how frequently do they occur and what is the likelihood that the event can be recalled accurately? We cannot conclude that a 28-day or 7-day recall validly assesses sexual desire in this context.

Further, we do not agree that a 28-day recall period is sufficiently precise for measuring many concepts in clinical trials, and particularly one that involves episodes of a cognitive, affective and motivational orientation that vary in intensity and duration, such as desire. The issues of recall based on global self-perceptions may be especially acute with a concept like sexual desire. PRO instruments that call for patients to rely on memory, especially if they must recall over a long period of time, compare their current state with an earlier period, or average their response over a period of time, are likely to undermine content validity. Response is likely to be influenced by the patient's state at the time of recall. For these reasons, items with short recall periods or items that ask patients

to describe their current or recent state are usually preferable. If detailed recall of experience over a period of time is necessary, we recommend the instrument use appropriate methods and techniques for enhancing the validity and reliability of retrospectively reported data (e.g., ask patients to respond based on their worst (or best) experience over the recall period or make use of a diary for data collection).

Based on the FSFI definition of sexual desire or interest that includes wanting, feeling receptive and fantasizing, it appears that sexual desire is best construed as a multi-domain psychological state. In the absence of a true understanding of what sexual desire means to HSDD patients through well-designed qualitative research, we assume that such mental events would be expected to be transient, a relatively short recall period should be used.

No documentation or discussion has been identified in protocol 511.147 (revision D) that describes what, if any, steps were taken to provide evidence of a minimum change in score that defines an improvement in the FSFI sexual desire primary endpoint a priori. We recommend that an a priori level of change be specified in order to ensure the change is clinically meaningful to patients. Statistically significant change does not provide sufficient evidence of clinically meaningful change.

**3. Please comment on whether you agree with the conclusions made by Rosen and Derogatis in Study SPR-FSFI- 01, which summarized and findings from the 7 validation studies listed above as well as from the literature.**

We agree that the studies 511.144 and 511.151, in addition to the original instrument development work, provide sufficient evidence that the items in the FSFI use words and phrases that are understood by patients and are relevant to their condition . However, we do not agree that these studies provide sufficient evidence that the items in the sexual desire domain are comprehensive, and accurately and fully reflect all of the components of the concept of sexual desire to patients. Therefore, these studies do not provide sufficient evidence of content validity for the FSFI sexual desire domain. These cognitive interviews do not provide the complete concept elicitation data needed to ensure comprehensiveness of the items. We therefore encourage additional well-designed open-ended concept elicitation interviews with patients representative of the clinical trial population to fully elicit from the patient perspective, what are the key features of sexual dysfunction, including sexual desire, in order to assess, likely modify, and ensure content validity of the FSFI and FSFI sexual desire domain. Note that assessing factor structure of the items and domains does not ensure content validity.

Until content validity is confirmed, other measurement properties of the FSFI sexual desire domain, as well as interpretation assessments (e.g., minimal clinical important difference (MCID) or responder definitions) assessed in validation studies cannot be reviewed and interpreted.

**4. Any additional comments on the use of FSFI and SIDI instruments to support the proposed efficacy endpoints are welcome.**

The SIDI is not identified as a primary or secondary endpoint in study protocol 511.147. As SEALD reviews are limited to those instruments that are proposed to support only primary or secondary endpoints, the SIDI was not reviewed.

While this review has focused on the FSFI desire domain in study 511.147, the FSDS-R item 13 to assess sexual distress raises similar concerns as the FSFI sexual desire items, and the SSE endpoint. Sexual distress is also a multi-domain concept that cannot be validly assessed using a single item (FSDS-R item 13).

If DBRUP determines the study findings based on the FSFI are sufficient to support an approval of flibanserin in the treatment of HSDD, we offer specific recommendations for describing the efficacy findings in the clinical studies section of labeling. These recommendations include: we recommend [REDACTED] (b) (4)

[REDACTED] with the recall period clearly noted.

[REDACTED] (b) (4)

## **C. STUDY ENDPOINT REVIEW**

This is a resubmission for flibanserin, a serotonin 5-HT agonist and 5-HT antagonist being developed for the treatment of hypoactive female sexual disorder (HSDD) in pre-menopausal women. The original NDA included two pivotal efficacy trials which used as co-primary endpoints of number of sexually satisfying events (SSE) and eDiary measurements (two questions) on sexual desire. The NDA received a CR action in 2010. In the CR letter, the Division recommended a new clinical trial be conducted to “assess the effects of flibanserin on SSEs and sexual desire as coprimary endpoints. If an instrument other than the eDiary was used, it would need to have adequate content validity, including recall validity, and acceptable measurements” consistent with the 2009 PRO guidance.

The resubmission also includes validation studies and a summary report on the FSFI instrument by Rosen and Derogatis (**Study SPR-FSFI-01**), entitled “The Female Sexual Function Index (FSFI): Update on Content Validity, Recall Period Effects, and other Measurement Properties of the FSFI.”

## **1 CLINICAL OUTCOME ASSESSMENT MEASURE(S)**

### FSFI

- The FSFI is a multidimensional 19 item self-report questionnaire developed to assess female sexual function (see Appendix A) in women with HSDD. The instrument consists of 6 domains: sexual desire, arousal, lubrication, orgasm, satisfaction, pain. The version provided in protocol 511.147 uses a 4 week recall period. Items 1 and 2 are proposed for use to support the primary endpoint related to change in sexual desire. Item 1: How often did you feel sexual desire or interest? Response options range from 5 (Almost always or always) to 1 (Almost never or never). Item 2: How would you rate your level (degree) of sexual desire or interest? Response options range from 5 (Very high) to 1 (Very low or none at all).
- A user manual was not identified for review.
- Protocol 511.147 indicates that the FSFI will be given to subjects during clinic visits at screening, baseline, and periods 4, 5, 7, 8, and 9 (occurring every 4 weeks). The instrument mode of administration is not identified, however it appears it will be a pen and paper administration.
- Training method/materials were not identified for review.
- Scoring of the assessment is as follows:

**FSFI® DOMAIN SCORES AND FULL SCALE SCORE**

The individual domain scores and full scale (overall) score of the FSFI can be derived from the computational formula outlined in the table below. For individual domain scores, add the scores of the individual items that comprise the domain and multiply the sum by the domain factor (see below). Add the six domain scores to obtain the full scale score. It should be noted that within the individual domains, a domain score of zero indicates that the subject reported having no sexual activity during the past month. Subject scores can be entered in the right-hand column.

Domain	Questions	Score Range	Factor	Minimum Score	Maximum Score	Score
Desire	1, 2	1 – 5	0.6	1.2	6.0	
Arousal	3, 4, 5, 6	0 – 5	0.3	0	6.0	
Lubrication	7, 8, 9, 10	0 – 5	0.3	0	6.0	
Orgasm	11, 12, 13	0 – 5	0.4	0	6.0	
Satisfaction	14, 15, 16	0 (or 1) – 5	0.4	0.8	6.0	
Pain	17, 18, 19	0 – 5	0.4	0	6.0	
<b>Full Scale Score Range</b>				<b>2.0</b>	<b>36.0</b>	

*Reviewer comment: It is unclear why the items in the sexual desire domain are scored 1-5, with a minimum score for the domain as 1.2. We recommend that a minimum score should be 0, not 1 (nor 1.2 for the total domain score).*

**2 TARGETED CLAIMS**

Based on the sponsor’s proposed labeling (dated March 2013; excerpts below), labeling claims are being sought are related to improvement in sexual desire, improvement in SSEs, (b) (4)

(b) (4)



(b) (4)

*Reviewer's comments: While this review has focused on the FSFI desire domain in study 511.147, the FSDS-R item 13 to assess sexual distress raises similar concerns as the FSFI sexual desire items, and the SSE endpoint. Sexual distress is a multi-domain concept that cannot be validly assessed using a single item.*

(b) (4)



(b) (4)

(b) (4)

### **3 ENDPOINT MODEL**

The sponsor proposes the following trial objectives/endpoints:

(b) (4)



#### 4 CONCEPTUAL FRAMEWORK

The FSFI conceptual framework:

Item	Domains	Concept
1. How often feel sexual desire/interest	Sexual Desire	Sexual Function
2. Rate level of sexual desire		
3. How often feel sexually aroused	Arousal	
4. Rate level of sexual arousal		
5. How confident about becoming sexually aroused		
6. How often been satisfied with arousal		
7. How often become lubricated	Lubrication	
8. How difficult to become lubricated		
9. How often maintain lubrication		
10. How difficult to maintain lubrication		
11. How often reach orgasm	Orgasm	
12. How difficult to reach orgasm		
13. How satisfied with ability to reach orgasm		
14. How satisfied with amount of emotional closeness	Satisfaction	

15. How satisfied with sexual relationship with partner		
16. How satisfied with overall sexual life		
17. How often experience discomfort/pain during	Pain	
18. How often experience discomfort/pain following		
19. Rate level of discomfort/pain following		

The Sponsor is proposing to use the first two items, the sexual desire domain of the FSFI, to support a primary endpoint related to change in sexual desire. The conceptual framework corresponds to the desired endpoint in that they are both related to sexual desire. However, significant concerns exist with the content validity of the instrument, and whether the two items are in fact an adequate measure of sexual desire in the HSDD population. See content validity section below.

## **5 CONTENT VALIDITY**

The Sponsor has provided Study SPR-FSFI-01 that summarizes the evaluation and validation of the FSFI, including the 2-item sexual desire domain. Initial development work of the FSFI was completed using experts and patients with FSAD (not HSDD), although patients were not involved in the development of the instrument in a way consistent with the recommendations of the FDA PRO Guidance. Additional evaluation work in patients with HSDD has been subsequently completed or otherwise provided by the Sponsor.

In the CR action in 2010, the Division indicated that “the instrument that is used to measure sexual desire should have adequate content validity, including recall validity, and acceptable measurement properties when used to evaluate premenopausal women with HSDD, consistent with the concepts set forth in the [FDA PRO Guidance].” The Sponsor indicates that “the Division’s concerns were addressed by two recent validation studies performed subsequent to the CR letter.”

The Sponsor includes description and study reports of two studies that attempt to address content validity concerns (Study 511.144 and 511.151), which are summarized in a publication by Revicki et al (2011). These studies of the content validity have been reviewed by SEALD previously for another Sponsor and our conclusions have not changed:

*The first study included premenopausal women aged 18-50 years with a diagnosis of generalized HSDD. Participants were required to have been in stable relationships, defined as having a duration  $\geq 6$  months. Participants also needed a Female Sexual Distress Scale score  $\geq 15$  to qualify for inclusion. The second study used similar criteria, although it allowed recruitment of postmenopausal and premenopausal women, but excluded women who might have any other form of FSD.*

*Both studies were described as cognitive debriefings on the entire FSFI, augmented with general questions regarding the comprehensiveness of the instrument, and a few*

*questions on the redundancy or completeness of the sexual desire items. As this was not a complete concept elicitation, there was no evidence for concept saturation collected or attempted beyond the questions asking if the two items were sufficient. The results of those queries suggested that 53% in one study and 70% in the other felt FSFI captured their feelings about reduced sexual desire.*

*Study participants were also queried about their preference for a recall period that fit the most appropriate time frame over which to assess frequency and intensity of sexual desire. The findings were not wholly conclusive, as the authors report “[a]mong those who had preference, most women in both studies thought that a recall period of 4 weeks or 1-2 weeks was the most appropriate time frame over which to assess the frequency of sexual desire (question 1) or level of sexual desire (question 2)... Overall, there was no clear preference for 1-2 week recall, or a 4-week recall period.” It was clearer that a minority of participants favored a 24-hour recall; the total across studies was 17%.*

No evidence of open-ended concept elicitation interviews with the intent to identify all of the relevant experiences related to sexual function or dysfunction, including the sexual desire domain (and its components) has been provided. The cognitive interviews described in the two studies submitted by the Sponsor begin with the administration of the FSFI instrument and then include a few open ended questions, none of which seek to understand what sexual desire means to patients with HSDD. Patients are asked if the questions are relevant and comprehensive, however on review of the transcripts it is clear that most patients agree that multiple components make up the concept of sexual desire and include, but are not limited to the components described in the definition of sexual desire in the FSFI instructions: wanting to initiate sexual activity, being receptive to sexual activity, or just thinking or fantasizing about it. Engaging in open ended concept elicitation interviews may reveal there are additional components of sexual desire that should be included as separate items in an assessment of sexual desire, or may conclude that the elements currently being captured are comprehensive. However, concerns remain about assessing these multiple elements using single items (i.e., double barreled items) that query on sexual desire intensity and frequency. For example, a treatment effect may be driven solely by women experiencing more sexual fantasies, and reporting increased sexual desire based on the FSFI definition, but this may not be the relevant component of treatment benefit to women suffering from HSDD.

*Reviewer’s comment: We agree that the studies 511.144 and 511.151, in addition to the original instrument development work, provide sufficient evidence that the items in the FSFI use words and phrases that are understood by patients and are relevant to their condition. However, we do not agree that these studies provide sufficient evidence that the items in the sexual desire domain are comprehensive, and accurately and fully reflect all of the components of the concept of sexual desire to patients. Therefore, these studies do not provide sufficient evidence of content validity for the FSFI sexual desire domain. These cognitive interviews do not provide the complete concept elicitation data needed to ensure comprehensiveness of the items. We therefore encourage additional well-designed open-ended concept elicitation interviews with patients with*

*HSDD to fully elicit from the patient perspective, what are the key features of sexual dysfunction, including sexual desire, in order to assess, potentially modify, and ensure content validity of the FSFI and FSFI sexual desire domain. It is expected that the FSFI items would need to be modified in order to adequately evaluate sexual desire and support claims of improved sexual desire in a way that is not misleading.*

Recall period:

The Sponsor includes description and study reports of two studies that attempt to address the recall validity concerns (Study 511.144 and 511.151), which are summarized in a publication by Revicki et al (2011). These studies have been reviewed by SEALD previously for another Sponsor and our conclusions have not changed:

!

*Study participants were also queried about their preference for a recall period that fit the most appropriate time frame over which to assess frequency and intensity of sexual desire. The findings were not wholly conclusive, as the authors report “[a]mong those who had preference, most women in both studies thought that a recall period of 4 weeks or 1-2 weeks was the most appropriate time frame over which to assess the frequency of sexual desire (question 1) or level of sexual desire (question 2)...Overall, there was no clear preference for 1-2 week recall, or a 4-week recall period.” It was clearer that a minority of participants favored a 24-hour recall; the total across studies was 17%.*

In addition, the Sponsor provides results from a nested crossover study in 511.147, and indicates that no significant differences exist between subjects randomized to first receive a 7-day recall instruction, compare to the responses of subjects randomized to first receive a 28-day recall instruction. Each participant also served as their own control with the crossover design. No significant differences or meaningful trends were observed between the measures, with the 28-day recall having equivalent means and distribution of responses compared to the 7-day recall.

*Reviewer’s comment: We agree that the 7-day and 28-day recall periods provide similar results and can be considered similarly reliable. However, we do not agree that the results provide adequate documentation that a 7-day or 28-day recall period provide a valid assessment of the concept of sexual desire as experienced by patients. It is true that the cognitive debriefing study participants did not have a clear preference for a shorter recall period, however, patients generally do not understand the rigorous needs of clinical trial data collection. Patient preference on recall period is only one small piece of the information needed to identify an appropriate recall period. In addition, one needs to understand the nature of the experience – does it wax and wane over time, is the feeling persistent for long periods of time or are there discrete events, and if so how frequently do they occur and what is the likelihood that the event can be recalled accurately? In the case of sexual desire, that is best conceptualized as a psychological state based on the definition in the DSM-IV, and a state that may change daily or even hourly, a shorter (e.g., 24 hour) recall is needed.*

## **6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)**

Literature review and study details providing documentation of other measurement properties have been provided by the Sponsor. Many of the details provided are evidence of reliability, construct validity and ability to detect change from populations other than the HSDD population. In addition, MCID information is provided, however, this relates to the overall instrument score, and no information is provided for the clinically meaningful change in the sexual desire domain of the FSFI. Because content validity must be fully established prior to evaluating other measurement properties, it is premature to review these data.

*Reviewer's comment: Until content validity is confirmed, it is premature to evaluate and review other measurement properties of the FSFI sexual desire domain.*

## **7 INTERPRETATION OF SCORES**

The mean change from baseline was compared across treatment groups for statistically significant differences on the FSFI sexual desire domain scores. However, the 511.147 protocol (revision D) does not describe an a priori minimum change in score that is clinically relevant or describe what if any steps were taken to provide evidence of a minimum change in score that defines an improvement in the measurement concept of sexual desire. Study 511.147 study results describe an anchor based approach to define responders, however, this does not appear to have been established a priori, and study results do not clearly describe how it was applied to interpret the primary sexual desire domain endpoint study results.

*Reviewer's comment: No documentation or discussion has been identified that describes what, if any, steps were taken to provide evidence of a minimum change in score that defines an improvement in the FSFI sexual desire primary endpoint a priori. We recommend that an a priori level of change be specified in order to ensure the change is clinically meaningful to patients. Statistically significant change does not provide sufficient evidence of clinically meaningful change.*

## **8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION**

No details have been provided related to translation and cultural adaptation. All study sites are in the U.S.

## **9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION**

N/A

## **10 PROTOCOL AND ANALYSIS PLAN**

Study protocol 511.147:

- There is a planned hierarchy of study endpoints that is consistent with the endpoint model and presumed targeted claim(s)
- No user manuals were submitted, however, plans for measure administration do not appear inconsistent or inappropriate. Instructions to study coordinator are clear.
- Each COA endpoint is clearly stated as a specific study objective and multiplicity concerns are addressed by using a hierarchical testing approach.
- Study 511.147 is a double-blind placebo controlled study of 24 weeks duration. Appropriate blinding procedures seem to be in place.
- Instructions provided in the protocol indicate the FSFI instrument will be completed first at each clinic visit. Other procedures and training related to the clinical outcome assessments are not well-described or provided for review.
- Protocol plans appear appropriate for scoring of the measures consistent with development of the measure
- Protocol procedures include assessment of COA endpoint prior to or shortly after a patient withdraws from the study. Patients who discontinue study medication will continue making clinic visits per protocol. For patients who withdraw from the study, end of study procedures will be followed at the time of withdrawal.
- Frequency and timing of COA assessments are appropriate given patient population, study design, study objectives, and demonstrated measurement properties of the COA, although concerns about recall period persist (described elsewhere in this review)
- Duration of study, 24 weeks, appears adequate to support COA objectives

## D. APPENDICES

### FSFI Instrument

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

In answering these questions the following definitions apply:

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

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

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

**CHECK ONLY ONE BOX PER QUESTION.**

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

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?
  - 5  = Almost always or always
  - 4  = Most times (more than half the time)
  - 3  = Sometimes (about half the time)
  - 2  = A few times (less than half the time)
  - 1  = Almost never or never
  
2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?
  - 5  = Very high
  - 4  = High
  - 3  = Moderate
  - 2  = Low
  - 1  = Very low or none at all

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Thank you for completing this questionnaire**

e-Diary

**10.11 ELECTRONIC DIARY (E-DIARY FOR HSDD TRIALS)**

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

1. Did you have sex. . .

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

NO

YES

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

*The following questions are asked only if the patient answers "yes" to the previous question.*

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

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

<Number spinner to increase by increments of 1>

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

3. Select the day of your sexual activity.

3a. Was the sex satisfying for you? <sup>1</sup>

NO

YES

3b. Did you have an orgasm?

NO

YES

---

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

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/s/  
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ASHLEY F SLAGLE  
08/14/2013

ELEKTRA J PAPADOPOULOS  
08/15/2013

LAURIE B BURKE  
08/19/2013

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

**Label and Labeling Memo**

Date: August 13, 2013

Reviewer: Walter Fava, RPh, MSED., Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader: James Schlick, RPh, MBA, Team Leader  
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Addyi (Flibanserin) Tablets  
100 mg

Application Type/Number: NDA 22526

Applicant: Sprout Pharmaceuticals

OSE RCM #: 2013-870

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

## **1 INTRODUCTION**

This memo acknowledges the labels and labeling submitted on April 10, 2013 for Addyi, NDA 22526, however, the Division of Medication Error Prevention and Analysis will provide our review comments for the labels and labeling during the next review cycle.

## **2 CONCLUSIONS**

If you have further questions or need clarifications, please contact Marcus Cato, project manager, at 301-796-3903.

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/s/  
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WALTER L FAVA  
08/13/2013

JAMES H SCHLICK  
08/14/2013



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF NEUROLOGY PRODUCTS**

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**CONSULT M E M O R A N D U M**

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DATE: July 26, 2013

TO: Charlene Williamson, Bone, Reproductive and Urologic Products

THROUGH: Eric Bastings, MD, Acting Director, Division of Neurology Products

FROM: Ronald Farkas, MD, PhD, Clinical Team Leader, Division of Neurology Products

RE: Flibanserin, NDA 22526

---

**1. Background**

Flibanserin is a 5-HT<sub>1A</sub> agonist/5-HT<sub>2A</sub> antagonist intended for the treatment of hypoactive female sexual disorder (HSDD) in pre-menopausal women. The NDA was recently resubmitted to the Division of Bone, Reproductive and Urologic Products (DBRUP) following a Complete Response action taken August 27, 2010 (based largely on insufficient evidence of efficacy). The PDUFA goal date is September 29, 2013.

DBRUP notes the following about flibanserin. The proposed dosing regimen is 100 mg qhs. Following oral administration, peak plasma flibanserin concentration is achieved in 45 to 60 minutes, and the mean terminal half-life at steady stated is about 10 hours. In addition, based on preliminary review of data submitted, the Controlled Substance Staff have indicated that flibanserin has abuse potential and would likely be a scheduled drug. The safety data reviewed in the first cycle showed an approximately 10% incidence of somnolence as well as higher rates in flibanserin-treated subjects than placebo-treated subjects of accidental injuries (including motor vehicle accidents). Incidence of somnolence is exacerbated significantly when used with alcohol (shown in a dedicated flibanserin-ethanol drug interaction study submitted with the complete response).

DBRUP requests responses from DNP to the following questions:

1. Please comment on whether you would consider the degree of somnolence-related events to be clinically significant.
2. In light of the frequency of these adverse events, do you think a driving simulation study is warranted?
3. If a driving simulation study is deemed necessary, we would appreciate any high-level comments on study design and optimal timing of such a study in relation to oral administration.
4. In your experience with other sedating drugs, is a labeled contraindication to concomitant alcohol use warranted? Or would you recommend alternative labeling?

## 2. Somnolence and Driving

### *PK*

The half life of flibanserin is about 10 hours with steady-state reached after about 3 days of dosing. Peak plasma concentrations of flibanserin occur about 2 hours post-dosing.

**DNP note: the long half life (10 hours) increases concern about residual next-day impairment after bedtime dosing**

Absolute bioavailability of flibanserin following oral dosing is 33%, but exposure is increased up to 53% after a high-fat, high caloric meal. AUC and C<sub>max</sub> were inversely correlated to body weight.

**DNP note: variability in exposure from a given dose (including both inter- and intra-subject variability) can increase risk of exposure-related adverse effects.**

Flibanserin did not appear to have active metabolites. CYP3A4 inhibition or liver impairment increases flibanserin exposure about 5-fold.

**DNP note: the large increase from CYP3A4 inhibition increases safety concern for driving; while strong CYP3A4 inhibitors can be contraindicated, it is likely that the drug would be used with moderate and weak CYP3A4 inhibitors, which are common.**

### *Phase 1 studies*

The primary review by Dr. Olivia Easley from the flibanserin NDA submission of October 26, 2009, reports that in phase 1 studies that flibanserin had mild, dose-dependent sedative properties in healthy volunteers from one to 2.5 hours post-dose, as evidenced by declines in alertness and attention. Similarly, cognitive tests in phase 2 studies revealed mild, transient sedative-type effects that were maximal at two hours after the 100 mg dose, but mostly reversed six hours post-dose.

**DNP note: shortcomings of these PD studies are discussed in more detail below**

### *Phase 2/3 studies*

The primary review found that sedating adverse events (fatigue, somnolence, and sedation) occurred in approximately 18% of subjects taking flibanserin 100 mg qhs, and the frequency of these events was dose-proportional. The review additionally showed that about 90% of these

events first occurred in the first week of treatment. About 1% of patients discontinued due to somnolence or fatigue.

The primary review found that in phase 2/3 studies a greater percentage of subjects on flibanserin experienced accidental injury than those on placebo (table reproduced below). A number of AE categories were combined to derive 'accidental injury' including injury, fracture, and various descriptions of types of injuries (e.g. wound, tendon rupture, accident at work).

**Table 31: Frequency of Adverse Events Related to Accidental Injury – HSDD and MDD Data**

User-defined AE category* or (SOC)/Preferred Term**	Placebo	FLI 25 BID	FLI 50 qhs	FLI 50 BID	FLI 100 qhs	FLI 150 total daily	FLI 100 BID
<b>Phase 2/3 placebo-controlled HSDD trials</b>							
Total N	1,508	733	2,072	862	978	NA	NA
<b>Accidental injury</b> n (%)	21 (1.4)	19 (2.6)	30 (1.4)	18 (2.1)	19 (1.9)	NA	NA
<b>Double-blind portion of Study 511.74 (randomized withdrawal)</b>							
Total N	170	NA	35	13	115	NA	NA
<b>Accidental Injury</b> n (%)	4 (2.3)	NA	2 (5.7)	0	5 (4.3)	NA	NA
<b>HSDD Open-Label</b>							
Total N	NA	57	2197	305	1791	NA	NA
<b>Accidental Injury</b> n (%)	NA	1 (1.8)	26 (1.2)	6 (2.0)	48 (2.7)	NA	NA
<b>MDD Database</b>							
Total N	417	240 <sup>†</sup>	33	313	65	4	113
<b>Injury, poisoning and procedural</b>	11 (2.6)	4 (1.7)	1 (3.0)	6 (1.9)	1 (1.5)	0	4 (3.5)
Accident at	7 (1.7)	2 (0.8)	1 (3.0)	5 (1.6)	0	0	3 (2.7)
Road traffic	2 (0.5)	0	0	0	1 (1.5)	0	1 (0.9)

\* User-defined refers to preferred terms identified by the Applicant as belonging to a particular category.

\*\*MDD database provides information by SOC/PT rather than user-defined AE category

<sup>†</sup>includes all subjects on < 50 mg total daily dose (tdd)

**Source: NDA 22-526 submission 0017, date of submission 4/30/10, Table 2.1.1, and NDA 22-526 submission 000, ISS, Table 5.8.2 and Table 2.1.3.2**

The open-label database included 4 different doses/schedules of flibanserin treatment (table above), with suggestion of positive correlation between dose and incidence of accidental injury.

There were 3 motor vehicle accidents (MVA) in flibanserin patients, vs. none in placebo patients. The first case (100 mg qhs) was a single-vehicle rollover accident off-road in an all-terrain vehicle. The subject reported no AEs related to sedative effects around the time of the accident. In the second (50 mg qhs), the patient reported she was hit from behind and was not

responsible for the MVA. She did not report any Aes related to sedative effects during the course of the study. In the third case (25 mg bid), the patient was reported to not be at fault, but other details of the MVA were not presented. The subject had no Aes related to sedative effects at the time of the accident. An additional motorcycle accident occurred in open-label treatment (50 mg qhs).

In studies of flibanserin in MDD, there were 2 MVA's in placebo (0.5%, total N= 417), vs. 1 MVA in flibanserin arms ( 0.002%, total N = 651)

**DNP note: as discussed below, adequate statistical power is generally lacking from drug development programs to support reliable conclusions about MVA risk; instead, pharmacodynamic effects (e.g. somnolence, psychomotor impairment) are generally used to determine if there is increased risk.**

### 3. Concomitant alcohol

The NDA review of the original submission concluded that concomitant administration of centrally acting drugs (e.g., SSRIs, alcohol) adversely effects flibanserin tolerability and may compromise patient safety. CNS-related adverse events were most frequent among subjects who were drinkers assigned to flibanserin 100 mg qhs (see Table below, from NDA primary review). The Applicant acknowledged that alcohol use among women receiving flibanserin may increase the rate of AEs and proposes (b) (4)

**Table 75: Frequency of Adverse Events in Flibanserin 100 Mg qhs vs. Placebo, by Alcohol**

**Use – phase 3 Placebo-Controlled  
HSDD Trials**

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

Source: NDA 22-526, submission 000, ISS, Table 5.2.7.1, pp 3025 – 88

In the Complete Response letter to the original submission, DBRUP noted that there was insufficient information to assess safety of flibanserin when used with alcohol. The Division recommended that the sponsor conduct a drug-drug interaction study determine the effect of simultaneous administration of flibanserin 100 mg with alcohol.

#### 4. GI Adverse Events

In phase 2/3 studies, Dr. Easley found that the most frequently reported SAE among flibanserin subjects was appendicitis. There were no cases in placebo (0/1508), compared to 6 events of appendicitis in flibanserin patients, for a rate of about 0.1- to 0.2%, without apparent relationship to dose (1/733 patients at 25 mg BID; 4/2072 at 50 mg qhs; 1/862 at 50 mg BID; 0/978 at 100 mg qhs). This was thought to only slightly greater than the background risk. It was noted that flibanserin causes constipation, which can slightly increase the risk of appendicitis, although none of the subjects experiencing appendicitis reported an adverse event of constipation.

#### 5. DNP Response to Consult Questions

The first three consult questions about somnolence-related risk, including impaired driving, are addressed below together, followed separately by a response to the question about labeling for risk with concomitant use of flibanserin and alcohol. Lastly is a discussion of GI adverse events from flibanserin, in the context of a drug with 5-HT<sub>2A</sub> antagonist activity reviewed by DNP that caused GI adverse events (potentially including appendicitis), and that increases concern that the cases of appendicitis in the flibanserin study were drug-related.

##### *CNS Depressant-Related Risk*

A number of different types of evidence raise concern that the CNS depressant effects of flibanserin 100 mg qhs present a safety risk, and suggest that additional safety data, including driving studies, may be warranted. Importantly, lack of symptoms of CNS depression in the specific patients that experience more serious events like injury or motor vehicle accident (MVA) provides little evidence that the events were not drug-related, as patients taking CNS-active drugs can be functionally impaired without being symptomatic for somnolence or other symptoms of CNS depression.

Events of actual MVA potentially can be informative about drug risk, but development programs are generally too small, and MVA's too infrequent, to adequately characterize the relatively small increases in risk of MVA (i.e. far less than a doubling) that would still be considered clinically meaningful. It is not clear that the increased incidence of MVA in flibanserin- vs. placebo-treated patients can be separated from a chance finding, but the observation does increase concern.

The review of the original NDA for flibanserin also identified an apparent increased risk of accidental injury. While these injuries were not serious or life-threatening, a drug-related

increase in common minor accidents and injuries also increases concern that the drug might increase the risk of more serious but less frequent events like MVA's.

The review of the original NDA cited pharmacodynamic (PD) studies that the sponsor asserted showed mild CNS impairment for about 2 hours post-dosing that resolved by about 6 hours post-dosing. This review finds the results of pharmacodynamic tests to be more concerning for clinically meaningful risk of impaired driving from flibanserin. While study design limits interpretation (for example there were no positive controls) adverse PD effects were identified in some studies that suggest additional information may be necessary to adequately characterize risk of impairment. The figure below, from study 511.3 U97-0097, shows results from a psychomotor test called 'Choice Reaction Time' (CRT). CRT is useful for testing general alertness and motor speed, skills important for driving and other activities requiring full mental alertness.

Boehringer Ingelheim Ltd  
 BI Trial No.: 511.3

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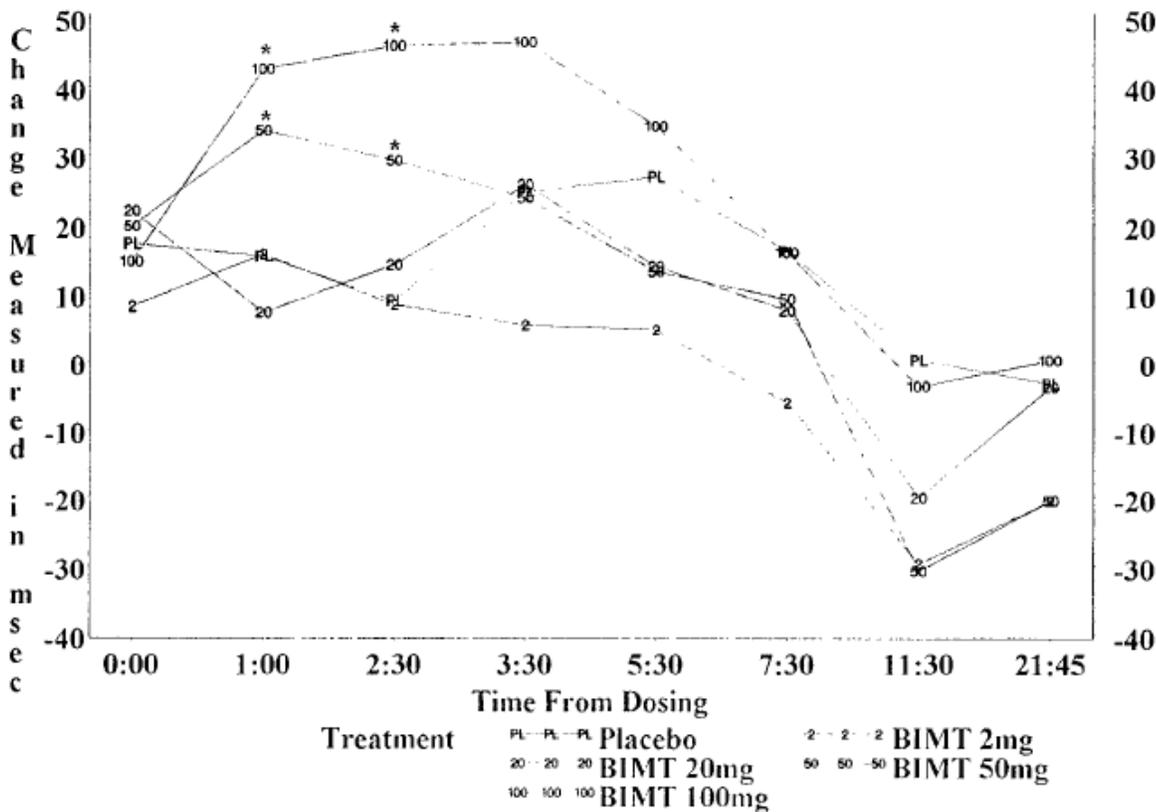
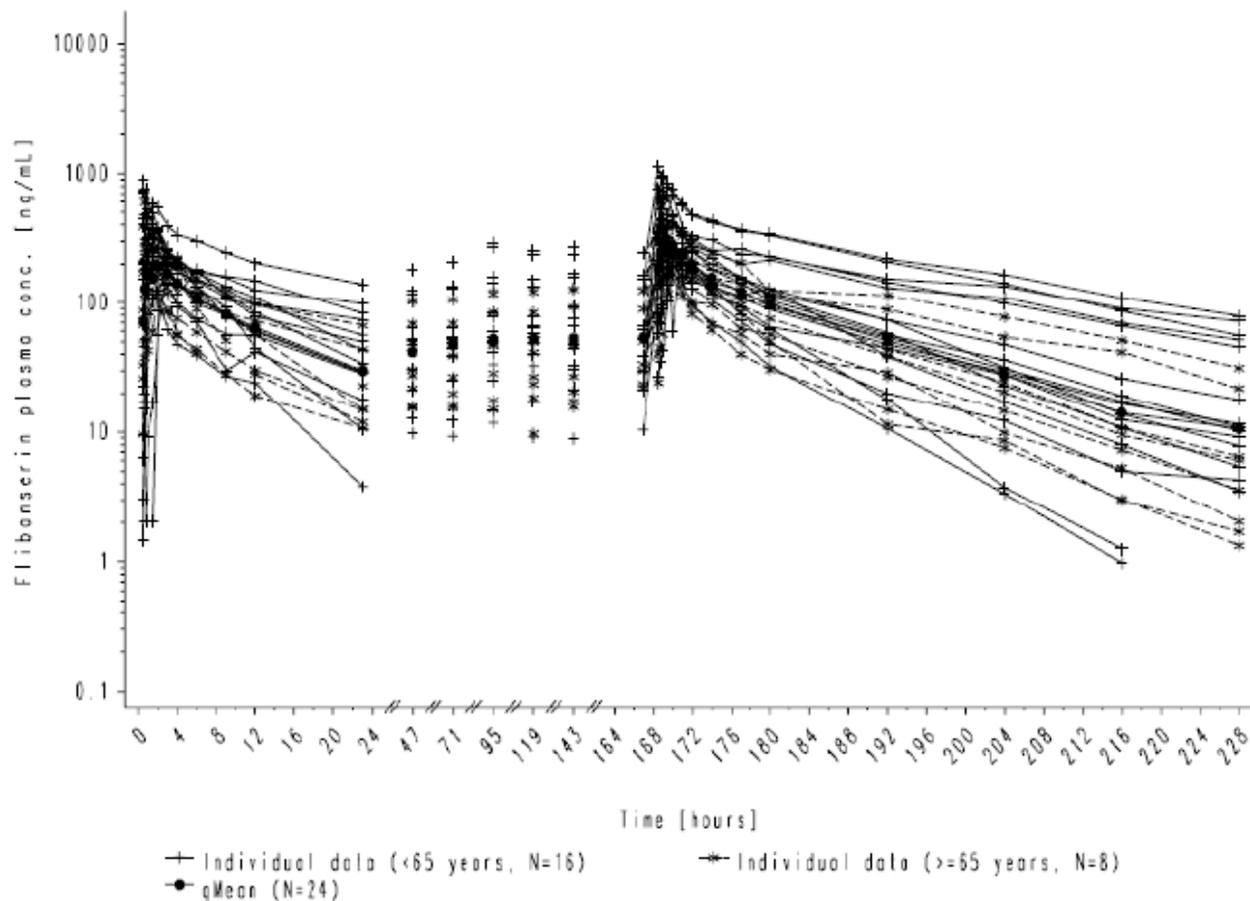


Figure 9.3.1.3: 3 CRT Total Response Times (msec), Change From Pre-dose, by Timepoint

An increase (or slowing) of CRT indicates CNS impairment. The study report states that a 50 ms increase in CRT is clinically meaningful (note: it is not clear that lesser changes in CRT are not clinically meaningful), and flibanserin did cause this magnitude of impairment, for up to 3.5

hours after dosing. Importantly, however, this study was not adequately designed to exclude impairment at later time points, as it lacked a positive control; PD studies are sensitive to effects that bias towards the null, like learning effects and inconsistent effort of study participants, such that negative findings (overall or at particular time points) need to be interpreted with caution (in fact, for the same reasons, the study also should not be interpreted as excluding that the impairment at 3.5 hours might not have been greater than 50 ms). Positive findings in the CRT study suggest that additional, more rigorously designed, studies may be warranted to adequately characterize the safety risk from flibanserin.

While the above PD study was interpreted in terms of *average* impairment of the test population, the usual approach for this type of PD study, DNP has recently become concerned that average impairment is not an appropriate basis to assess risk; an *unacceptable risk* in a meaningful number of *individuals* in the population can be masked by lack of impairment in the majority. Thus, in the CRT study, even though the *average* impairment in the flibanserin arm 5.5 hours after dosing was 35 msec (other concerns about assay sensitivity aside), some individuals, by definition, must have exhibited impairment on CRT greater than the average of 35 msec, and might be at risk for more severe impairment than represented by the 35 msec average change. This interpretation is based on the likelihood that the observed variability in the test result is due to true inter-patient differences in impairment; there is ample reason to believe that this is the case. For flibanserin, there are clear inter-individual differences in drug exposure (see figure below from the multiple-dose PK study of flibanserin) that would be expected to result in greater impairment in individuals with higher exposure compared to individuals with lower drug exposures, including greater impairment at 5.5 hours *or later* after dosing, entering the time period when patients using flibanserin qhs would be expected to drive the day after dosing. Individuals at the high end of the distribution of exposures to flibanserin have blood levels at 8 hours roughly as high as the average population C<sub>max</sub> that occurs at about 1 hour after dosing, and might experience a degree of impairment 8 hours after dosing that is roughly similar to the impairment experienced, by patients with average exposure, near C<sub>max</sub>.



Source Data: [Section 15, Figure 6.5.2: 2](#)

**Figure 11.5.2.1: 1** Individual and geometric mean plasma concentration-time profiles of flibanserin after single and multiple oral administration of flibanserin to postmenopausal female HSDD patients (logarithmic scale)

PD studies of flibanserin, like that described above, appear to raise substantial concern about driving impairment. Additional studies more specifically designed to characterize driving impairment may be warranted. Driving studies should have the following general characteristics:

- Studies with higher ecological validity for driving than more general tests of CNS function are expected to be more useful for estimating risk of MVA from drug. Perhaps ideally, testing should include challenging driving situations similar to those in which MVAs are more likely to occur, and that can only be safely recreated in a driving simulator, such as unexpected incursions of other cars, or extended periods of monotonous driving. However, some experts argue that testing during actual on-the-road driving, which is limited by safety considerations to measures such as ability to maintain appropriate vehicle position in the driving lane and vehicle speed, is advantageous because study subjects know that they are in real danger of harm if they perform poorly, increasing validity of findings. Both types of studies (driving

simulator and on-the-road studies) have been used in the labeling of drugs regulated by DNP.

- A positive control and placebo arm should be included in dedicated driving studies. The positive control should be selected based on the ability to confirm assay sensitivity for levels of impairment at the threshold of concern for clinically meaningful driving impairment. A number of drugs used for the treatment of insomnia are commonly used as positive controls in driving studies, including zopiclone 7.5 mg, a drug that is approved for insomnia in Europe and other regions, but not in the U.S. Testing for a drug used at bedtime would normally be conducted the next morning, at roughly 8-hours post-dosing.
- Studies of driving impairment should assess drug effects at up to the highest doses and exposures that could be encountered in clinical use. This includes exposures that might be experienced by patients with specific genetic traits or other characteristics that could lead to higher exposures from the same dose.
- For drugs taken chronically (or chronic-intermittently), studies generally should be conducted to evaluate both the single-dose effects of the drug, and effects after chronic exposure (at steady-state drug levels).

#### *Concomitant Alcohol*

In the Complete Response, the sponsor included a PD drug-interaction study of flibanserin and ethanol. Study interpretability is limited because the subjective endpoint VAS for sedation was the primary endpoint, and no objective endpoints were examined; patient subjective evaluation of sedation is known from other studies to correlate poorly with objective impairment. Interpretability of the flibanserin study is also limited because endpoints were only examined up to 4 hours after dosing; VAS for sedation was maximally affected by flibanserin + ethanol at 4 hours, and the time-course of recovery remains unknown (table below).

**Table 11. Mean Change From Baseline for Sedation on Visual Analog Scale (Safety Population)**

	<b>Treatment A</b>	<b>Treatment B</b>	<b>Treatment C</b>	<b>Treatment D</b>	<b>Treatment E</b>
	<b>0.8 g/kg ethanol + flibanserin 100 mg</b>	<b>0.8 g/kg ethanol + placebo</b>	<b>0.4 g/kg ethanol + flibanserin 100 mg</b>	<b>0.4 g/kg ethanol + placebo</b>	<b>flibanserin 100 mg</b>
	<b>N=24</b>	<b>N=25</b>	<b>N=23</b>	<b>N=24</b>	<b>N=24</b>
Visual Analog Scale (mm)					
Baseline <sup>a</sup> Mean, mm (SD)	16.3 (23.4)	16.3 (23.4)	16.3 (23.4)	16.3 (23.4)	16.3 (23.4)
Mean Change <sup>b</sup> , % (SD)					
Day 1, Hour 0.5	-2.3 (18.1)	0.4 (19.1)	0.3 (11.4)	-0.1 (13.0)	-7.2 (15.2)
Day 1, Hour 1	12.9 (27.7)	9.9 (22.9)	8.3 (20.6)	7.1 (17.5)	-0.9 (11.3)
Day 1, Hour 1.5	12.2 (28.5)	11.8 (26.2)	11.5 (20.4)	12.3 (23.1)	8.0 (17.9)
Day 1, Hour 2	20.5 (26.2)	10.0 (26.5)	18.0 (22.1)	10.4 (23.8)	15.7 (20.8)
Day 1, Hour 4	27.1 (30.4)	3.9 (26.3)	20.4 (21.4)	-2.9 (14.9)	14.6 (26.1)

Source: Section 14, Table 14.3.4.4

Abbreviations: mm = millimeters, SD = standard deviation, N = number of subjects included in mean change from baseline.

<sup>a</sup>Baseline was defined as predose on Period 1, Day 1. N=25 at baseline for all treatments.

<sup>b</sup>Mean change and standard deviation shown with a maximum of 3 significant figures.

As noted above (Section 3), DBRUP previously identified an increased incidence of a number of adverse events in patients that used alcohol with flibanserin in placebo-controlled trials. Dizziness from combined use may be a particular concern if it increases the risk of fall or injury. It is not clear to DNP that a contraindication to concomitant use of flibanserin and alcohol is warranted if risk can be mitigated by avoiding driving; however, increased risk of fall, injury, or other adverse events that can not be readily mitigated by patient behavior might warrant a contraindication.

#### *GI Adverse Events*

In the original NDA review, events of appendicitis appeared potentially to be associated with flibanserin. Flibanserin was more clearly associated with an increased risk of constipation, increasing the concern of DBRUP that appendicitis was drug-related. DNP is aware of a drug developed for insomnia that shares 5-HT<sub>2A</sub> antagonist activity with flibanserin, and that appears to increase concern that flibanserin was causally related to the cases of appendicitis. Review of the NDA for eplivanseran (NDA 22423) revealed a drug-related increase in risk of diverticulitis (27/2792 = 1.0%; 95% CI: 0.7 to 1.4 for eplivanseran, vs. 0/1428; 95% CI: 0 to 0.2 for placebo). Additionally there were two eplivanseran subjects (2/2792) who developed acute appendicitis, compared with no subjects treated with placebo (0/1428). Eplivanseran was also found to increase the risk of both diarrhea and constipation vs. placebo. DNP concluded that, against the background of the risk of diverticulitis and altered intestinal motility associated with eplivanseran treatment, there was a possibility that the two cases of appendicitis may also have been associated with eplivanseran treatment, representing an extension or continuum of the diverticulitis risk.

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/s/  
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RONALD H FARKAS  
07/30/2013

ERIC P BASTINGS  
07/31/2013

# DGCPC/OSI CONSULT: Request for Clinical Inspections

**Date:** May 10, 2013

**To:** Ann Meeker-O'Connell, Acting Division Director, DGCPC  
Susan Thompson, M.D. Acting Branch Chief, GCPAB  
Janice Pohlman, M.D., M.P.H., Team Leader, GCPAB  
CDEROCDSIPMOs@fda.hhs.gov  
Roy A Blay, Ph.D.  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
Office of Compliance/CDER

**Through:** *Daniel Davis, MD*  
*Christina Chang, MD*

**From:** *Charlene Williamson, Division of Bone, Reproductive and Urologic Products*

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 22-526

IND#: (b) (4)

Applicant: Sprout Pharmaceuticals

Address: 4208 Six Forks Road, Suite 1010, Raleigh, NC 27609

Regulatory Point of Contact: Richard A. Davan, Director, Regulatory Affairs

Regulatory Point of Contact Phone: (919) 882-0850

Regulatory Point of Contact Email: rdavan@sproutpharma.com

Drug Proprietary Name:

Generic Drug Name: Flibanserin

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): To treat Hypoactive Sexual Desire Disorder (HSDD) in premenopausal women.

PDUFA: September 29, 2013

Action Goal Date: September 27, 2013

Inspection Summary Goal Date: August 15, 2013

DGCPC/OSI Consult

version: 09/28/2011

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
1037 Lee, Elly 16263 Laguna Canyon Road, Suite 150 Irvine, CA 92618 US United States phone:949-753-1663 fax:949-753-4761 email:elee@irvineclinical.com	511.147	28	A 24 Week, Randomized, Double-Blind, Placebo Controlled, Safety And Efficacy Trial Of Flibanserin (100 mg) Administered Orally Once Daily In Premenopausal Women With HSDD In The US
1001 Ackerman, Ronald 603 Village Blvd., Suite 201-B West Palm Beach, FL 33409 US United States phone:561-478-3177 fax:561-683-3471 email:gobs@earthlink.net	511.147	51	A 24 Week, Randomized, Double-Blind, Placebo Controlled, Safety And Efficacy Trial Of Flibanserin (100 mg) Administered Orally Once Daily In Premenopausal Women With HSDD In The US
1033 Katz, Molly 71 E. Hollister Street Cincinnati, OH 45219 US United States phone:513-333-3023 fax:513-333-3024 email:katzres@one.net	511.147	39	A 24 Week, Randomized, Double-Blind, Placebo Controlled, Safety And Efficacy Trial Of Flibanserin (100 mg) Administered Orally Once Daily In Premenopausal Women With HSDD In The US

**III. Site Selection/Rationale**

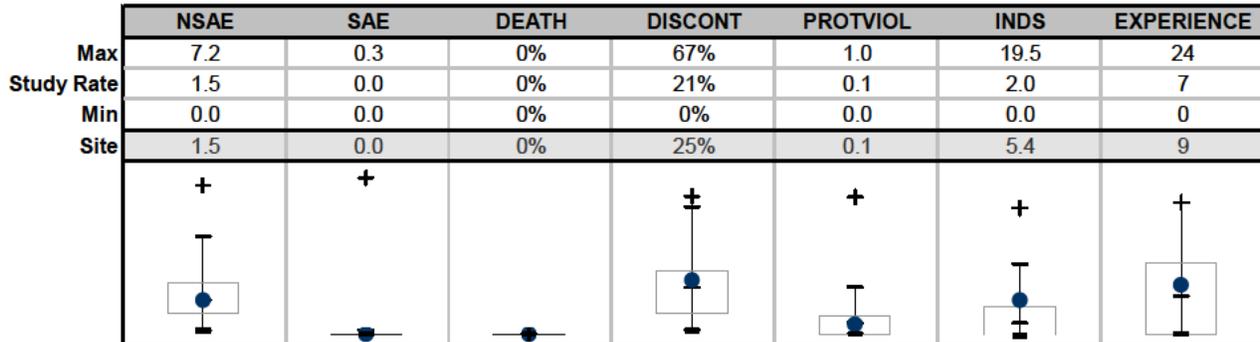
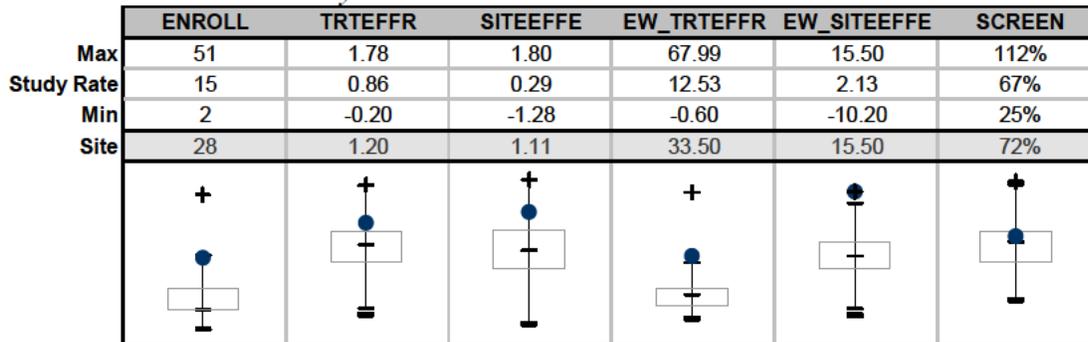
*Site Information*

<b>STUDY:</b>	511.147	<b>SITEID:</b>	1037
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<b>NAME</b>	Lee, Elly
<b>LOCATION</b>	16263 Laguna Canyon Road, Suite 150 Irvine, CA, US 92618
<b>PHONE/FAX</b>	949-753-1663 / 949-753-4761
<b>EMAIL</b>	elee@irvineclinical.com

<b>RANK</b>	4	<b>FINLDISC</b>	0	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	9.0	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

large treatment effect for both primary endpoints

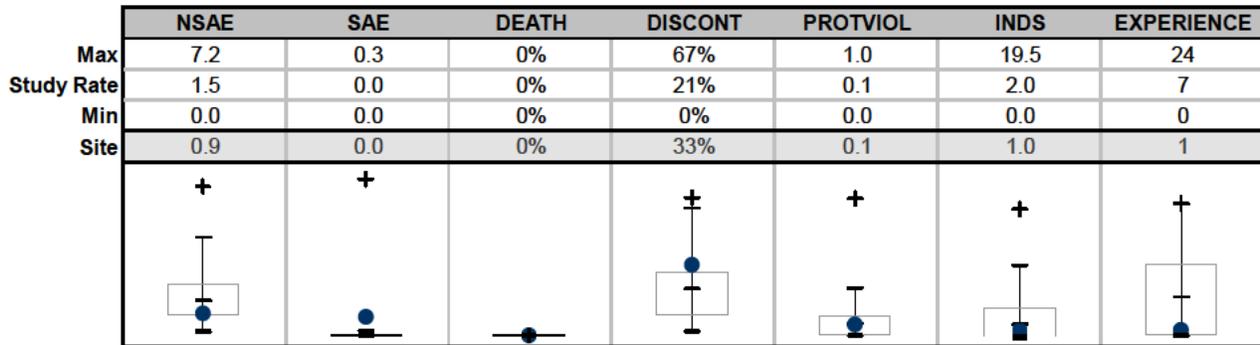
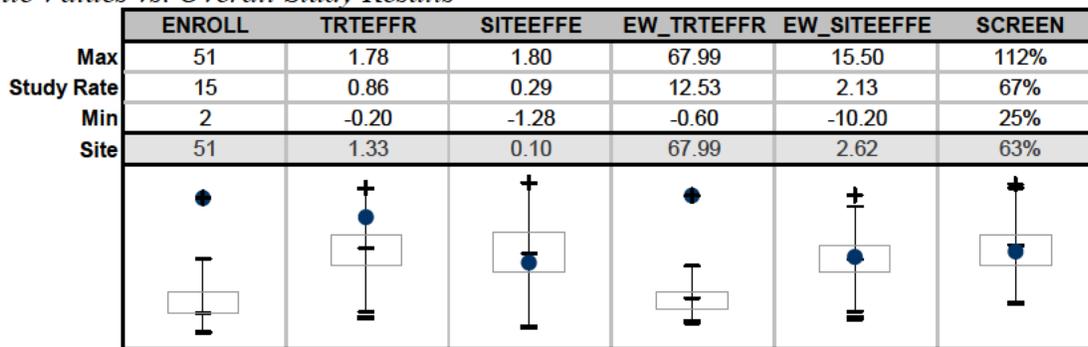
*Site Information*

<b>STUDY:</b>	511.147	<b>SITEID:</b>	1001
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<b>NAME</b>	Ackerman, Ronald
<b>LOCATION</b>	603 Village Blvd., Suite 201-B West Palm Beach, FL, US 33409
<b>PHONE/FAX</b>	561-478-3177 / 561-683-3471
<b>EMAIL</b>	gobs@earthlink.net

<b>RANK</b>	1	<b>FINLDISC</b>	0	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	12.9	<b>OAI</b>	0	<b>TSLI</b>	1

*Site Values vs. Overall Study Results*



*Site Memo*

Highest enrollment and ranking #1 for total risk for both endpoints

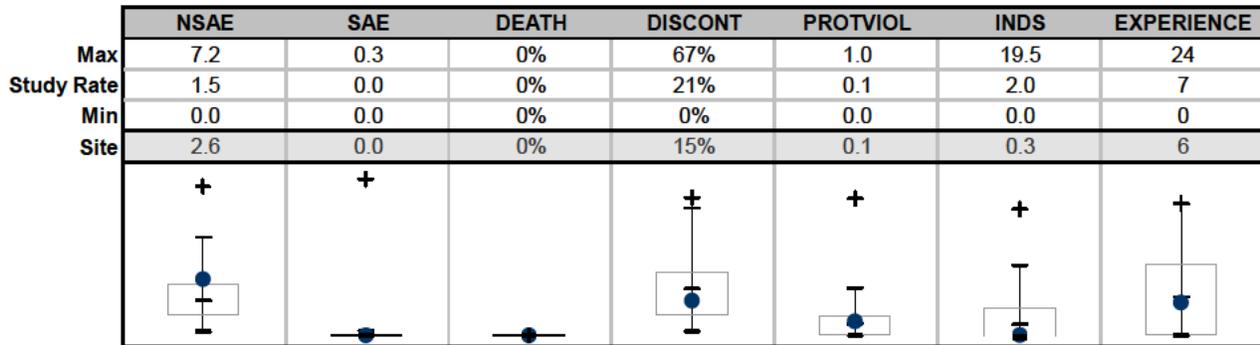
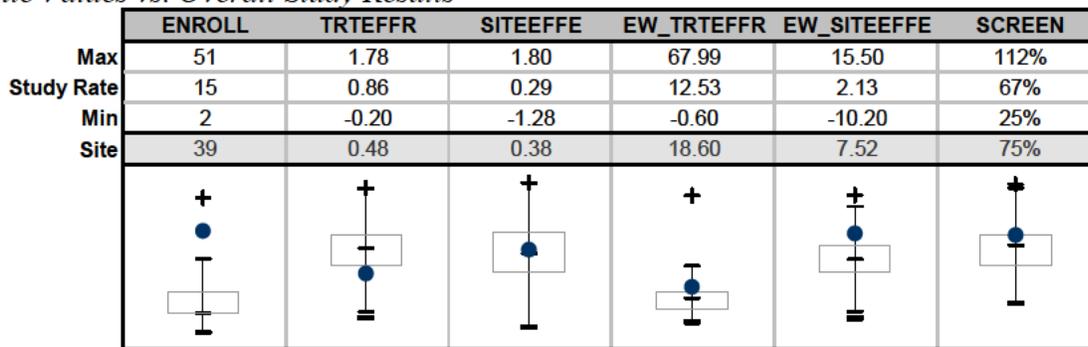
*Site Information*

<b>STUDY:</b>	511.147	<b>SITEID:</b>	1033
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<b>NAME</b>	Katz, Molly		
<b>LOCATION</b>	71 E. Hollister Street Cincinnati, OH, US 45219		
<b>PHONE/FAX</b>	513-333-3023 / 513-333-3024		
<b>EMAIL</b>	katzres@one.net		

<b>RANK</b>	5	<b>FINLISC</b>	0	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	8.8	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

Principal Investigator and high ranking and no recent inspections

*Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

***Rationale for OSI Audits***

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See\*\*\* at end of consult template for OSI's thoughts on things to consider in your decision making process*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Five or More Inspection Sites (delete this if it does not apply):**

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.**

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact *Christina Chang, M.D.* at 301-796-2078 or *Daniel Davis, M.D.* at 301-796-0880.

Concurrence: (as needed)

Christina Chang, M.D. Medical Team Leader  
Daniel Davis, M.D. Medical Reviewer

\_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**\*\*\*Things to consider in decision to submit request for OSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/  
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ZETA-MAE C WILLIAMSON  
05/10/2013

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*\*Pre-decisional Agency Information\*\*\***

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Date: August 26, 2010

To: Charlene Williamson  
Project Manager  
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer  
Carrie Newcomer, Pharm.D., Regulatory Review Officer  
Division of Drug Advertising, Marketing, and Communications (DDMAC)

Re: DDMAC labeling comments for Girosa (flibanserin)  
NDA #22-526

We acknowledge receipt of your January 14, 2010, consult requests for the proposed product labeling (Package Insert (PI) and Patient Package Insert (PPI)) for Girosa® (flibanserin). DDMAC was notified by DRUP on July 23, 2010, that final labeling negotiations would not be initiated during the current review cycle due to outstanding clinical deficiencies and that a Complete Response letter would be issued. Therefore, DDMAC will provide comments regarding labeling for these applications during a subsequent review cycle. DDMAC requests that DRUP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)  
(301) 796-3821, or [janice.maniwang@fda.hhs.gov](mailto:janice.maniwang@fda.hhs.gov)
- Carrie Newcomer (Consumer directed materials)  
(301) 796-1233, or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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JANICE L MANIWANG  
08/26/2010

CARRIE A NEWCOMER  
08/26/2010

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

---

**Date:** July 28, 2010

**To:** Scott Monroe, M.D., Director  
Division of Reproductive and Urology Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** Evaluation of Abuse Potential of Flibanserin (Giroso)  
NDA 22-526  
Indication: Treatment of Hyposexual Desire Disorder in  
Premenopausal Women (100 mg/day)  
Sponsor: Boehringer Ingelheim Pharma GmbH and Co.  
PDUFA Goal Date: August 27, 2010

**I. Executive Summary**

**A. Background**

This memorandum summarizes the findings related to the abuse potential assessment of flibanserin and provides recommendations to the Division of Reproductive and Urology Products.

Flibanserin is a new molecular entity that is not currently marketed in any country. It is the first 5-HT<sub>1A</sub> receptor agonist/5-HT<sub>2A</sub> receptor antagonist to be evaluated by FDA for abuse potential.

CSS was initially consulted by DRUP during the development of flibanserin under IND (b) (4), following an EOP2 meeting on April 21, 2005. On June 7, 2005, DRUP conveyed CSS post-meeting comments to the Sponsor that stated, "An abuse liability assessment is needed for any new molecular entity that has effects on the central nervous system, regardless of indication. Thus, flibanserin will require a formal abuse liability assessment by CSS." CSS provided a list of abuse-related studies that would need to be conducted, including a human abuse potential study. Finally, CSS informed the Sponsor that the NDA for flibanserin would need to include an Abuse Potential section.

CSS review of the abuse-related clinical and preclinical data in the NDA shows that:

1. Flibanserin is a central nervous system depressant. In rat and monkey toxicity studies, high doses of flibanserin produce a reduction in locomotor behavior.
2. Flibanserin has activity as a 5HT<sub>1A</sub> agonist and a 5HT<sub>2A</sub> antagonist. Neither of these mechanisms is associated with abuse potential. Flibanserin is also a ligand at 5HT<sub>2B</sub>, 5HT<sub>2C</sub> and dopamine D4 receptors, although no information was provided to determine whether it acts as an agonist or antagonist at these sites. Agonists at 5HT<sub>2C</sub> can produce hallucinations, while dopamine agonists can produce euphoria and hallucinations. These adverse events can be indicative of abuse potential.
3. In rats trained to self-administer the Schedule II opioid, morphine, substitution of flibanserin did not maintain self-administration.
4. Phase 1 pharmacokinetic studies have identified that flibanserin has two major metabolites that attain plasma concentrations similar to that of flibanserin: flibanserin-6-sulfate (M38) and flibanserin-6,21-disulfate (M25). However, neither metabolite was shown to have brain activity or bind to CNS receptors. In humans, the Tmax of flibanserin ranges from 45-60 minutes with dose-proportional Cmax values and a half-life of 10 hours.
5. In Phase 1 studies with flibanserin (20-300 mg/day) in healthy individuals (n = 803), there was a high incidence of fatigue (31.0%) and somnolence (22.4%), a lower incidence of sedation (2.7%) and disturbance in attention (2.2%), and a very low incidence of euphoria (n = 0, 0%).
6. In Phase 2/3 clinical efficacy studies with flibanserin (20-200 mg/day) in patients (n = 4717), there was a high incidence of somnolence (6.9% to 19.4%) and sedation (0.1% to 12.5%), a lower incidence (0.1 to 1.4%) of disturbance in attention, feeling abnormal, confusional state, cognitive disorder and mental impairment, and a very low incidence of euphoria (n = 4, 0.1%).
7. In a Phase 2/3 clinical efficacy study, discontinuation of flibanserin produced numerous adverse events following 24 weeks of drug administration that are indicative of a withdrawal syndrome. Thus, flibanserin produces physical dependence. These AEs were most frequently found in the following systems groupings: naso-bronchial system symptoms (1.2% to 11.2%), central nervous system symptoms (1.2% to 6.5%), gastrointestinal system symptoms (1.8 to 4.7%), female reproductive system symptoms (1.2% to 3.5%), musculoskeletal system symptoms (1.2% to 1.8%). Notably, discontinuation of flibanserin after 48 weeks of administration produced a very low incidence of adverse events (1.2% to 1.8% for headache, vomiting, nasopharyngitis and urinary tract infection).

**B. Conclusions:**

1. The Sponsor did not conduct a thorough abuse potential assessment of flibanserin. Although the Sponsor did submit data from limited abuse-related preclinical studies and data from a human physical dependence study, the Sponsor did not conduct a human abuse potential study. Additionally, an Abuse Potential section was not included in the NDA.
2. Based on a review of clinical data submitted in the NDA (adverse events profile and withdrawal symptoms upon drug discontinuation), flibanserin has central nervous system (CNS) sedative properties and produces physical dependence. These properties are suggestive of a drug with abuse potential.
3. However, in the absence of a human abuse potential study, it is not possible to draw definitive conclusions about the abuse potential of flibanserin.

**C. Recommendations (to be conveyed to Sponsor):**

After a review of the materials submitted in the NDA, we conclude that flibanserin is active in the CNS, has sedative properties and 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.

Thus, you should conduct a human abuse potential study in individuals with a history of sedative abuse and, pursuant to 21 CFR 314.50(d)(5)(vii), submit a proposal to schedule flibanserin in the Controlled Substances Act (CSA) and reasons for your proposal. CSS is available to comment on the proposed design of the human abuse potential study.

**D. Recommendation (to the Division only):**

Flibanserin should be evaluated to determine if it has agonist properties at the 5HT<sub>2B</sub> site. If so, FDA clinical guidelines should be used to evaluate flibanserin for its ability to induce valvulopathy, an adverse event that is known to be associated with this receptor site.

## **II. Summary and Discussion of Flibanserin Data Related to Abuse Potential**

### **A. Preclinical Data Related to Abuse Potential**

#### **i. Receptor Binding and Functional Studies with Flibanserin (Study #0611-W, 0410-A, BA1-A10, BA3-A14)**

In receptor binding studies, flibanserin was shown to have high to moderately-high affinity at 5HT<sub>1A</sub> receptors (K<sub>i</sub> = 6.6 nM), 5HT<sub>2A</sub> receptors (K<sub>i</sub> = 15.3 nM), 5HT<sub>2C</sub> receptors (K<sub>i</sub> = 88 nM), 5HT<sub>2B</sub> receptors (K<sub>i</sub> = 89 nM) and dopamine D4 receptors (K<sub>i</sub> = 167 nM).

When a GTPgammaS functional assay was conducted in 5HT<sub>1A</sub> receptors, flibanserin was shown to have an agonist profile (EC<sub>50</sub> = 39.5 nM) without any antagonism against agonist-induced activity.

Although the Sponsor states that flibanserin is an antagonist at 5HT<sub>2A</sub>, 5HT<sub>2B</sub> and 5HT<sub>2C</sub> sites, no primary *in vivo* data were submitted to support these conclusions.

In a GppNHp “shift” assay, flibanserin was shown to act as a weak agonist at the dopamine D4 receptor.

Flibanserin did not show significant interaction at any of the other 150 receptors, ion channels, transporters, enzymes tested, including the following CNS sites associated with abuse potential: glutamate, GABA, dopamine, serotonin, cannabinoid, histamine, acetylcholine, sigma, opioid, monoamine transporters, potassium channel, calcium channel, chloride channel or sodium channel.

#### **ii. Preclinical Behavioral Studies**

##### *Doses Used in Behavioral Studies*

In rats, the species used for behavioral studies with flibanserin, a 5 mg/kg dose (p.o.) produces C<sub>max</sub> values (~420 ng/ml) that are similar to those produced in humans by the proposed therapeutic dose of 100 mg (p.o.) (~430 ng/ml).

Although pharmacokinetic data were not provided in the NDA regarding intraperitoneal administration of flibanserin (the route used for the rat behavioral studies), this route produces results similar to oral administration pharmacokinetically. Thus, the animal behavioral studies use doses that are within the human therapeutic range, as well as doses that are many times greater than the therapeutic range (as would be expected during animal toxicity testing).

#### a. General Behavioral Responses to Flibanserin in Rats

##### *Serotonin-Related Behaviors in Rats (Study#PHBR16S)*

Flibanserin was tested in two behavioral models associated with serotonin receptors: blockade of head-twitch induced by a 5HT<sub>2</sub> agonist (indicating antagonism of 5HT<sub>2</sub> receptors) and the rodent serotonin syndrome (indicating stimulation of 5-HT<sub>1A</sub> receptors).

For the head-twitch antagonism test, rats were administered the 5HT<sub>2</sub> agonist, 2,5-diiodo-4-methamphetamine (DOI) and observed for head-twitches. Flibanserin (2-8 mg/kg, i.p.) pre-treatment blocked the ability of DOI to induce head-twitches, as did the 5HT<sub>2</sub> antagonist, ritanserin (0.03-0.12 mg/kg, i.p.).

At a dose of 64 mg/kg (i.p.), flibanserin induced the rodent serotonin syndrome, which consists of flattened body posture, forepaw treading and hindlimb abduction, although a lower dose of 8 mg/kg (i.p.) did not. The 5HT<sub>1A</sub> agonist, 8-OH-DPAT (1-8 mg/kg, i.p.) also induced the rodent serotonin syndrome, but the response was 61% greater than that observed after flibanserin administration at the doses tested.

It should be noted that the 5HT<sub>1A</sub>-associated serotonin syndrome in rats is not related mechanistically or behaviorally to the similarly-named human serotonin syndrome. In humans, the serotonin syndrome consists of such symptoms as clonus, hyperthermia and mental status changes (Ables and Nagulbilli, 2010). These symptoms are the result of excess amounts of serotonin in the brain, often following the co-ingestion of more than one serotonin-acting medication (e.g., a serotonin reuptake inhibitor antidepressant and a 5HT<sub>1D</sub> agonist anti-migraine drug). In contrast, human ingestion of 5HT<sub>1A</sub> agonist medications (such as buspirone for the treatment of anxiety or depression) do not produce any behavioral responses similar to those present in the rat serotonin syndrome.

##### *Irwin Test in Mice (Study #PHCE15S)*

Flibanserin was tested in a modified Irwin test for general behavioral responses. At 32 mg/kg (p.o.), flibanserin did not induce any observable changes in behavior. When the dose was increased to 64 mg/kg (p.o.), flibanserin induced a reduction in locomotion, a decrease in body temperature and the rodent serotonin syndrome in half of the mice (4 of 8). At the highest dose of flibanserin tested (128 mg/kg, p.o.), the drug induced a total inhibition of locomotor behavior, an increase in hot plate reaction time (either an indication of thermal analgesia or reflecting the animal's inability to move), a decrease in body temperature, and the rodent serotonin syndrome.

##### *Locomotor Behaviors in Rats and Mice (Study # PHBR34S, PHCE12S)*

Flibanserin induced impairment in locomotor coordination with an ED<sub>50</sub> of 45 mg/kg (i.p.), as did several serotonin antidepressants (maprotiline, imipramine and fluoxetine).

Flibanserin also interferes with exploratory behavior (spontaneous locomotion and rearings) in rats (8 and 16 mg/kg, i.p.) and mice (16 and 32 mg/kg, i.p.).

**b. Self-Administration Study in Rats (Study # U00-1227)**

A self-administration study was conducted in rats to determine if flibanserin has rewarding properties. Animals were exposed to the Schedule II stimulant, amphetamine, and were able to learn to self-administer this drug at levels above those produced by saline under an FR10 schedule of reinforcement. When flibanserin (25, 50, 100 µg/infusion) was substituted for cocaine, it did not maintain self-administration. Instead, flibanserin produced levels of self-administration that were equivalent to those produced by administration of saline.

**c. Conditioned Place Preference Study in Rats (Study #0409-1, PCHE28S, )**

Two conditioned place preference studies were conducted with flibanserin:

In the first study, rats were exposed to the Schedule II stimulant, cocaine (5 mg/kg, s.c.), the Schedule II opioid, morphine (5 mg/kg, s.c.), or flibanserin (3, 10, 30 mg/kg, i.p.) during a conditioned place preference procedure. Both cocaine and morphine induced conditioned place preference for the side of the experimental cage in which rats received the drug. In contrast, flibanserin at the three doses tested induced conditioned place aversion, whereby rats spent more time on the side of the cage in which they had received saline.

In the second study, rats were exposed to the Schedule II opioid, morphine (2 mg/kg, route not provided) or flibanserin (32 and 64 mg/kg, route not provided) during a conditioned place preference procedure. Morphine induced conditioned place preference for the side of the experimental cage in which rats received the drug. In contrast, flibanserin at both doses induced conditioned place aversion, whereby rats spent more time on the side of the cage in which they had received saline.

**iii. Animal Physical Dependence Assessment**

A physical dependence study with flibanserin was not conducted in animals. Thus, no preclinical data are available to evaluate whether flibanserin induces a withdrawal syndrome upon discontinuation. (*See below for data regarding a clinical physical dependence study conducted in humans*).

**B. Clinical Data Related to Abuse Potential**

**i. Abuse-Related Adverse Events in Phase 1 and Phase 2/3 Clinical Studies**

Clinical studies conducted with flibanserin were evaluated for abuse-related AEs. There was a very low incidence of euphoria as an AE in Phase 1 safety studies with healthy volunteers (n = 0; 0%) and in Phase 2/3 efficacy studies with adult female patients with hyposexual desire disorder (n = 4; 0.1%).

*Phase 1 Clinical Studies*

In Phase 1 studies with flibanserin (20-300 mg/day) in healthy individuals (n = 803), there was a high incidence of fatigue (31.0% vs. 6.2% for placebo) and somnolence (22.4% vs. 1.9% for placebo) with a lower incidence of sedation (2.7% vs. 0% for placebo) and disturbance in attention (2.2% vs. 0.6% for placebo) (see Table 1, below). There were no other abuse-related AEs at an incidence greater than 1.0% reported in Phase 1 studies. These data suggest that flibanserin has sedative properties. However, in the absence of euphoria-related AEs, the sedative responses are not likely to be indicative of abuse potential.

**Table 1: Phase 1 Abuse-Related AEs in Clinical Studies with Flibanserin**

<b>AE Preferred Term</b>	<b>Placebo (n = 161)</b>	<b>Flibanserin (n = 803)</b>
Fatigue	10 (6.2%)	249 (31.0%)
Somnolence	3 (1.9%)	180 (22.4%)
Sedation	0	22 (2.7%)
Disturbance in Attention	1 (0.6%)	18 (2.2%)

*Phase 2/3 Clinical Studies*

In Phase 2/3 clinical efficacy studies with flibanserin (20-200 mg/day) in patients (n = 4717), there was a similar pattern of abuse-related AEs (see Table 2, below) as those seen in Phase 1 safety studies. Specifically, there was a high incidence of somnolence (6.9% to 19.4% vs. 2.7% for placebo) and sedation (0.1% to 12.5% vs. 0.5% for placebo), with a lower incidence (0.1 to 1.4%) of disturbance in attention, feeling abnormal, confusional state, cognitive disorder and mental impairment. Notably, the 1.4% incidence is accounted for by a single patient report in the 100 mg dose group for each of these AEs.

As with the Phase 1 data, the Phase 2/3 data suggest that flibanserin has sedative properties. However, in the absence of euphoria-related AEs, the sedative responses are not likely to be indicative of abuse potential.

**Table 2: Phase 2/3 Abuse-Related AEs in Clinical Studies with Flibanserin**

<b>AE Preferred Term</b>	<b>Placebo (n = 1508)</b>	<b>Flib 25 mg BID (n = 733)</b>	<b>Flib 50 mg QHS (n = 2072)</b>	<b>Flib 50 mg BID (n = 862)</b>	<b>Flib 100 mg QHS (n = 978)</b>	<b>Flib 100 mg BID (n = 72)</b>
Somnolence	43 (2.7%)	51 (7.0%)	142 (6.9%)	117 (13.6%)	51 (5.2%)	14 (19.4%)
Sedation	7 (0.5%)	1 (0.1%)	14 (0.7%)	25 (2.9%)	15 (1.5%)	9 (12.5%)
Disturbance in Attention	4 (0.3%)	2 (0.3%)	6 (0.3%)	8 (0.9%)	4 (0.4%)	1 (1.4%)
Feeling Abnormal	2 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.2%)	1 (1.4%)
Confusional State	0	0	0	2 (0.2%)	1 (0.1%)	1 (1.4%)
Cognitive Disorder	1 (0.1%)	1 (0.1%)	2 (0.1%)	3 (0.4%)	0	1 (1.4%)
Mental Impairment	0	0	0	0	0	1 (1.4%)

“Flib” = flibanserin

**ii. Human Abuse Potential Pharmacology Study**

A human abuse potential pharmacology study of flibanserin was not conducted.

**iii. Human Physical Dependence Assessment (Study #511.74)**

The ability of flibanserin to induce physical dependence was assessed in female patients with hypoactive sexual desire disorder. The design of the study allowed for two phases in which physical dependence could be evaluated:

- 1) The first phase occurred in a group of patients (n = 170) that received flibanserin for 24 weeks of drug administration (50 mg/day titrated to 100 mg/day) in an open-label phase and was then randomized to receive placebo for the next 24 weeks, and
- 2) The second phase occurred in a group of patients (n = 163) that received flibanserin (50 mg/day titrated to 100 mg/day) for a total of 48 weeks (during the 24-week open-label phase and the 24 week randomization phase) and then was switched to placebo for 30 days.

In the first discontinuation phase group, there were numerous adverse events reported when patients who had been given flibanserin for 24 weeks were switched to placebo for the next 24 weeks (see Table 3, below). These results cannot be compared to a placebo-only group because all patients in the study initially received flibanserin treatment.

**Table 3: Adverse Events Following 24-Week Flibanserin Discontinuation**

<b>AE Preferred Term</b>	<b>Flibanserin (n = 170)</b>
Nasopharyngitis	19 (11.2%)
Upper respiratory tract	12 (7.1%)
Sinusitis	12 (7.1%)
Headache	11 (6.5%)
Nausea	8 (4.7%)
Gastroenteritis viral	8 (4.7%)
Menorrhagia	6 (3.5%)
Bronchitis	5 (2.9%)
Insomnia	5 (2.9%)
Dizziness	5 (2.9%)
Sinus congestion	4 (2.4%)
Hypertension	4 (2.4%)
Anxiety	4 (2.4%)
Breast tenderness	4 (2.4%)
Fatigue	4 (2.4%)
Irritability	4 (2.4%)
Musculoskeletal pain	3 (1.8%)
Myalgia	3 (1.8%)
Dysmenorrhea	3 (1.8%)
Vomiting	3 (1.8%)
Pharyngolaryngeal pain	3 (1.8%)
Depression	2 (1.2%)
Paresthesia	2 (1.2%)
Vertigo	2 (1.2%)
Hot flush	2 (1.2%)
Cough	2 (1.2%)
Dermal cyst	2 (1.2%)
Arthralgia	2 (1.2%)
Arthritis	2 (1.2%)
Back pain	2 (1.2%)
Muscle spasms	2 (1.2%)
Pain in extremity	2 (1.2%)
Metrorrhagia	2 (1.2%)

The most frequent AEs reported during flibanserin discontinuation can be grouped into:

- ***naso-bronchial system symptoms***: nasopharyngitis (11.2%), upper respiratory tract (7.1%), sinusitis (7.1%), bronchitis (2.9%), sinus congestion (2.4%), pharyngolaryngeal pain (1.8%), cough (1.2%)
- ***central nervous system symptoms***: headache (6.5%), nausea (4.7%), dizziness (2.9%), anxiety (2.4%), fatigue (2.4%), irritability (2.4%), depression (1.2%), paresthesia (1.2%), vertigo (1.2%), hot flush (1.2%)
- ***gastrointestinal system symptoms***: gastroenteritis viral (4.7%), vomiting (1.8%)
- ***female reproductive system symptoms***: menorrhagia (3.5%), breast tenderness (2.4%), dysmennorhea (1.8%), metrorrhagia (1.2%)
- ***musculoskeletal system symptoms***: musculoskeletal pain (1.8%), myalgia (1.8%), arthralgia (1.2%), arthritis (1.2%), back pain (1.2%), muscle spasms (1.2%), pain in extremity (1.2%)
- ***symptoms not grouped in other systems***: hypertension (2.4%), dermal cyst (1.2%)

In the second discontinuation phase group, patients were switched to placebo for 30 days following 48 weeks of flibanserin administration (see Table 4, below). Notably, the comparator placebo group represents the patients who had initially received flibanserin for 24 weeks, were then switched to placebo for 24 weeks and continued to receive placebo for an additional 30 days (i.e., the same patients who are shown in Table 3, prior to the 30-day continuation of placebo treatment). Thus, patients in the placebo group had been discontinued from flibanserin for 28 weeks when the AE assessments shown in Table 4 were made.

**Table 4: Adverse Events Following 48-week Flibanserin Discontinuation**

<b>AE Preferred Term</b>	<b>Placebo (n = 170)</b>	<b>Flibanserin (n = 163)</b>
Headache	0	3 (1.8%)
Vomiting	0	2 (1.2%)
Nasopharyngitis	0	2 (1.2%)
Urinary Tract Infection	0	2 (1.2%)
Depression	2 (1.2%)	0
Pap Smear Abnormal	2 (1.2%)	0

Following discontinuation of flibanserin after 48 weeks of drug administration, there were fewer AEs reported (Table 4) compared to those reported following discontinuation of flibanserin after 24 weeks of drug administration (Table 3). It is not possible to evaluate the differences between flibanserin and placebo AE frequency because a statistical analysis was not performed on these data.

## **REFERENCES**

Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician*. 2010 May 1;81(9):1139-42.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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/s/

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KATHERINE R BONSON  
07/28/2010

SILVIA N CALDERON  
07/28/2010

MICHAEL KLEIN  
07/28/2010

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

DATE: July 6, 2010

TO: Charlene Williamson, Regulatory Project Manager  
Dan Davis, M.D., Medical Officer  
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-526

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.  
Attn: Alexander Rochefort  
Director, Drug Regulatory Affairs  
900 Ridgebury Road, P.O. Box 368  
Ridgefield, CT 06877  
203-778-7610

DRUG: GIROSA (flibanserin) Tablets 100 mg

NME: Yes

THERAPEUTIC  
CLASSIFICATION: Standard Review

INDICATION: Treatment of Hypoactive Sexual Desire Disorder (HSDD) in  
premenopausal women

CONSULTATION  
REQUEST DATE: March 31, 2010

**DIVISION ACTION**

GOAL DATE: August 27, 2010

PDUFA DATE: August 27, 2010

**I. BACKGROUND:**

The conduct of Protocols #511.71 and #511.75 entitled “A 24-Week, Randomized, Double-blind, Placebo-controlled, Safety and Efficacy Trial of Flibanserin 50 and 100 Milligrams Each Evening in Premenopausal Women with Hypoactive Sexual Desire Disorder”, and “A Twenty-four Week, Randomized, Double-blind, Placebo-controlled, Safety and Efficacy Trial of Flibanserin 50 milligrams Daily and, with Uptitration, 100 milligrams Daily in Premenopausal Women with Hypoactive Sexual Desire Disorder”, respectively, was inspected.

The primary objectives of both protocols were to document the safety profile and to establish the efficacy of flibanserin in producing a clinically meaningful therapeutic response with 24 weeks of treatment in premenopausal women with Hypoactive Sexual Desire Disorder (HSDD). The co-primary efficacy endpoints were the number of satisfying sexual events and the level of sexual desire as collected daily by an electronic diary (eDiary).

These clinical sites of Drs. Conter, Komer, Baron, and Muckerman were selected for inspection because of their high enrollments and the significance of their contributions to the overall primary efficacy results. In addition, Dr. Muckerman’s site was closed, as described by the sponsor, because of a lack of involvement and oversight by the Principal Investigator, failure to adhere to protocol, and suspected misconduct in another flibanserin trial (#511.84).

**II. RESULTS (by Site):**

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site #2001 Howard Conter, M.D. MSHJ Research Associates, Inc. 6155 North Street, Suite 403 Halifax, Nova Scotia B3K 5R3	511.71/ 38 (screened)/	21-25 June 2010	Pending. Interim classification VAI.
Site #2004 Dr. Larry Komer Brant Medical Research 760 Brant Street, Suite 408A Burlington, Ontario L7R 4B8	511.71/ 39 (screened)/	28-30 June 2010	Pending. Interim classification VAI.
Site #1024 Richard Muckerman, M.D. PPS Clinical Research 16216 Baxter Road, Suite 100 Chesterfield, MO 63017	511.75/ 51 (screened)/	4-28 May, 2010	Pending. Interim classification OAI.

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Mira Baron, M.D. Rapid Medical Research 3619 Park East Drive, Suite 109 Cleveland, OH 44122	511.75/ 42 (screened)/	18-27 May, 2010	NAI
Boehringer Ingelheim Pharmaceuticals, Inc. Attn: Alexander Rochefort Director, Drug Regulatory Affairs 900 Ridgebury Road, P.O. Box 368 Ridgefield, CT 06877	511.71 and 511.75/	8-16 June 2010	Pending. Interim classification NAI.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and complete review of EIR is pending.

1. Site #2001

Howard Conter  
MSHJ Research Associates, Inc.  
6155 North Street, Suite 403  
Halifax, Nova Scotia B3K 5R3

- a. **What was inspected:** At this site, 38 subjects were screened, 30 were randomized, 25 completed the study, and 15 subjects' records were reviewed in depth, including primary efficacy endpoint data, adverse events, concomitant medications, informed consent, and sponsor and IRB correspondence.
- b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Inspection revealed that at least one subject (#26036) experienced an adverse event that was treated with a concomitant medication, and that neither the event nor the concomitant medication was reported; specifically, this subject experienced a rash on the torso which was treated with Reactine and Benadryl.
- c. **Assessment of data integrity:** The isolated deviations noted above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

2. Site #2004

Dr. Larry Komer  
Brant Medical Research  
760 Brant Street, Suite 408A  
Burlington, Ontario L7R 4B8

- a. **What was inspected:** At this site, 39 subjects were screened, 32 were randomized, 22 completed the study, and 17 subjects' records were reviewed in depth, including

primary efficacy endpoint data, adverse events, informed consent, and sponsor and IRB correspondence.

- b. General observations/commentary:** A Form FDA 483 was issued noting that a study progress report was delayed by approximately two months in its submission to the IRB. Otherwise, the study appears to have been conducted appropriately.
- c. Assessment of data integrity:** The isolated deviation noted immediately above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

3. Site #1024

Richard Muckerman, MD  
PPS Clinical Research  
16216 Baxter Road, Suite 100  
Chesterfield, MO 63017

- a. What was inspected:** The sponsor terminated this site's participation in the studies submitted in support of this NDA. As a result of this closure, the scope of the inspection was expanded to include Protocol #511.84, entitled "A Twelve Month Open-label, Safety Trial of Flibanserin 50 Milligrams Daily in Women with Hypoactive Sexual Desire Disorder", in addition to Protocol #511.75 as noted above.

Protocol #511.75

At this site, 51 subjects were screened, ten subjects failed screening, 41 were randomized to the study, 37 completed the study and four subjects withdrew.

Protocol #511.84

At this site, 28 subjects were screened and randomized with eight subjects completing the study and 20 withdrawing from the study.

For both studies, Form FDA 1572s, delegation of authority logs, monitoring correspondence, subject enrollment logs, and IRB correspondence were inspected. Timeframes for study visits, laboratory analyses, qualifications of study personnel, and test article storage and accountability were also reviewed.

- b. General observations/commentary:** A seven-page Form FDA 483 was issued noting numerous observations for both protocols. These observations included, but were not limited to, the following:

Protocol #511.75

For this study, 16 of 51 subjects had one or more visits outside of protocol-specified time windows. In addition, 2 of 28 subjects were randomized to the study despite

being ineligible because randomization took place more than 28 days after screening (Subjects 68 and 91).

Multiple subjects were randomized to the study despite either an incomplete assessment of inclusion criteria or actually meeting exclusion criteria; e.g., Subject 78 had an abnormal PAP smear and should have been a screen failure.

The study coordinator was responsible for conducting Clinical Global Impression (CGI) evaluations of multiple subjects despite lacking the qualifications to perform such evaluations.

Multiple subjects did not have actual study visits as required by protocol; instead, visits were conducted by telephone and study medications were mailed to subjects.

#### Protocol #511.84

For this study, 14 of 28 subjects had one or more visits outside of protocol-specified time windows, In addition, nine of 28 subjects were randomized to the study despite being ineligible because randomization took place more than 28 days after screening (Subjects 54, 58, 59 60, 61, 62, 64, 78, and 85).

Multiple subjects were randomized to the study prior to the completion and evaluation of screening procedures such as laboratory results and pelvic examinations.

Drug accountability was inadequate for both studies.

- c. **Assessment of data integrity:** As this inspection was conducted as a result of notification by the sponsor that the sponsor terminated the site, the noted findings are not surprising. The principal investigator was minimally involved in the conduct of these studies and much of the responsibility for the conduct of these studies was delegated to an unqualified study coordinator. Data generated by this site are not considered acceptable in support of the relevant indication and should be excluded from any data analysis.

Note: In response to questions regarding data inclusion/exclusion e-mailed to the sponsor on March 11, 2010, by the review division, the sponsor replied that data from trial 511.75 were included in the final analyses (for both data sets and the study report) . The results of the sensitivity analyses excluding data from Dr. Muckerman's site were consistent with the results of the primary analysis. For trial 511.84, data from Dr. Muckerman's site were excluded in the final analyses (for both datasets and the study report).

4. Site #1038

Mira Baron, MD  
Rapid Medical Research  
3619 Park East Drive, Suite 109  
Cleveland, OH 44122

- a. **What was inspected:** At this site, 42 subjects were screened, 28 were enrolled, and 12 completed the study. The records of 14 subjects were audited. The events diary completed by subjects was transmitted directly to the CRO, [REDACTED] (b) (4). A disc with this diary information was forwarded by the CRO to the site during the inspection. Source documents were compared with data listing, particularly with respect to the co-primary endpoints (satisfying events and desire rating). Other records reviewed included, but were not limited to screening/enrollment logs, IRB and monitor correspondence, informed consent, test article accountability records, and financial disclosure forms.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

5. Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Road, P.O. Box 368  
Ridgefield, CT 06877

- a. **What was inspected:** At this sponsor site, trial and site master file documents including the Form 1572s for U.S. sites and investigator agreements for Canadian sites, and contracts transferring obligations to CROs were inspected. Also inspected was documentation of training and qualifications of clinical investigator and monitors, including monitoring procedures and reports. Other areas of inspection included correspondence with clinical sites, procedures for data collection and handling, and documentation of computerized systems, test article packaging, labeling, and accountability, and adverse event reporting.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Baron, Conter, Komer, and Muckerman, in addition the sponsor site, Boehringer Ingelheim, were inspected in support of this NDA. No significant regulatory violations were noted during the inspections of Dr. Baron's clinical site or of the sponsor. Although regulatory violations were noted at the sites of Drs. Conter and Komer, the findings are considered isolated nature and are unlikely to impact data integrity. Thus, the data generated by the clinical sites of Drs. Baron, Conter, and Komer, and the sponsor appear acceptable in support of the respective indication. However, significant regulatory violations were noted at Dr. Muckerman's site, although this is not surprising as the inspection was conducted as a result of notification that this site was terminated. The review division should consider excluding all data generated by Dr. Muckerman's site because of the numerous deficiencies detailed above. Otherwise, the data are considered reliable in support of the application.

Note: The final classifications of the inspections of Drs. Conter, Komer, Muckerman, and the sponsor, Boehringer Ingelheim, are pending receipt and/or review of their respective EIRs. Addenda to this clinical inspection summary will be forwarded to the review division should there be a change in the final classifications or if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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ROY A BLAY  
07/06/2010

TEJASHRI S PUROHIT-SHETH  
07/06/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 30, 2010

To: Scott Monroe, M.D., Director  
**Division of Reproductive and Urologic Products (DRUP)**

Through: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Product Information Reviewer, Acting Team Leader  
**Division of Risk Management (DRISK)**

From: Robin Duer, RN, MBA, BSN  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert) submitted October 27, 2009, and EU Risk Management Plan submitted May 26, 2010

Drug Name(s): GIROSA (flibanserin) tablets

Application Type/Number: NDA 22-526

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2010-135

The Division of Reproductive and Urologic Products (DRUP) requested that the Division of Risk Management (DRISK) review the proposed patient labeling and proposed EU Risk Management Plan for New Drug Application (NDA) 22-526 submitted by Boehringer Ingelheim Pharmaceuticals, Inc. for GIROSA (flibanserin) tablets.

Due to outstanding clinical deficiencies, DRUP plans to issue a Complete Response (CR) letter. DRISK defers review of the proposed Patient Labeling (Patient Package Insert) and EU Risk Management Plan until the sponsor resubmits a complete response.

Please send us a new consult request at that time. This memo serves to close out the consult request for GIROSA, NDA 22-526.

Please let us know if you have any questions.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22526

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ORIG-1

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BOEHRINGER  
INGELHEIM  
PHARMACEUTICA  
LS INC

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FLIBANSERIN

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/s/  
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ROBIN E DUER  
06/30/2010

SHARON R MILLS  
06/30/2010

Medical Officer's Consult Review of NDA 22-526  
Ophthalmology Consultation

Submission date: 10/27/09  
Review date: 5/19/10  
Sponsor: Boehringer Ingelheim, Inc.  
Drug: Flibanserin

Pharmacologic Category: SSRI  
Proposed Indication: Treatment of hypoactive sexual desire disorder in pre-menopausal women

Requested: DRUP is requesting your consultative review of the NDA 22-526 (flibanserin for hypoactive sexual desire disorder in pre-menopausal women) with regards to the ophthalmology testing done.

Please answer the following questions:

1) Was the testing appropriate and comprehensive enough to evaluate the potential signals noted in animals (In chronic toxicity studies, focal, transient, corneal opacities were observed in dogs treated with high doses of flibanserin)?

**Reviewer's Comments:** *Based on the signals identified in the animals, appropriate ocular testing was performed.*

2) Do you agree with the Sponsor's interpretation of the ophthalmology testing results (see Summary of Clinical Safety, section 4.2.3 located in Module 2.7.4)?

**Reviewer's Comments:** *There were some typographical errors in the reporting of some of the ocular findings [example: patient 23159, sphere change from -2.25 to +3.75][patient 23350, sphere -3.15][patient 24361, sphere -0.28]; however, they do not suggest an altered conclusion. The observation of a congenital cataract at a follow-up visit [patient 25791] but not at a baseline visit raises a question about the ability to detect all lens changes, but this type of discrepancy appears to have occurred in only a small number of patients.*

3) Do you see any signal of concern regarding the ophthalmologic safety that should be labeled?

**Reviewer's Comments:** *The ophthalmic findings do not rise to a level to warrant inclusion in the Warnings and Precautions sections. Dry eye, blurred vision and keratitis should be included in the Adverse Events section of the labeling.*

4) Would you recommend any postmarketing evaluation of ophthalmologic signals or adverse events? For your reference, your division provided consultation to DRUP on this product in the past (memoranda dated June 23, 2005, and December 14, 2005).

**Reviewer's Comments:** *No post-marketing evaluations of ophthalmic signals are recommended at this time.*

**BI Trial No.: 511.71: A 24-week, randomized, double-blind, placebo controlled, safety and efficacy trial of flibanserin 50 and 100 milligrams each evening in premenopausal women with Hypoactive Sexual Desire Disorder**

A 4-week baseline period without any study medication, a 24-week double-blind period with study medication, and a 4-week follow-up period after discontinuation of study medication

Enrolled:

placebo at bedtime q.h.s.: entered: 295 analyzed (for primary endpoint): 290

50 mg flibanserin q.h.s.: entered: 295 analyzed (for primary endpoint): 293

100 mg flibanserin q.h.s.: entered: 290 analyzed (for primary endpoint): 280

Ophthalmologic Examinations

Ophthalmologic examinations were to be performed at the Screen Visit and End of Treatment Visit. The Screen Visit examination could be performed anytime prior to the Baseline Visit (Visit 2), provided that the results were available at the Baseline Visit. The End of Treatment (Visit 9) examination was to be performed within four weeks of discontinuation of study medication. Each examination included the best corrected distance visual acuity; tonometry (intraocular pressure measurement); and, with pupils dilated, slit lamp examination of the anterior segment including the cornea and lens. The Wisconsin system was used as a common grading system for lens opacities. Examiners or a qualified designee were to take 9 color digital slit lamp and retro-illumination images of each eye at baseline and again at end of treatment. For each eye four slit lamp images were focused at the lens nucleus, two retro-illumination images were focused on the papillary margin and a second two at the posterior lens surface. Lastly, for each eye, an external image was to be taken to document laterality for identification. Each set of eighteen images was evaluated by a blinded central reader (b) (4)

In accord with the Wisconsin Lens Grading System, images were assessed for nuclear opacity, cortical opacity, and posterior subcapsular opacity (R08-5698).

Ocular adverse events

Full ophthalmologic examinations were included at Screening and End of Treatment Visits in this trial. Thus, eye-related adverse events may be elicited compared to spontaneous reporting of other adverse events reported in this trial. Investigators independently determined if the patient was experiencing an eye adverse event based on the elicited ophthalmologic information collected. There were 16 patients (5.4%) in the 50 mg flibanserin group and eight patients (2.8%) in the 100 mg flibanserin group with eye adverse events compared to nine patients in an individual treatment group were dry eye, vision blurred, asthenopia, eye pain, ocular hyperaemia, photophobia, and visual disturbance.

	Placebo		FLI 50		FLI 100	
	N	%	N	%	N	%
Dry eye	3	(1.0)	3	(1.0)	1	(0.3)
Vision blurred	2	(0.7)	3	(1.0)	2	(0.7)
Asthenopia	0		2	(0.7)	0	
Eye pain	1	(0.3)	2	(0.7)	1	(0.3)
Ocular hyperaemia	2	(0.7)	0		0	
Photophobia	0		2	(0.7)	0	
Visual disturbance	0		0		2	(0.7)
Abnormal sensation in eye	0		1	(0.3)	0	
Accommodation disorder	0		1	(0.3)	0	
Conjunctival discoloration	0		0		1	(0.3)
Conjunctivitis	1	(0.3)	0		1	(0.3)
Dacryostenosis acquired	0		1	(0.3)	0	
Eye irritation	1	(0.3)	1	(0.3)	0	
Eye pruritus	1	(0.3)	0		0	
Lacrimation increased	0		1	(0.3)	1	(0.3)
Photopsia	0		1	(0.3)	0	
Retinal tear	0		1	(0.3)	0	
Vitreous floaters	1	(0.3)	1	(0.3)	0	

There were three patients (1%) in the 50 mg flibanserin group (photophobia, dry eye, blurred vision) and one patient (0.3%) in the 100 mg flibanserin group (blurred vision) who discontinued due to eye adverse events compared to 0 patients (0.0%) in the placebo group.

#### Ophthalmologic Examination

In the placebo group worsening of visual acuity (VA) (one or more lines of the ETDRS chart) was recorded in 19 patients (9%) for the right eye and 24 patients (11%) for the left eye. In the 50 mg flibanserin group worsening of VA was recorded in 26 patients (11%) for the right eye and 25 patients (11%) for the left eye. In the 100 mg flibanserin group worsening of VA was recorded in 20 patients (9%) for the right eye and 21 patients (10%) for the left eye. Almost all cases of worsening of VA were worsening of only one line on the ETDRS chart. The exceptions in the placebo group were for three patients (1%) with worsening of two lines in the right eye and one patient (0.5%) with worsening of two lines in the left eye. The exceptions for the 50 mg flibanserin group were three patients (1%) with worsening of two lines and one patient (0.4%) with worsening greater than two lines in the right eye, and two patients (1%) with worsening of two lines and one patient (0.4%) with worsening greater than two lines in the left eye. The exceptions for the 100 mg flibanserin group were one patient (0.5%) with worsening of two lines in the right eye and one patient (0.5%) with worsening of two lines in the left eye.

In the placebo group there were 10 patients (5%) with a decrease in intraocular pressure (greater than 4 mm Hg) for the right eye and eight patients (4%) for the left eye. In the 50 mg flibanserin group there were nine patients (4%) with a decrease for the right eye and 10 patients (4%) for the left eye. In the 100 mg flibanserin group there were 11 patients (5%) with a decrease for the right eye and eight patients (4%) for the left eye. In the placebo group there were four patients (2%) with an increase in intraocular pressure (greater than 4 mm Hg) for the right eye and six patients (3%) for the left eye. In the 50 mg flibanserin group there were three patients (1%) with an increase for the right eye and two patients (1%) for the left eye. In the 100 mg flibanserin group there were six patients (3%) with an increase for the right eye and nine patients (4%) for the left eye. Change from baseline values for intraocular pressure ranged from -0.2 mm Hg for the placebo group to -0.6 for the 50 mg flibanserin group and -0.5 to -0.3 for the 100 mg flibanserin group.

Corneal staining with fluorescein is used to evaluate corneal epithelial abrasions, infections, and other defects. In the placebo group there were 14 patients (6%) with worsening of one or more grades in corneal staining for the right eye and 18 patients (8%) for the left eye. In the 50 mg flibanserin group there were 20 patients (9%) with worsening of one or more grades for the right eye and 20 patients (9%) for the left eye. In the 100 mg flibanserin group there were 23 patients (11%) with worsening of one or more grades for the right eye and 19 patients (9%) for the left eye. Almost all cases of worsening were worsening by only one grade.

For assessment of presence of corneal stromal opacities, in the placebo group there were three patients (1%) with worsening (i.e., absent at baseline but present at end of treatment) in the right eye and four patients (2%) with worsening in the left eye. In the 50 mg flibanserin group there were two patients (1%) with worsening in the right eye and three patients (1%) with worsening in the left eye. In the 100 mg flibanserin group there were two patients (1%) with worsening in the right eye and two patients (1%) with worsening in the left eye.

The retinal examination included assessment of the macula, optic nerve, blood vessels, and periphery. In each case an assessment of “normal” or “abnormal” was made. In the placebo group there was one patient (0.5%) with worsening (i.e., change from “normal” to “abnormal”) in the right eye on the retinal examination and 0 patients with worsening in the left eye. In the 50 mg flibanserin group there were six patients (3%) with worsening in the right eye and two patients (0.9%) with worsening in the left eye. In the 100 mg flibanserin group there were 0 patients (0.0%) with worsening in the right eye and five patients (2%) with worsening in the left eye. Most cases of worsening were in the periphery, with the exception of one patient (0.5%) in the placebo group with worsening in blood vessels in the left eye, two patients (1%) in the 50 mg flibanserin group with worsening in the macula of the right eye and one patient (0.4%) in the 50 mg flibanserin group with worsening of the macula in the left eye, and one patient (0.5%) in the 100 mg flibanserin group with worsening in the optic nerve of the left eye.

For the digital imaging, each set of 18 images was evaluated by a blinded central reader (b) (4)

(b) (4) In accord with the Wisconsin Lens Grading System, images were assessed for nuclear opacity, cortical opacity, and posterior subcapsular opacity (R08-5698). For nuclear opalescence, change was defined as any change of 0.7 units or greater and abnormal values were defined as any values of 3.0 or greater. For cortical opacity and posterior subcapsular opacity, change was defined as any change of 7% or greater. Using these criteria, there were no patients in the placebo group with any changes in any of the assessments. There was one patient (0.4%) in the 50 mg flibanserin group (No. 25136) with worsening in the right eye and one patient (0.4%) in the 50 mg flibanserin group (No. 26830) with worsening in the left eye. There was one patient (0.5%) in the 100 mg flibanserin group (No. 24354) with worsening in the right eye and two patients (0.9%) in the 100 mg flibanserin group (Nos. 24354, 26696) with worsening in the left eye.

There were no changes in nuclear opalescence or in posterior subcapsular opacity for any of the patients in any treatment group. There were no patients in any of the treatment groups with any abnormal values for nuclear opalescence. Patient 25136 (50 mg flibanserin) had worsening from grade of 0 to 10 in the right eye for the cortical opacity central zone. Patient 26830 (50 mg flibanserin) had worsening in the left eye from grade 0 to 10 for the cortical opacity circle diameter and grade 0 to 20 for cortical opacity central zone. Patient 24354 (100 mg flibanserin) had worsening in both eyes from grade of 2 to 15 for cortical opacity circle diameter. Patient 26696 (100 mg flibanserin) had worsening in the left eye from grade 80 to 90 for cortical opacity central zone. After the trial was complete a consultation was conducted with the central reader, (b) (4) and another expert consultant in lens photography, (b) (4).

(b) (4). After reviewing the images for the above patients it was clear that none of the changes were likely of clinical significance or predictive of eye toxicity, and likely were due to inherent variability in the lens images and grading technique. Further it became evident that the changes for patient 26830 were a result of a data entry error at the site and did not represent a grading change for this patient.

**Reviewer's Comments:** *There was a low frequency of reported ocular adverse events in all three arms of this trial.*

**BI Trial No.: 511.84: A twelve month, open-label, safety trial of flibanserin 50 milligrams to 100 milligrams daily in women with hypoactive sexual desire disorder (interim report using a data cutoff as of 13 Feb 2009)**

Ocular adverse events

There were 52 patients reporting 57 AEs of the eye disorder SOC while on treatment in this trial. The most common eye AEs were conjunctivitis (occurring in 11 patients), vision blurred (10 patients), dry eye (four patients) and myodesopsia (four patients). Two of the 57 eye AEs were of severe intensity (conjunctivitis [Pt. 27457] and eye pruritus [Pt. 31952]).

Twelve of the events were considered by the investigator to be related to study medication. These included one event each of choroiditis, dry eye, eye swelling, myodesopsia, photopsia, visual acuity reduced, two events of visual impairment and four events of vision blurred. Five patients discontinued the trial due to eye AEs; these included No. 13820 (vision blurred) No. 29333 (choroiditis, photopsia, and vision blurred), No. 25125 (eye edema), No. 30800 (eye swelling), and No. 26777 (vision blurred). As of the cutoff date, a total of 12 patients had not recovered from their eye AEs (Nos. 13820 [vision blurred], 16202 [dry eye], 18245 [visual impairment], 18548 [myodesopsia], 19539 [myodesopsia], 21094 [vision blurred], 21391 [vision acuity reduced], 25120 [vision blurred], 25125 [eye edema and vision blurred], 26479 [vision blurred], 29333 [vision blurred, photopsia], 39086 [giant papillary conjunctivitis]) and one patient (Pt. 26777 [vision blurred]) had a reported outcome of 'unknown'.

Ophthalmologic Examination

Ophthalmologic examinations were continued for patients from parent trial 511.71 who entered Trial 511.84. As of the cutoff date for this interim report, there were 233 patients who had visual acuity data included from their Week 26 visit and 153 patients who had these data included from their Week 52 visit. At Week 26, worsening of visual acuity (one or more lines of the ETDRS chart) was recorded in 29 patients (12%) for the right eye and 26 patients (11%) for the left eye. At Week 52, worsening of visual acuity was recorded in 19 patients (12%) for the right eye and 21 patients (14%) for the left eye. The majority of cases of worsening of visual acuity were worsening on only one line on the ETDRS chart. However, one patient reported worsening of two lines in the right eye and two patients reported worsening of two lines in the left eye at Week 26 and two patients reported worsening of two lines in the right eye and three patients (2%) reported worsening of two lines in the left eye at Week 52. Additionally, at Week 52, one patient reported worsening of seven lines in the right eye and worsening of more six lines in the left eye.

At Week 26, 13 of 231 patients (6%) had a clinically relevant decrease in intraocular pressure (greater than 4 mm Hg) for the right eye and five patients (2%) had a decrease in intraocular pressure for the left eye. At Week 52, five of 152 patients (3%) had a decrease in intraocular pressure for the right eye and four patients (3%) had a decrease in intraocular pressure for the left eye.

At Week 26, seven patients (3%) had an increase in intraocular pressure (greater than 4 mm Hg) for the right eye and nine patients (4%) had an increase in intraocular pressure for the left eye. At Week 52, six patients (4%) had an increase in intraocular pressure for the right eye and four patients (3%) had an increase in intraocular pressure for the left eye. Mean change from baseline values for intraocular pressure were -0.3 mm Hg for the right eye and -0.1 for the left eye at Week 26 and were -0.4 mm Hg for the right eye and -0.1 for the left eye at Week 52.

Corneal staining with fluorescein is used to evaluate corneal epithelial abrasions, infections, and other defects. At Week 26, there were nine of 232 patients (4%) with worsening of one or more grades in corneal staining for the right eye and eight patients (3%) with worsening for the left eye. At Week 52, six of 153 patients (4%) had with worsening of one or more grades in corneal staining for the right eye and two patients (1%) had worsening for the left eye. Almost all cases of worsening were worsening by one grade. For assessment of presence of corneal stromal opacities, there were four patients (2%) with worsening (i.e., absent at baseline but present at the end of treatment) in the right eye and one patient with worsening in the left eye at Week 26 and three patients (2%) with worsening in the right eye and one patient with worsening in the left eye at Week 52.

Retinal examination included assessment of the macula, optic nerve, blood vessels and periphery. In each case an assessment of “normal” or “abnormal” was made. At Week 26, there were four patients (2%) with worsening (i.e., change from “normal” to “abnormal”) in the right eye on the retinal examination and three patients (1%) with worsening in the left eye. At Week 52, there were six patients (4%) with worsening in the right eye on the retinal examination and six patients (4%) with worsening in the left eye. Most cases of worsening were in the optic nerve or periphery; worsening of the blood vessels was reported in one patient each for the right eye and left eye at each of the assessment timepoints (Weeks 26 and 52).

For the digital imaging, each of 18 images was evaluated by a blinded central reader (b) (4). In accordance with the Wisconsin Lens Grading System, images were assessed for nuclear opacity, cortical opacity, and posterior subcapsular opacity (R08-5698). For nuclear opalescence, change was identified as any change of 0.7 units or greater and abnormal values were defined as any values of 3.0 or greater. For cortical opacity and posterior subcapsular opacity, change was defined as any change of 7% or greater. Using these criteria, there was one patient with worsening in cortical opacity in the right eye and one patient with worsening cortical opacity in the left eye at Week 26, and there was one patient with worsening cortical opacity in the left eye at Week 52.

Adverse Event	# Age Gender	Start	Duration	Intensity	Action	The rapy	Outcome
Abnormal sensation in eye	32402 39/F	75	22	Mild	Continuing	No	Recover
Angle closure glaucoma	25336 41/F	365	15	Moderate	Continuing	Yes	Recover
Choroiditis	29333 36/F	142	48	Moderate	Discontinue	Yes	Recover
Conjunctivitis	17061 37/F	24	11	Mild	Continuing	Yes	Recover
Conjunctivitis	21421 43/F	11	4	Mild	Continuing	Yes	Recover
Conjunctivitis	25805 26/F	3	14	Mild	Continuing	No	Recover
Conjunctivitis	29741 43/F	51	4	Mild	Continuing	Yes	Recover
Conjunctivitis	30566 43/F	114	7	Mild	Continuing	Yes	Recover
Conjunctivitis	21415 43/F	230	4	Moderate	Continuing	Yes	Recover
Conjunctivitis	25827 26/F	70	8	Moderate	Continuing	Yes	Recover
Conjunctivitis	32026 23/F	51	5	Moderate	Continuing	Yes	Recover
Conjunctivitis	32048 38/F	302	29	Moderate	Continuing	Yes	Recover
Conjunctivitis	39086 35/F	52	8	Moderate	Continuing	Yes	Recover
Conjunctivitis	27457 38/F	59	15	Severe	Continuing	Yes	Recover
Conjunctivitis allergic	16605 48/F	21	8	Mild	Continuing	Yes	Recover
Corneal edema	17271 39/F	1	4	Moderate	Continuing	Yes	Recover
Dry eye	25490 42/F	32	33	Mild	Reintroduced	No	Recover
Dry eye	16202 51/F	15	460	Mild	NA	No	Not Recovered
Dry eye	23980 48/F	178	159	Mild	Continuing	No	Recover
Dry eye	24805 47/F	294	31	Mild	Continuing	No	Recover
Eye edema	25125 41/F	189	162	Mild	Discontinue	No	Not Recovered
Eye irritation	20703 36/F	108	19	Mild	Continuing	Yes	Recover
Eye irritation	26012 35/F	110	51	Mild	Continuing	No	Recover
Eye irritation	17114 31/F	24	7	Moderate	Continuing	Yes	Recover
Eye pruritus	11106 36/F	297	58	Mild	Continuing	No	Recover
Eye pruritus	24805 47/F	294	31	Mild	Continuing	No	Recover
Eye pruritus	31952 34/F	122	154	Severe	Completed	No	Recover
Eye swelling	30800 24/F	129	11	Moderate	Discontinue	No	Recover
Eye swelling	30092 39/F	227		Moderate	Continuing	No	Recover
Eyelid edema	33328 25/F	2	2	Mild	NA	No	Recover
Giant papillary conjunctivitis	39086 35/F	308	101	Moderate	Continuing	Yes	Not Recovered
Myodesopsia	25490 42/F	32	5	Mild	Reintroduced	No	Recover
Myodesopsia	18548 35/F	188		Mild	Continuing	No	Not Recovered
Myodesopsia	19539 27/F	30		Mild	Continuing	No	Not Recovered
Myodesopsia	15705 50/F	164	3	Moderate	Continuing	No	Recover
Open angle glaucoma	25336 41/F	365	15	Moderate	NA	Yes	Recover
Photophobia	29326 38/F	202	1	Moderate	Continuing	No	Recover
Photopsia	29333 36/F	24	197	Moderate	Discontinue	Yes	Not Recovered
Presbyopia	26776 47/F	37	125	Mild	Continuing	No	Recover
Retinal tear	30625 46/F	112	1	Mild	Continuing	Yes	Recover

Adverse Event	# Age Gender	Start	Duration	Intensity	Action	The rapy	Outcome
Ulcerative keratitis	18153 31/F	260	15	Moderate	Continuing	Yes	Recover
Ulcerative keratitis	27932 35/F	21	13	Moderate	Continuing	Yes	Recover
Vision blurred	13820 39/F	169	278	Moderate	Discontinue	No	Not Recovered
Vision blurred	29333 36/F	24	197	Moderate	Discontinue	Yes	Not Recovered
Vision blurred	26777 48/F	2	63	Moderate	Discontinue	No	Unknown
Vision blurred	25120 40/F	80	288	Mild	Discontinue	No	Not Recovered
Vision blurred	21094 44/F	201	193	Mild	Continuing	No	Not Recovered
Vision blurred	25125 41/F	125	232	Mild	Continuing	No	Not Recovered
Vision blurred	18010 34/F	27	28	Mild	Continuing	No	Recover
Vision blurred	21007 29/F	8	10	Mild	Continuing	No	Recover
Vision blurred	29326 38/F	202	1	Moderate	Continuing	No	Recover
Vision blurred	31377 41/F	133	125	Moderate	Continuing	No	Recover
Vision blurred	26479 40/F	175		Moderate	Completed	No	Not Recovered
Visual acuity reduced	21391 49/F	70	459	Mild	Continuing	No	Not Recovered
Visual impairment	18245 40/F	157	244	Mild	Continuing	No	Not Recovered
Visual impairment	12808 42/F	15	23	Mild	Continuing	No	Recover
Visual impairment	16711 43/F	92	154	Mild	Continuing	No	Recover

**Reviewer's Comments:** *The ophthalmic findings do not rise to a level to warrant inclusion in the Warnings and Precautions sections. Dry eye, blurred vision and keratitis should be included in the Adverse Events section of the labeling.*

**Summary Comments:**

1. A consultant report has been prepared and is on file with the applicant. It is recommended that the report be submitted to the NDA.
2. The ophthalmic findings do not rise to a level to warrant inclusion in the Warnings and Precautions sections. Dry eye, blurred vision and keratitis should be included in the Adverse Events section of the labeling.
3. There appear to be some typographical errors in the reporting of some of the ocular findings [example: patient 23159, sphere change from -2.25 to +3.75][patient 23350, sphere -3.15][patient 24361, sphere -0.28]. Since spherical lens are only made in quarter diopters increments and patient 23159 more likely had a value of -3.75, it is unlikely that these values are correct. The dataset therefore appears to contain typographical errors, but not to a level that would suggest an altered conclusion. The sponsor should be encouraged to re-check data entered into the dataset.
4. The observation of a congenital cataract at a follow-up visit [patient 25791] but not seen at a baseline visit raises a question about the ability to detect all lens changes. If it had occurred in more patients, this discrepancy would raise concerns about the validity of the testing.
5. There are no apparent ophthalmic concerns which would preclude approval of this drug product.

Wiley A. Chambers, M.D.  
Supervisory Medical Officer, Ophthalmology

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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/s/

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WILEY A CHAMBERS  
05/20/2010

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA  
CONSULT # 11209**

**Consultant Reviewer:** Silvana Borges, M.D.  
Medical Officer  
Division of Psychiatry Products (DPP)

**Consultation Requestor:** Charlene Williamson  
Regulatory Project Manager  
DRUP

**Subject of Request:** NDA 22526 – Flibanserin: assessment of suicidality during clinical development

**Date of Request:** January 20, 2010  
**Date Received:** April 21, 2010

## **I. Background**

Boehringer Ingelheim Pharmaceuticals submitted NDA 22-526 (flibanserin) to the Division of Reproductive and Urologic Products (DRUP) on October 27, 2009, seeking for the indication of hypoactive sexual desire disorder (HSDD) in pre-menopausal women. Flibanserin is a new molecular entity, acting preferentially as a post-synaptic 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2A</sub> receptor antagonist, having no relevant activity on 5-HT uptake and monoamine oxidases A or B. Flibanserin was originally developed for the treatment of major depressive disorder but failed to prove efficacy in Phase II trials. However, the sponsor observed that, in those Phase II depression trials, flibanserin was superior to placebo on improving the “sex drive” in women. This was their basis for pursuing the indication of HSDD in pre-menopausal women. Given flibanserin pharmacological profile, DRUP requested the sponsor to assess suicidality during its clinical development for HSDD. No suicidality assessment was performed in the MDD trials.

DRUP is now consulting DPP regarding the adequacy of the referred suicidality evaluation, posing the questions described below.

## **II. Review of Clinical Issues**

In the flibanserin clinical development for HSDD, suicidality was assessed with the Beck Scale for Suicide Ideation (BSS). The BSS is a structured, 21-item instrument (self-reported or administered by a professional) that elicits information about suicidality during the past week and is used to detect and measure the severity of suicidal ideation in adults and adolescents. The first 5 items serve as screening for suicidal ideation, and the following 14 items measure severity of suicidal wishes, attitudes, and plans. The statement gradations range from "0" (no inclination to suicidality) to "2" (moderate to strong inclination to suicidality). The last two items (20 and 21) are on background characteristics: the number of previous suicide attempts and the seriousness of intention to die associated with the last attempt. The BSS is considered a reliable method of estimating current suicidal ideation, but does not predict future suicidal behavior.

In the development of flibanserin, the BSS was used as a self-reported instrument or administered by professionals. If a subject chose zero statements for item 4 and/or 5 (indicating no active suicidal intention), she was instructed to skip the next 14 items and answer item 20 (the number of previous suicide attempts). If a subject chose non-zero statements for Item 4 and/or 5

(indicating suicidal ideation), then she was instructed to complete the next 14 items, in addition to items 20 and 21.

The BSS was performed at Screening, Baseline, at each clinic and telephone visit throughout the trial, and in the post-treatment visits in the following flibanserin pivotal clinical trials, whose co-primary endpoints were the number of satisfying sexual events and level of sexual desire collected daily by an electronic diary:

**Study 511.70:** (conducted in North America in Aug 2006 through May 2008) 24-week, randomized, double-blind, placebo-controlled, parallel design of three flibanserin dosage regimens (25 mg BID, 50 mg QD, and 50 mg BID) in premenopausal women with HSDD. Total: 1385 patients treated (349 on placebo, 337 on flibanserin 25 mg BID, 363 on 50 mg QD, and 336 on 50 mg BID).

**Study 511.71:** (conducted in North America in July 2006 through April 2008) 24-week, randomized, double-blind, placebo-controlled, parallel design of two flibanserin doses (50 and 100 mg QD) in premenopausal women with HSDD. Total: 880 patients treated (295 on placebo, 295 on flibanserin 50 mg QD, and 290 on 100 mg QD).

**Study 511.75:** (conducted in North America in July 2006 through March 2008) 24-week, randomized, double-blind, placebo-controlled, parallel design of three flibanserin dosage regimens (25 mg BID, 50 mg QD for 14 days, then titration to 50 mg BID, and 50 mg QD for 14 days, then titration to 100 mg QD) in premenopausal women with HSDD. Total: 1581 patients treated (398 on placebo, 396 on flibanserin 25 mg BID, 392 on 50 mg QD then 50 mg BID, and 395 on 50 mg QD then 100 mg QD).

The BSS was also performed in the following non-pivotal clinical trials:

**Study 511.77:** (conducted in the European Union in June 2007 through March 2009) A 24-week, randomized, double-blind, placebo-controlled trial of flibanserin 50 mg QD and 100 mg QD in premenopausal women with HSDD.

**Study 511.74:** (conducted in the U.S. in Jan 2006 through July 2007) A 48-week, randomized discontinuation trial of flibanserin in women with HSDD, containing a 24-week open-label, flexible dose period followed by a 24-week double-blind, randomized, placebo-controlled period.

**Study 511.84:** (conducted in North America in Feb 2007 through May 2009) A 12-month, open-label, safety trial of flibanserin 50 mg to 100 mg QD in women with HSDD (ongoing study).

**Study 511.118:** (conducted in Europe in Jan 2008 through October 2009) A 28-week, open-label, safety study of flibanserin 50 mg to 100 mg QD in premenopausal women with HSDD.

The sponsor identified subjects with suicidality using two methods: the BSS instrument described above and spontaneous reports from the study participants. In the Phase III placebo-controlled HSDD trials (trials 511.70, .71, .75, .74, and .77), a total of 3283 subjects were treated with flibanserin, and 1312 received placebo. In these trials, the sponsor reports that 0.4% of subjects receiving flibanserin (12 cases in 3283 subjects exposed) and 0.5% of subjects receiving placebo (6 cases in 1312 exposed) had a change from a BSS zero response at baseline to a non-zero response on treatment in the suicidal ideation screening part of the scale. In addition, four subjects receiving flibanserin spontaneously reported suicidality (including one case of suicide attempt) on treatment, while having zero responses on the BSS. The sponsor has excluded those cases from their suicidality rate calculation. No spontaneous report of suicidality occurred in the placebo groups. When the spontaneously reported suicidality cases are included in the analysis, the suicidality rate increases from 0.4 % to 0.5 % in the flibanserin group, while the rate in the placebo group remained the same (0.5 %).

## **Questions from DRUP**

### **1) Was the testing appropriate and comprehensive enough to evaluate for any potential signal of suicidality?**

**DPP response:** Since late 2008, DPP has been requesting sponsors to prospectively evaluate suicidality in every clinical protocol, at every planned visit, and in every phase of development conducted to support psychiatric indications. DPP considers an acceptable instrument to be one that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), such as the Columbia Suicide Severity Rating Scale (C-SSRS). Alternative instruments could be acceptable, provided the sponsor justifies that the proposed instrument meets this criteria.

The BSS is under copyright restrictions and a full version of the scale was not provided in the NDA submission. In addition, a comprehensive review of the sensitivity, specificity, and reproducibility of the BSS and its comparison with the C-SSRS is beyond the scope of this review. It is of note that the BSS shares in part the structure of the C-SSRS in that it begins with screening questions about suicidal ideation, followed by the characterization of such thoughts, attitudes, and plans, when applicable. However, the BSS does not directly map the C-CASA. In similar cases, when sponsors use instruments that do not directly map the C-CASA, DPP has requested that sponsors reclassify the events detected with such instruments according to the C-CASA and reanalyze the results. If DRUP wants to pursue such venue, DPP could provide specific recommendations for the sponsor on how to proceed with the event reclassification.

In this case, however, given the small number of subjects experiencing suicidality relative to the number of subjects exposed to flibanserin, the reclassification of events will most likely have no significant effect on the event rate currently calculated using the BSS score (please refer to our review of clinical issues above and our response to question #2 for further discussion on this matter).

### **2) Do you agree with the Sponsor's interpretation of the suicidality testing results (see Summary of Clinical Safety, section 4.2.1 located in Module 2.7.4)?**

**DPP response:** The sponsor concludes that there was no increase in suicidal ideation in HSDD subjects treated with any dose of flibanserin compared to placebo. It is of note that the sponsor has taken the approach of using the BSS as a screening tool and to classify BSS non-zero responders as suicidality cases according to the investigator's evaluation in a post-BSS interview. Following this approach, the sponsor considers most of the BSS-positive subjects not to be true suicidality cases. However, there is no structured interview or guidelines for the investigator on how to proceed in such interviews. DPP considers this procedure to be a source of bias. In this context, DPP would consider all changes from a BSS zero response to a non-zero response after initiation of treatment as suicidality cases. In addition, the sponsor has excluded spontaneously reported suicidality cases from their suicidality rate calculation, and it is not clear how these spontaneous reports of suicidality were ascertained. DPP has specific advice for sponsors on procedures for searching suicidality events in their databases. These procedures are described in Appendix I at the end of this review. However, although the inclusion of spontaneously reported cases increases the suicidality rate in the drug-treated group (from 0.4% to 0.5%), given the overall small number of non-zero responses relative to the number of subjects exposed to the drug, it does not significantly change the sponsor's conclusion. Similar results would be expected in the case of the reclassification of cases using C-CASA, as mentioned in our response to question #1.

**3) Do you see any signal of concern regarding the psychiatric safety that should be labeled?**

**DPP response:** On face, no suicidality or other psychiatric safety signals arise from the flibanserin safety analysis reported by the sponsor. However, the complete risk-benefit analysis, including suicidality and neuropsychiatric adverse events, will be a matter of review for DRUP. It is of note that, given the low frequency of treatment-emergent suicidal ideation and behavior, the detection of a suicidality signal is unlikely when analyzing the development program of a single drug. However, extensive analyses of controlled antidepressant trials (in numerous psychiatric and non-psychiatric indications), demonstrates that there is an increased risk of suicidality with these drugs, compared to placebo. Flibanserin is a post-synaptic 5-HT1A receptor agonist and a 5-HT2A receptor antagonist, and would be considered to have antidepressant properties. For safety labeling purposes, DPP recommends that labeling for flibanserin include the boxed warning for suicidality, as well as other relevant class warnings and precautions, regardless of the indication or the specific premarketing findings on suicidality and neuropsychiatric events. The standard language for the boxed warning and for the Warning's and Precautions section for antidepressants follows in Appendix II at the end of this review.

**4) Would you recommend any post-marketing evaluation of suicidality signals or adverse events?**

**DPP response:** Since flibanserin is a new molecular entity, it would be subject to the post-marketing safety reporting requirements applicable to all NMEs. DPP has not adopted a policy of requesting additional post-marketing evaluations for drugs carrying the boxed warning for suicidality in labeling.

**III. Conclusions and Recommendations**

- On face, no suicidality or other psychiatric safety signals arise from the flibanserin safety analysis reported by the sponsor. However, the complete risk-benefit analysis, including suicidality and neuropsychiatric adverse events, will be a matter of review for DRUP.
- Given its mechanism of action, flibanserin would be considered to have antidepressant properties. For safety labeling purposes, DPP recommends that labeling for flibanserin include the boxed warning for suicidality and other relevant antidepressant class warnings and precautions, in the case DRUP decides to approve flibanserin for the treatment of HSDD.

Silvana Borges, M.D.  
May 12, 2010

cc: NDA # 22526  
HFD-130/Borges  
/Dubitsky  
/Khin  
/Laughren  
/Berman  
HFD-580/Williamson

## APPENDIX I

### **ADVICE FOR THE PHARMACEUTICAL INDUSTRY IN EXPLORING THEIR PLACEBO-CONTROLLED CLINICAL TRIALS DATABASES FOR SUICIDALITY AND PREPARING DATA SETS FOR ANALYSIS BY FDA**

Given the finding of a signal for an increased risk of suicidality (suicidal ideation and behavior) in pediatric patients exposed to various antidepressants in placebo-controlled trials, and possible signals for treatment-emergent suicidality for antidepressants and other drugs in adult trials, including nonpsychiatric drugs and indications, there is interest in re-examining data from trials of a broader range of drugs and indications. In exploring these clinical trials databases, we recommend that similar methods to those used in evaluating the pediatric antidepressant data be utilized. We have outlined in this guidance document an approach that we recommend for these exploratory efforts.

#### **Clinical Trials to Include in the Suicidality Exploration**

Precisely which trials to include will depend in part on the study designs used in the indications of interest. In general, however, we recommend that the explorations be limited to double-blind, randomized, placebo-controlled trials which have been completed. Duration of the trials should not be a limiting factor, however, we recommend that only trials with at least 20 patients or subjects per treatment arm be included. Before beginning the exploration, we ask that you provide a list of the trials that you intend to include, and also a list of the RCTs that you have chosen not to include, along with a brief explanation for their exclusion.

Once there is agreement with FDA on which trials to include in the exploration, we ask that you provide certain descriptive information about these trials. We ask that you provide this information in table format at the same time that you submit a dataset with the suicidality data (see later). Attached to this document is the information that should be included in the requested tables.

#### **Search for “Possibly Suicide-Related” Adverse Events and Preparation of Narrative Summaries**

##### Time Frame for “Possibly Suicide-Related” Adverse Events

This search should be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Adverse events should not be included if they occurred prior to randomization or more than 1 day after discontinuing from randomized treatment. The end of trials with a tapering period should be set to be at the beginning of the tapering period. Events occurring more than 1 day after discontinuing from randomized treatment should be excluded even if discontinuation occurred before the nominal endpoint of the trial. For example, if a patient either discontinued of his or her own volition or was asked to discontinue by the investigator after 2 weeks of randomized treatment in a trial of 8 weeks duration, and the patient then experienced a “possibly suicide related” adverse event 2 days after stopping, that event should not be included.

Generally, events that are preexisting at baseline are not counted as treatment emergent if they recur during the course of a trial. However, in the requested analysis, suicidality-related events

that occur during the course of the double-blind phase or within 1 day of beginning taper, switching or stopping treatment should be counted, even if they occur in a patient who had such events at some prior time. The rationale for this rule is that it is generally very difficult to determine for the quality of data available in most of these trials whether suicidality occurring during the context of these trials is new or a continuation of some prior event.

### Search Strategies for Possibly Suicide-Related Adverse Events (PSRAEs)

The following search strategies should be employed to identify adverse events of possible interest with regard to suicidality:

- The following text strings should be used in searches of (1) all preferred terms; (2) all verbatim terms; and, (3) any comment fields:

“accident-”, “attempt”, “burn”, “cut”, “drown”, “gas”, “gun”, “hang”, “hung”, “immolat”, “injur-”, “jump”, “monoxide”, “mutilat-”, “overdos-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “suic-”, “poison”, “asphyxiation”, “suffocation”, “firearm” should be included. All events identified by this search should be included among the PSRAEs, unless they can be considered false positives.\_

Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string “cut” might identify the word “acute”). These terms might be characterized as “false positives” in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

<u>Study #</u>	<u>Patient #</u>	<u>Treatment Assignment</u>	<u>Term in Which Text String Occurred</u>
----------------	------------------	-----------------------------	---

The patients in this table will have as many rows as they have potential events.

- All deaths and other serious adverse events (SAEs) should be included among the PSRAEs.
- All PSRAEs identified by these 2 search strategies (and not excluded as “false positives”) should have narrative summaries prepared, as described in the following section.

### Preparation of Narrative Summaries for “Possibly Suicide-Related” Adverse Events

A complete set of narrative summaries should be prepared and collected for all PSRAEs that were not otherwise excluded as false positives. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. Many of these may be acceptable, however, some may need to be re-written if important information is missing (see below). In other cases, however, sponsors will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. They should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

- Patient ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- Recent dose change – elaborate on timing and amount of dose change
- Sex
- Age
- Diagnosis
- History of suicidal thoughts
- History of suicide attempt
- History of self harm
- Adverse event Preferred term
- Adverse event Verbatim term
- Serious adverse event (y/n)
- Number of days on drug at time of event
- Treatment was discontinued following event (y/n)
- Patient had an emergency department visit and was discharged (y/n)
- Patient was hospitalized (y/n)
- Patient died (y/n) – if yes, elaborate on cause of death
- Associated treatment emergent adverse events
- Concurrent psychosocial stressors
- Psychiatric comorbidities
- Concomitant medications
- Other pertinent information (e.g., family history of psychiatric disorders)-

Other relevant information for preparing narrative summaries:

-Patients may be identified as having events of interest in one or more of the above searches, and they may have more than one event of interest. In no case, however, should there be more than one narrative summary per patient. In cases where there is more than one event for a given patient, each different event should be clearly demarcated in the narrative.

-Only events occurring during the “exposure window” defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., sponsors should not include any prerandomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period.

-As noted, sponsor should not exclude events of interest on the basis of a judgment that they might not represent “treatment-emergent” events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

The narrative summaries do not need to be submitted to FDA. However, we may at some point request a random sample of the summaries to audit your classification process.

## Classification of “Possibly Suicide-Related” Adverse Events

Once the narrative summaries for “possibly suicide-related” adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA’s website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA’s website [Slides [http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1\\_06\\_FDA-Posner.ppt](http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt) and Briefing Document, transcripts, etc. <http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>]

The categories of interest from FDA’s standpoint are as follows:

- Completed suicide (code 1)
- Suicide attempt (code 2)
- Preparatory acts toward imminent suicidal behavior (code 3)
- Suicidal ideation (code 4)
- Self-injurious behavior, intent unknown (code 5)
- Not enough information (fatal) (code 6)
- Self-injurious behavior, no suicidal intent (code 7)
- Other: accident; psychiatric; medical (code 8)
- Not enough information (nonfatal) (code 9)

Those individuals who classify the narratives must have the appropriate expertise and training to accomplish this task. Thus, this task could be accomplished by seeking the help of an outside contractor who has this expertise. However, it is also possible that a sponsor may have internal expertise to accomplish this classification. Even in the latter instance, you may consider at least obtaining training of your internal staff from an outside contractor. Such training might help to increase the reliability of the classifications for subsequent meta-analyses of the data across programs.

Prior to their rational classification, the narratives must be blinded to details that might bias their assessments. The details of appropriate blinding of the narratives can also be obtained in the transcript from the advisory committee meeting referred to above, and the materials available on FDA’s website pertinent to that meeting. We request that you block out the following information that could reveal treatment assignment:

- Identifying patient information, identity of study drug, and patient's randomized drug assignment
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial
- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)
- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out

- Names of medications involved in overdoses; the number of pills consumed should not be blocked out
- Indications for medications started during or after the study
- Indications for study drug

## Data Submission

In order to perform additional analyses investigating the relationship between exposure to the drug of interest and PSRAEs among the patients of interest, we would appreciate your submitting the following variables as outlined in the next table. As noted, we are requesting information from placebo controlled trials only. Please do not submit data from active control only studies, uncontrolled extensions of placebo controlled studies, or combination drug studies. We would expect that you will provide us with a SAS transport file. We are requesting that you provide this file to the Agency by [insert date].

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
TRIAL	Character	Trial ID	
INDICATION	Character	Indication that is focus of the trial	
CTPID	Character	Patient ID within each trial	
UNIQUEID	Character	A unique ID for every patient	
AGE	Numeric	Patient age	In years
AGECAT	Numeric	Age category	1=5-17 y 2=18-24 y 3=25-64 y 4=65 y or more
GENDER	Numeric	Patient gender	1=female 2=male
RACE	Numeric	Patient race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing
RANTXCAT	Numeric	Treatment category (assuming drugs can be categorized by class)	1= 2= 3= 6=placebo
SETTING	Numeric	Setting of trial	1=inpatient 2=outpatient 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America
TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control

Variable name	Type	Description	Coding notes
			No missing values are allowed in this variable.
TXACTIVE	Character	Name of drug used as active control	Leave patients in other treatment arms blank
SCALE	Character	Primary scale used to rate indication that is focus of the trial (this variable is required only for depression trials)	This should be a text field. As noted, please submit an electronic copy of whatever instrument was used for the primary protocol-specified endpoint(s).
SCOREA	Numeric	Score of primary scale at baseline (this variable is required only for depression trials)	No missing values are allowed in this variable.
SCOREB	Numeric	Score of primary scale at end of trial (this variable is required only for depression trials)	No missing values are allowed in this variable.
RESPONSE	Numeric	Response status (this variable is required only for depression trials)	0=non-responder 1=responder <sup>1</sup> . = Missing
EVENT	Numeric	This variable contains the code for the first suicidality event. If a patient had more than one event in the desired “exposure window”, then the most severe event should be listed. Severity is decided based on the following order of codes: 1>2>3>4>5>6>9. Every patient in every trial will be classified on this variable. For the majority of patients who are not identified as having a “possibly suicide-related AE”, the classification will be 0 (no event). Similarly, those patients who have “possibly suicide-related AEs” that are coded as 7 or 8 will also be classified for this variable as 0 (no event), because we will not be using codes 7 or 8 in our analyses.	0=no event 1=completed suicide 2=suicide attempt 3=preparatory acts toward imminent suicidal behavior 4=suicidal ideation 5=self-injurious behavior, intent unknown 6= not enough information, fatal 9= not enough information, non-fatal No missing values are allowed in this variable.

<sup>1</sup> Please specify the criteria used to define patients as responders

Variable name	Type	Description	Coding notes
		Patients with event codes 1 through 6 for SRE's will be classified with their most severe event code.	
EVENTDAY	Numeric	The number of days to the first most severe suicidal event, counting from the day of the first dose.	<p>For patients without events, this variable should contain days until end of trial or until premature discontinuation</p> <p>For patients with more than one event, this variable should contain days until the first most severe event that is listed under the variable "EVENT"</p> <p>No missing values are allowed in this variable.</p>
DISCONT	Numeric	The patient discontinued before the end of the controlled portion of the trial	<p>0=No 1=Yes</p> <p>No missing values are allowed in this variable</p>
HXSUIATT	Numeric	The subject had a history of suicide attempt prior to entering the RCT as defined by: HAMD item 3=4 or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	<p>0=No 1=Yes</p> <p>. = Missing or no information available</p>
HXSUIID	Numeric	The subject had a history of suicidal ideation prior to entering the RCT as defined by: HAMD item 3=3, MADRS item 10 >=3, or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	<p>0=No 1=Yes</p> <p>. = Missing or no information available</p>

## Attachment

For each trial included in the analysis, please provide a summary of important study characteristics in tabular form as shown in Tables 1 and 2 below. Many of the column headings are self-explanatory. However, the following headings merit clarification:

- **Number of Patients:** number of patients randomized to the drug and placebo treatment groups.
- **DB TX Duration:** the nominal duration of the analyzed double-blind treatment phase.
- **Protocol Dose:** the protocol-specified daily target dose expressed as a range for flexible dose studies and as individual doses for fixed dose trials.

Note: The following headings apply only to depression trials:

- **Extensive DX Screening:** indicate yes if the study required confirmation of the diagnostic entry criteria by two or more independent raters. Otherwise, indicate no.
- **Exclude TX Resistant:** indicate yes if a study exclusion criterion was a history of treatment resistance or poor response of the index illness to previous treatment. Otherwise, indicate no.
- **Exclude Bipolar D/O:** indicate yes if a study exclusion criterion was a history or presence of bipolar disorder or mania in the patient. Otherwise, indicate no.
- **Exclude Family H/O Bipolar Disorder:** indicate yes if a study exclusion criterion was any family history of bipolar disorder or mania. Otherwise, indicate no.

TABLE 1: BASIC STUDY DESIGN							
Drug	Study	Indication	Age Range (years)	Number of Patients		DB TX Duration (weeks)	Protocol Dose (mg/day)
				Drug	Placebo		
XYZ	123	MDD	18 to 60	120	119	6	120 to 160
	456	MDD	55 to 85	148	148	8	120, 140, 160
	789	OCD	18 to 65	119	110	12	120, 140
	1111	OCD	18 to 70	71	69	13	120 to 160

TABLE 2: SCREENING AND KEY EXCLUSIONARY CRITERIA									
Drug	Study	Indication	Extensive DX Screen	Placebo Lead-In	Exclude TX	Excl. Current Suicide Risk	Excl. H/O Suicide	Excl. Bipolar	Excl. Family H/O
XYZ	123	MDD	No	Yes	No	Yes	No	Yes	No
	456	MDD	Yes	Yes	No	No	No	Yes	Yes
	789	OCD	Yes	Yes	Yes	Yes	No	Yes	Yes
	1111	OCD	No	No	No	Yes	No	Yes	Yes

## ADDENDUM

### TO

#### **ADVICE FOR THE PHARMACEUTICAL INDUSTRY IN EXPLORING THEIR PLACEBO-CONTROLLED CLINICAL TRIALS DATABASES FOR SUICIDALITY AND PREPARING DATA SETS FOR ANALYSIS BY FDA**

##### **Information on Deaths Occurring Up to 90 Days After the Nominal Treatment Endpoint**

As noted in the Advice Document, FDA's primary analysis of suicidality events will focus on events occurring during the double-blind phase of treatment, or within 1 day of stopping randomized treatment (**DB+1**). This primary analysis will include an exploration of any deaths occurring during this DB+1 period. However, for purposes of exploring the robustness of any suicidality findings, we intend to also examine deaths that can be considered to represent suicides occurring beyond this DB+1 window. Thus, for this addendum, we ask that all known deaths occurring in subjects after assignment to randomized treatment up until 90 days after the nominal treatment endpoint be reported (**Nom DB+90**). For example, if the double-blind treatment phase of a study is given as 10 weeks (70 days), deaths occurring within a 160 day period after initiation of double-blind treatment should be reported regardless of whether a subject completed the intended 10 week course of treatment. Narrative summaries should be submitted for each death. The narratives should include trial ID (TRIAL), subject ID within the trial (CTPID), the date of death relative to the initiation of double-blind treatment, the date when double-blind treatment was stopped, and the date of the event that was the likely cause of death (if known); e.g., myocardial infarction, trauma, overdose, etc. If double-blind treatment was stopped before death, the narrative should describe any subsequent treatment the subject received. The circumstances of death should be classified using the same methodology as for any "possibly suicide-related" adverse event. In the case of deaths, such classifications would, obviously, be limited to completed suicide (code 1), not enough information (fatal) (code 6), and other (code 8). [Note: We recognize that information on deaths occurring during the DB+1 period will already have been provided in response to our earlier request. Nevertheless, we ask that the response to this addendum include information on the entire set of deaths occurring in the Nom DB+90 period, even though this will repeat information for DB+1 deaths.]

3 Pages have been Withheld in Full as B4 (CCI/TS)  
Immediately Following this Page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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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.**

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/s/

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SILVANA BORGES  
05/12/2010

NI A KHIN  
05/12/2010

THOMAS P LAUGHREN  
05/12/2010

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	22526
<b>Brand Name</b>	Flibanserin Tablet 100 mg
<b>Generic Name</b>	BIMT 17 BS
<b>Sponsor</b>	Boehringer Ingelheim Pharmaceuticals, Inc.
<b>Indication</b>	Pre-menopausal Hypoactive Sexual Desire Disorder
<b>Dosage Form</b>	tablets
<b>Drug Class</b>	5-HT1A receptor agonist and a 5-HT2A receptor antagonist
<b>Therapeutic Dosing Regimen</b>	100 mg q.d.
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	100 mg single dose, 100 mg t.i.d.
<b>Submission Number and Date</b>	SDN 001 / 27 OCT 2009
<b>Review Division</b>	DRUP / HFD 580

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

No significant QT prolongation effect of flibanserin (50 mg bid and 100 mg tid) was detected in this TQT study.

In this randomized, blinded, multiple dose, four-period crossover study, up to 56 healthy subjects received flibanserin 50 mg bid, flibanserin 100 mg tid, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings on QTcI is presented in Table 1 below.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Flibanserin (50 mg bid and 100 mg tid) and the Largest Lower Bound for Moxifloxacin (FDA Analysis of QTcI)**

<b>Treatment</b>	<b>Time (hour)</b>	<b><math>\Delta\Delta\text{QTcI}</math> (ms)</b>	<b>90% CI (ms)</b>
Flibanserin 50 mg bid	1.5	0.7	(-1.2, 2.7)
Flibanserin 100 mg tid	1.5	2.0	(0.01, 4.0)
Moxifloxacin 400 mg*	3	13.0	(10.7, 15.3)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 7 time-points is 9.6 ms.

Change in mean QTcI from baseline (Day -1) to Day 5 was compared between flibanserin (50 mg bid and 100 mg tid) and placebo. As seen from Table 1 above, the largest upper bounds of the 2-sided 90% CI for the mean difference between flibanserin

(50 mg bid and 100 mg tid) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcI}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4 in section 5.2.1.3 below, indicating that assay sensitivity was established.

The therapeutic dose used in this study (50 mg bid) produces subtherapeutic  $C_{\text{max}}$  values. The suprathreshold dose (100 mg tid) produces flibanserin mean  $C_{\text{max}}$  values 1.2-fold higher than the mean flibanserin  $C_{\text{max}}$  for the therapeutic dose (100 mg qd). The  $C_{\text{max}}$  of the metabolite BIML 7 at the suprathreshold dose was only 77% of the value previously observed after the 100-mg qd dose. Therefore, the “suprathreshold” dose used in this study can be considered to provide therapeutic  $C_{\text{max}}$ . At these therapeutic concentrations there are no detectable prolongations of the QT-interval. Asians are expected to have a 57% higher flibanserin  $C_{\text{max}}$  and therefore may not be covered by the exposures observed in this study. Interaction with potent inhibitors of CYP3A4, such as itraconazole and ketoconazole increase  $C_{\text{max}}$  1.69- to 1.8-fold. Hepatic impairment may also increase flibanserin concentration as hepatic metabolism is the route of metabolism. The results of this 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. Currently, the sponsor is not recommending use of flibanserin in these populations.

## 2 PROPOSED LABEL

*The sponsor proposed a brief description in the PI for (b) (4). We have the following recommendations which are suggestions only. We defer all final labeling decisions to the review division.*



### 3 BACKGROUND

#### 3.1 PRODUCT INFORMATION

Flibanserin (INN) or BIMT 17 BS is under clinical development as an oral treatment of Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women. Flibanserin is purported to act preferentially as a post-synaptic 5-HT<sub>1A</sub> receptor agonist and a 5-HT<sub>2</sub> A receptor antagonist. Additionally, it displays moderate affinity for 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, and dopamine D<sub>4</sub> receptors.

#### 3.2 MARKET APPROVAL STATUS

Flibanserin is not approved for marketing in any country.

#### 3.3 PRECLINICAL INFORMATION

*Source: Pharmacology Written Summary, Section 4.2.*

“A non-GLP study was conducted to determine the effect of flibanserin on hERG (human ether-a-go-go related gene)-mediated K<sup>+</sup> current. Experiments on hERG-mediated K<sup>+</sup> current were performed using HEK293 (human embryonic kidney) cells stably expressing the hERG-mediated K<sup>+</sup> current. Whole-cell experiments were carried out by means of the patch-clamp technique. Effects on the hERG-mediated current amplitude by flibanserin were measured for each test concentration (0.3 - 10 μM) over 5 min. Flibanserin blocks hERG-mediated K<sup>+</sup> current in the protein-free test system of HEK293 cells with an IC<sub>50</sub> of 1.18 μM. Based on a previous study on action potential configuration in isolated guinea pig papillary muscle, this activity has no relevance to the effects of flibanserin on the myocardial action potential. Considering the high plasma protein binding of flibanserin of 98%, total plasma drug levels of approximately 50 μM would be needed to elicit any effect on the myocardial AP. Such high plasma concentrations are not reached clinically due to other dose-limited effects, e.g. clinical symptoms.

“A GLP study was designed to assess the potential cardiovascular effects of oral administration of flibanserin using telemetric monitoring in the conscious Beagle dog. Prior to the first test session, a 12-hour telemetric recording was performed to obtain baseline data which was used to calculate individual regression lines for QT corrections (QTcR). Each animal received a single oral dose of flibanserin at 3, 10 or 30 mg/kg or a vehicle control. A dose-dependent systemic exposure to flibanserin was shown (C(1h) values of 0.25, 0.55, 1.2 μg/mL, respectively). At 30 mg/kg one dog showed clinical signs of ill-being (such as muscle tremor, splayed limbs, salivation, panting, reddening of gums and ears). Effects of flibanserin on cardiovascular parameters were only seen at 30 mg/kg. These included mild elevations in mean arterial BP and HR. There were treatment-related changes in the RR, PR and uncorrected QT interval which are considered to be due to the mild elevation of HR observed after 30 mg/kg. Flibanserin did not produce adverse changes to the ECG (lead

II) rhythm or waveform morphology at any dose. There was no evidence of adverse effects on cardiac conduction. The QT interval corrected for heart rate (QTcR) did not change as a result of treatment with flibanserin although a small, significant reduction was evident at 6 h after 30 mg/kg.”

### **3.4 PREVIOUS CLINICAL EXPERIENCE**

*Source: Summary of Clinical Safety*

This Summary of Clinical Safety (SCS) includes data of flibanserin in 5007 premenopausal women with HSDD and data from men and women from the Major depressive disorder (MDD) trials.

The mean duration of treatment exposure during double-blind treatment in the Phase III placebo-controlled trials was 145.5 days (approximately 21 weeks) in the placebo group and 137.7 days (approximately 20 weeks) in the flibanserin group. Exposure to flibanserin 100 mg q.h.s. was 373.3 subject-years.

One subject died among all clinical studies with flibanserin: A subject in Study 511.74 receiving placebo died as a passenger in an airplane crash on Day 19 of the double-blind period.

Subject 37779 in Trial 511.77, receiving flibanserin 100 mg q.h.s., suffered “circulatory collapse” on Day 11, fell and suffered a concussion and was hospitalized. Concurrent AEs were nausea, headache, and pain. The subject had a medical history of hypotension and orthostatic dysregulation. There was no relevant concomitant therapy in this subject.

The following tables provide changes in ECG - Phase III placebo-controlled trials (511.70, 511.71, 511.75).

Table 4.1.3.1: 1 Changes in HR, PR and QRS intervals - Phase III placebo-controlled HSDD Trials 511.70, 511.71, and 511.75

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

	Placebo N (%)	Flibanserin N (%)
QRS interval [ms] <sup>c</sup>		
N	898	2397
Mean of change	1.0	0.7
SD	5.6	5.8
Notable QRS increase		
N	898	2397
No	898 (100.0)	2396 (100.0)
Yes	0 (0.0)	1 (0.1)

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

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

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

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

Source: Appendix 7, Table 4.1.5

Table 4.1.3.1: 3 Frequency of subjects exceeding QTc thresholds based on the maximum on treatment QTc interval - Phase III placebo-controlled HSDD Trials 511.70, 511.71, and 511.75

Parameter	Placebo N (%)	Flibanserin N (%)
Number of subjects	1042	2804
QTcF threshold [N (%)]		
N	899 (100.0)	2397 (100.0)
>450 ms	3 ( 0.3)	10 ( 0.4)
>480 ms	0 (0.0)	1 ( 0.0)
>500 ms	0 (0.0)	0 (0.0)

Table 4.1.3.1: 4 Frequency of categorized mean changes in QT(c) intervals over the treatment period - Phase III placebo-controlled HSDD Trials 511.70, 511.71, and 511.75

	Placebo	Flibanserin
Number of subjects	1042	2804
QTcF - mean change [msec]		
N	898 (100.0)	2397 (100.0)
≥30	11 ( 1.2)	55 ( 2.3)
≥60	0 ( 0.0)	0 ( 0.0)

Includes Trials 511.70, 71 and 75. Trial 511.77 is not included because ECGs were read locally, unlike Trials 511.70, 511.71, and 511.75, which had central ECG readings.

Source: [Appendix 7, Table 4.1.8](#)

*Reviewer's Comments: No subject in the HSDD trials with central ECG over-read experienced an absolute QTcF over 500 ms or a change from baseline > 60 ms. ECGs were performed at screening, baseline and week 24. There are no reports of sudden death, seizure or significant ventricular arrhythmias in the summary of safety.*

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of flibanserin's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 22526. The sponsor submitted the study report BI 511.90 for the study drug, including electronic datasets and waveforms to the ECG warehouse. The Sponsor submitted data in the SAS transport file qtpk.xpt were used in preparing this report. The study report: BI 511.90 and protocol- BI511.90 from [\\Fdswa150\nonecnd\I64558\O\\_214\2009-11-25\0192](#) were also used in preparing this report.

## **4.2 TQT STUDY**

### **4.2.1 Title**

Assessment of electrophysiological effects of 50 mg bid and 100 mg tid of flibanserin given for 5 days on the QT interval in healthy female and male subjects, a double-blind, randomized, placebo and positive controlled (moxifloxacin, open label), four-way crossover study

### **4.2.2 Protocol Number**

BI Trial No.:511.90

### **4.2.3 Study Dates**

Study initiation date: 16 OCT 06

Study completion date: 16 MAY 07

### **4.2.4 Objectives**

Evaluate QT/QTc prolongation and Proarrhythmic potential for flibanserin by using a placebo control and moxifloxacin as the positive control in adult healthy volunteers.

### **4.2.5 Study Description**

This study was conducted in healthy female and male volunteers in a single centre. It was a double-blind, randomized, placebo and positive controlled (moxifloxacin, open label), four-way crossover study. The Williams design involving four sequences, periods, and treatments was used, which possesses the variance-balance property. A total of 48 subjects were sufficient for detecting a treatment difference between moxifloxacin and placebo of 7 ms in the mean time-matched QTcI change from baseline with a power of 90% using a t-test with a 0.05 one-sided significance level. To ensure a sufficient number of evaluable subjects for the primary analysis, a total of fifty-six healthy female and male volunteers were selected for this study. Subjects were recruited from the subject's pool of PHAROS. The following visits were planned:

Visit1: Screening (within 28 days before visit 2)

Visits 2, 5: Baseline ECG profile day (day -1) prior to the first and last randomized crossover period with three double-blind dosing regimens of either flibanserin 50 mg bid or 100 mg tid or matching placebo or open-label single dose of 400 mg moxifloxacin

Visits 3, 4: Second and third randomized crossover period with three double-blind dosing regimes of either flibanserin 50 mg bid or 100 mg tid or matching placebo or open-label single dose of 400 mg moxifloxacin

Visit 6: End of study examination

There were washout periods of at least 14 days following visits 2 to 4. The end of study examination (visit 6) was performed after a washout period of at least 7 days after the last drug administration at visit 5.

Visits 2 and 5 included a baseline ECG profile day prior to the treatment period consisting of either five days of dosing with an ECG profile on day 5 (flibanserin or placebo) or one day of dosing with an ECG profile (moxifloxacin, day 1). Visits 3 and 4 are identical to visits 2 and 5 without a preceding baseline ECG day. Thus in each subject six ECG profiles were recorded during visits 2 and 5. Duration of treatment was 5 days for flibanserin and placebo and 1 day for moxifloxacin. See section 6.2 for the schedule of ECG measurements and the study flow chart.

#### 4.2.5.1 Design

This is a randomized, double-blind, double-dummy, positive-, placebo-control, 4-period, crossover study with four dosing occasions. Each dosing occasion will be followed by a 7-day washout period. It was a single-site study of flibanserin in adult healthy volunteers to be conducted in conformance with Good Clinical Practice.

#### 4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

#### 4.2.5.3 Blinding

All treatment arms involving placebo and flibanserin were administered double-blinded. Moxifloxacin treatment was open label.

### 4.2.6 Treatment Regimen

#### 4.2.6.1 Treatment Arms

Treatment schedule for crossover treatments

Treatment	8:00 h	16:00 h	20:00 h	24:00 h
A	1×50mg tablet 1×placebo	2×placebo	1×50mg tablet 1×placebo	2×placebo
B	2×50mg tablet	2×50mg tablet	2×placebo	2×50mg tablet
C	2×placebo	2×placebo	2×placebo	2×placebo
D	1×moxifloxacin	--	--	--

#### 4.2.6.2 Sponsor’s Justification for Doses

“In the Phase I studies of flibanserin, the highest single dose tested was 150 mg. The 150 mg dose was well-tolerated in the first rising-dose safety/PK study, in which the six volunteers tested had been exposed to a smaller dose previously. However, the same dose in the second rising-dose safety/PK study, in which the volunteers were not exposed to any dose previously, was intolerable. The 150 mg dose caused AE reports from all subjects dosed. Of the 6 subjects dosed with 150 mg, a median of 5 AE occurred per

subject. The maximum severity of AE was severe in half (3), moderate in 2, and mild in 1. Sedative AE (tiredness, somnolence) were the most frequent type of AE (in all 6 flibanserin subjects). AE unexpected from lower doses were also present in all of the six - particularly orthostasis, pallor, slurred speech, and nausea, in half of the subjects each, plus more AE in 4 of the 6: vertigo and restlessness in one; dysphagia and hot flushes in another; weakness in a third subject; and headache in a fourth subject. Orthostatic hypotension occurred in 2 along with AE of sufficient severity to require cancelling of some study procedures. Mild tachycardia (111 or 119 bpm) occurred in another 2.

“The highest well-tolerated repeated dosage was 100 mg bid. Dose-related dizziness and fatigue were more prominent with 100 mg tid, but there were no dropouts for adverse events over the 14 days of repeated dosing.

“The scheduled doses of flibanserin for this study were 50 mg bid and 100 mg tid for 5 days. The 50 mg bid dose is within the therapeutic range. The 100 mg tid dose is a clinically acceptable suprathreshold dose, as recommended by the ICH Guideline E14 [R05-2311] for QT studies. The therapeutic dose 50 mg bid resulted in maximum steady state plasma concentrations of approximately 220 ng/mL whereas with administration of the suprathreshold dose of 100 mg tid 3.3-fold higher maximum plasma concentrations of approximately 730 ng/mL were achieved [U97-2256]. For safety reasons doses higher than 100 mg tid cannot be administered to healthy volunteers.”

*Reviewer’s Comment: The 50-mg bid dose is not the therapeutic dose. The therapeutic dose of 100 mg qd has been shown in a previous study (Study 511.105) to provide a  $C_{max}$  of 469 ng/mL, which is 2-fold higher the observed value in this study following the 50-mg bid dose. The “suprathreshold” dose used in the study, 100 mg tid is the maximum tolerated dose and is therefore an acceptable dose. Unfortunately, it gives rise to a  $C_{max}$  that is only 1.2-fold higher than that of the 100-mg qd therapeutic dose. Furthermore, the  $C_{max}$  of the metabolite BIML 7 ZW in this study (495 ng/mL) was lower than what was previously observed after the 100-mg qd dose (641 ng/mL). Therefore, the suprathreshold dose used in the study provides therapeutic  $C_{max}$  values. Asians are expected to have a 57% higher flibanserin  $C_{max}$  and therefore may not be covered by the exposures observed in this study. Interaction with potent inhibitors of CYP3A4, such as itraconazole and ketoconazole increase  $C_{max}$  1.69- to 1.8-fold. Hepatic impairment may also increase flibanserin concentration as hepatic metabolism is the route of metabolism. Currently, the sponsor is not recommending use of flibanserin in patients with impaired liver function or patients receiving potent inhibitors of CYP3A4. The reviewer agrees that the results of this study do not support the QT-related safety of the 100-mg qd dose in these populations.*

#### **4.2.6.3 Instructions with Regard to Meals**

Doses on Day 5 were administered after a light breakfast.

*Reviewer’s Comment: Administration of a light meal prior to dosing is acceptable. A light breakfast has previously been shown to increase AUC by 18%, but have no effect on  $C_{max}$ . Previous studies suggest administration of a high fat and caloric meal would have increased AUC by a greater extent (37% – 56%), but the effect on  $C_{max}$  is equivocal.*

#### 4.2.6.4 ECG and PK Assessments

ECG measurements for assessment of QTc were obtained one hour pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 12 and 24 hours post-dose on Day 5 in all treatment periods and on Day -1 for treatment periods 1 and 4. ECG measurements were also collected for the moxifloxacin treatment period on Day 1 one hour pre-dose and 0.5, 1, 2, 3, 4 and 6 hours post-dose. Blood samples for measurement of flibanserin and its metabolites BIMA 23 BS, BIML 7 ZW and TFMPP were obtained before the first flibanserin administration on Day 1, before every flibanserin administration on Days 4 and 5 and 0.5, 1, 1.5, 2, 3, 4, 6, 12 and 24 hours following flibanserin administration on Day 5.

*Reviewer's Comment: The PK and ECG assessments are adequate to capture the QT effect at peak concentrations of flibanserin ( $T_{max} \sim 1$  hour) and its metabolites ( $T_{max} \sim 1$  to 3 hours). In addition, the sampling time points are sufficient to cover the potential delayed effect up to 24 hours post-dose.*

#### 4.2.6.5 Baseline

Time-matched baseline was used for the analysis.

#### 4.2.7 ECG Collection

*From the Protocol*

“Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) of 10 s duration will be recorded after 10 minutes rest in the supine position using the Eagle 4000 patient monitors (GE Marquette Hellige GmbH, Freiburg, Germany) or another system provided by nabios. The triple ECGs to be recorded during the treatment period will be digitally performed at defined time-points.

“All ECGs except those from screening and the end-of-study examination are sent to a central laboratory for interval measurement. Each interval measurement will be performed by a single reviewer for a given subject as a batch in random and blinded sequence. The ECG laboratory is blinded with regard to the treatment and the date of the ECGs. No more than two different blinded readers will do the readings of all ECGs of this study. Interval measurements will be performed on one lead, usually lead II. If lead II shows a flat T wave or is immeasurable for any reason, lead I will be used, or, if that lead is immeasurable, then lead V2 will be used. The lead information will be recorded. As far as possible, all measurements in one subject (or if not possible, for each visit of a single subject) will be recorded on the same lead. For interval measurement analysis, measurements of each four QT, RR, PQ and QRS intervals will be made on four wave forms from the chosen lead (usually lead II). The measurements of the single wave forms will be stored in the data base. For each QT interval, the RR interval preceding the QT will be measured and used for frequency correction.”

#### 4.2.8 Sponsor's Results

##### 4.2.8.1 Study Subjects

Fifty-six (56) subjects, among them 26 male and 30 female subjects, 20-49 yrs of age with a normal baseline ECG and BMI between 19-30 kg/m<sup>2</sup> participated in the treatment

phase of the study. Two female subjects (# 7 and 24) discontinued the study due to adverse events following administration of 100 mg tid flibanserin.

#### **4.2.8.2 Statistical Analyses**

##### **4.2.8.2.1 Primary Analysis**

The Sponsor analyzed the change in QTcI from time matched baseline (Day -1) to day 5 by time using ANOVA model for 4-way crossover extracting the effects due to treatment, sequence, period, subject, and baseline as a covariate.

There was no evidence that flibanserin has an adverse impact on cardiac electrophysiology as assessed by mean changes or outliers in the QT interval corrected for heart rate by any method (QTcI, QTcI, QTcB) or uncorrected QT interval. The upper limit of the two-sided 90% confidence intervals was less than 10 ms at both flibanserin dose levels, indicating no clinically relevant increase in the QT/QTc interval following administration of 50 mg bid and 100 mg tid flibanserin compared with placebo (by any correction method).

The ability to detect relevant changes in the QTcI interval duration with great precision in this study was confirmed by observing significant differences in the QTcI interval along with a narrow confidence interval (Least-squares mean change from baseline in QTcI interval over 1 to 4 h of 10 ms with a confidence interval of 7.7 ms to 12.3 ms,  $p < 0.0001$ ) with moxifloxacin as compared with placebo.

*Reviewer's comment: The Sponsor's conclusions are acceptable.*

##### **4.2.8.2.2 Categorical Analysis**

Maximum QTcI interval durations over 0.5 to 24 h were categorized by QTc interval limits ( $QTcI \leq 450$  ms,  $450 < QTcI \leq 480$  ms,  $480 < QTcI \leq 500$  ms and  $500$  ms  $< QTcI$ ). Maximum changes from baseline in the QTcI interval over 0.5 to 24 h were categorized by the magnitude of the change ( $\Delta QTcI \leq 30$  ms,  $30 < \Delta QTcI \leq 60$  ms and  $60$  ms  $< \Delta QTcI$ ). Notable findings were neither observed with respect to QTcI interval ( $>500$  ms or increase from baseline  $\geq 60$  ms) nor to uncorrected QT interval ( $>500$  ms) at any time during the study. The results of categorical QTcI interval analyses were confirmed by those obtained for the QTcF interval. In conclusion, the categorical analyses essentially support the results obtained for central tendency.

##### **4.2.8.2.3 Additional Analyses**

#### **4.2.8.3 Safety Analysis**

No deaths or serious adverse events occurred during the course of the study. Two female subjects (#7: moderate dizziness and severe nausea, subject #24: moderate hypoaesthesia and severe gait disturbance) discontinued the study due to adverse events following administration of 100 mg tid flibanserin. Both completed two treatment periods (flibanserin 50 mg, moxifloxacin).

Subject no 48 experienced a syncopal episode while on treatment with flibanserin 100 mg but did not discontinue from the study. No ECG changes were reported.

Overall, no clinically relevant ECG abnormalities were observed in any of the subjects.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 2 and Table 3 and the mean concentration-time profiles are illustrated in Figure 1 and Figure 2.  $C_{max}$  and 24-hour AUC values of flibanserin in the thorough QT study were 2.4-fold and 3.5-fold higher, respectively following administration of 100 mg tid flibanserin compared with 50 mg bid flibanserin.  $C_{max}$  and 24 hour AUC values of flibanserin's metabolites in the thorough QT study ranged from 2.3- to 3.2-fold and 2.9- to 4.1-fold higher, respectively following administration of 100 mg tid flibanserin compared with 50 mg bid flibanserin.

**Table 2: Summary of Selected Pharmacokinetic Parameters [Geometric Mean (%CV)] for Flibanserin and Metabolites following 50-mg bid Dose**

Pharmacokinetic Parameter [unit]	Flibanserin N=55	BIMA 23 BS N=55	BIML 7 ZW N=55	TFMPP N=55
AUC <sub>τ,ss</sub> [ng h/mL]	1160 (46.5)	208 (43.4)	785 (31.7)	26.1 (69.3)
C <sub>max,ss</sub> [ng/mL]	233 (42.3)	28.0 (36.0)	201 (30.8)	3.67 (61.1)
T <sub>max,ss</sub> [h]*	1.55 (0.533 – 4.08)	1.58 (0.533 – 4.12)	1.55 (0.533 – 4.05)	2.07 (1.05 – 6.10)

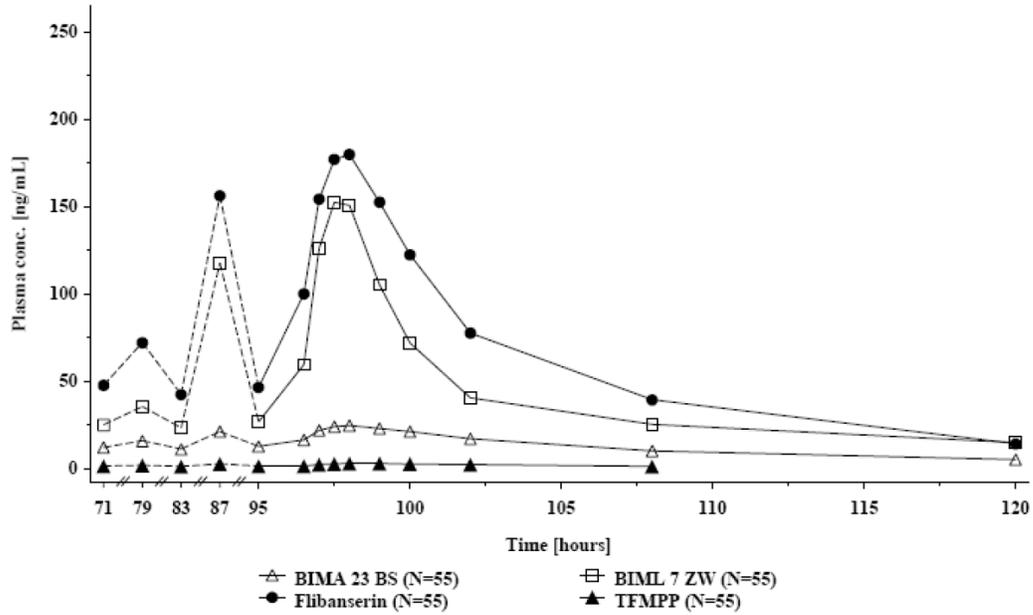
\* Median and range

**Table 3: Summary of Selected Pharmacokinetic Parameters [Geometric Mean (%CV)] for Flibanserin and Metabolites following 100-mg tid Dose**

Pharmacokinetic Parameter [unit]	Flibanserin N=53	BIMA 23 BS N=53	BIML 7 ZW N=53	TFMPP N=53
AUC <sub>τ,ss</sub> [ng h/mL]	2670 (49.1)	575 (48.9)	1890 (30.5)	50.8 (64.8)
C <sub>max,ss</sub> [ng/mL]	565 (41.6)	89.9 (45.3)	495 (37.2)	8.52 (59.9)
T <sub>max,ss</sub> [h]*	1.55 (0.550 – 6.10)	1.60 (0.550 – 6.07)	1.55 (0.550 – 4.12)	2.05 (1.03 – 6.10)

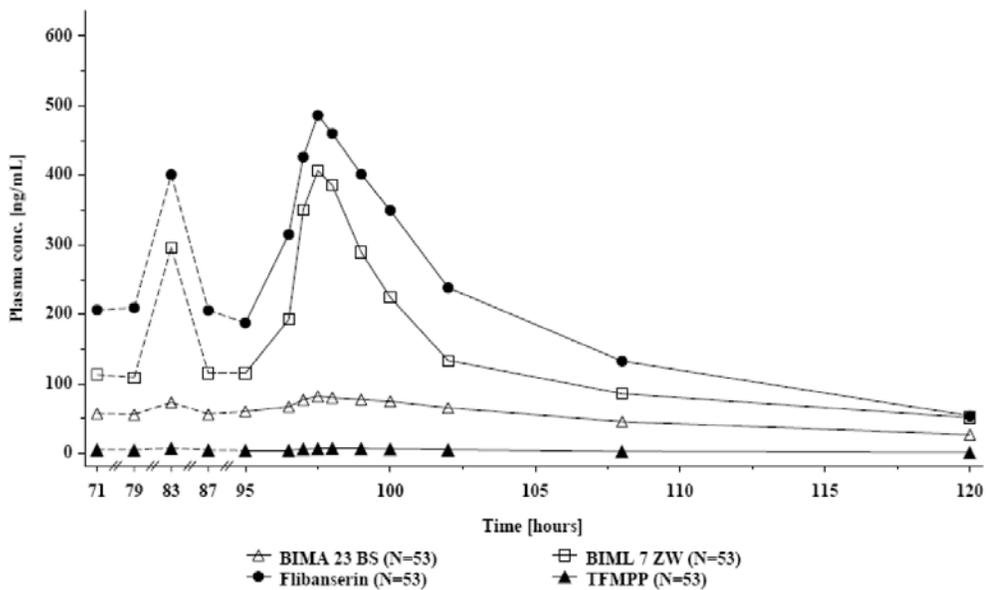
\* Median and range

**Figure 1: Geometric Mean Plasma Concentration-Time Profiles of Flibanserin and Metabolites following 50-mg bid Dose**



Source: Clinical Study Report P-67 Figure 11.5.2.1:1

**Figure 2: Geometric Mean Plasma Concentration-Time Profiles of Flibanserin and Metabolites following 100-mg tid Dose**



Source: Clinical Study Report P-67 Figure 11.5.2.1:2

**4.2.8.4.2 Exposure-Response Analysis**

Reviewer's Analysis: Plots of  $\Delta\Delta QTc$  vs. drug concentrations are presented in Figure 5 to Figure 8.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

We also evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in Table 4 and Table 5 below, it appears that QTcI is the best correction method.

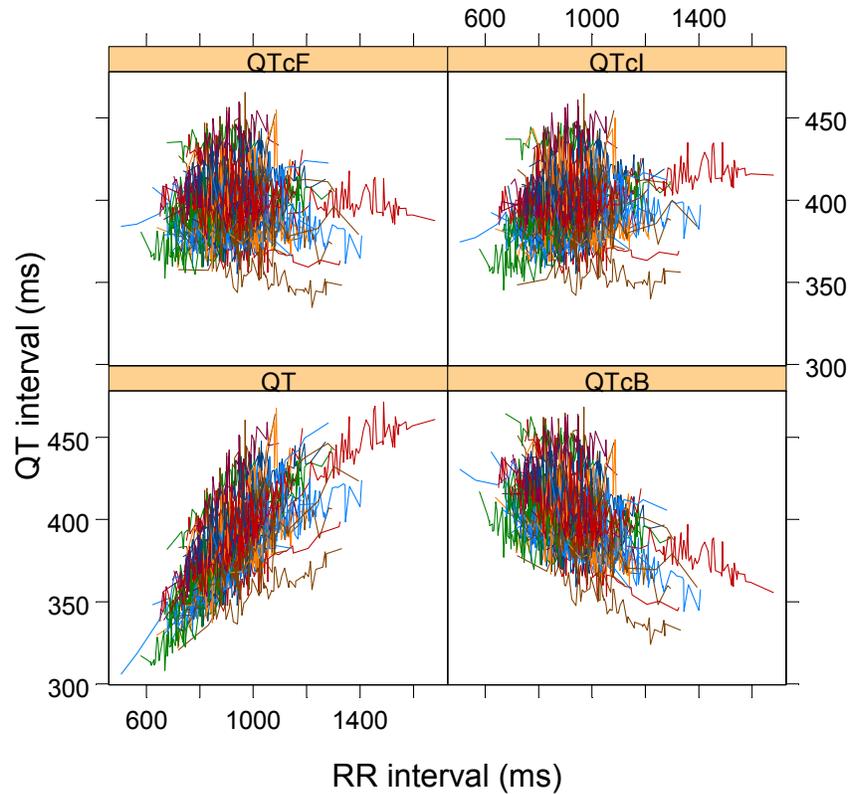
**Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods (Day 1 or 5; 0.5 <= Time <= 6)**

Method	Treatment									
	Moxifloxacin		Placebo		Flib 100 tid		Flib 50 bid		Z	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	56	0.0079	54	0.0073	54	0.0099	56	0.0087	56	0.0064
QTcF	56	0.0036	54	0.0019	54	0.0042	56	0.0032	56	0.0014
QTcI	56	0.0040	54	0.0015	54	0.0035	56	0.0031	56	0.0016

**Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods (Day 5; 0.5 <= Time <= 24)**

Method	Treatment							
	Flib 100 tid		Flib 50 bid		Placebo		Z	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	54	0.0083	56	0.0080	54	0.0077	56	0.0064
QTcF	54	0.0015	56	0.0016	54	0.0012	56	0.0008
QTcI	54	0.0011	56	0.0016	54	0.0009	56	0.0010

**Figure 3: QT, QTcB, QTcI, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer analyzed the Sponsor's SAS dataset qtpk.xpt using a linear mixed model. The primary endpoint was  $\Delta$ QTcI, the mean QTcI change from baseline to 0.5, 1, 1.5, 2, 3, 4, 6, 12 and 24 hours of Day 5, where QTcI is the individual subject corrected QT interval length. The flibanserin 50 mg bid and flibanserin 100 mg tid were compared with placebo. The primary analysis was performed on all time points using mixed-effect analysis of covariance model including treatment, sequence, and period of ECG as fixed effects and subject as a random effect. Baseline values were not included in the model as a covariate.

As seen from Table 6 and Table 7, the upper limit of the 90% confidence interval for the mean difference in QTcI change from baseline between flibanserin and placebo was below 10 ms at all time points for both 50-mg bid and 100-mg tid regimens, which demonstrates that this is a negative TQT study using the proposed dose.

For 400 moxifloxacin, the largest lower 90% confidence interval for the baseline adjusted mean difference of 400 mg moxifloxacin and placebo is 10.7 ms at hour 4 after dosing without multiple endpoint adjustment. If Bonferroni multiple endpoint correction method is applied (corrected for 7 time points), the largest lower bound of  $\Delta\Delta QTcI$  between moxifloxacin and placebo is 9.6 ms. Since Bonferroni correction is the most conservative approach by assuming the independence of the data, this reviewer believes that the assay sensitivity of the study has been established.

**Table 6: Analysis Results of  $\Delta QTcI$  and  $\Delta\Delta QTcI$  for Treatment Group = A:  
Flibanserin 20 mg**

Time(hr)	$\Delta QTcI$ : Flibanserin 50 mg bid			$\Delta QTcI$ : placebo			$\Delta\Delta QTcI$		
	N	Mean	SE	N	Mean	SE	Mean	SE	90% CI
0.5	56	-7.07	1.3	54	-5.66	1.31	-1.41	1.19	(-3.38, 0.57)
1.0	56	-4.43	1.05	54	-4.79	1.07	0.36	1.34	(-1.85, 2.58)
1.5	56	-3.25	1.10	54	-4.00	1.11	0.74	1.18	(-1.21, 2.71)
2.0	56	-2.91	1.08	54	-3.26	1.10	0.35	1.18	(-1.61, 2.31)
3.0	56	-1.75	1.06	54	-1.99	1.08	0.25	1.10	(-1.57, 2.07)
4.0	56	-3.02	1.03	54	-1.03	1.05	-1.99	1.11	(-3.83, -0.16)
6.0	56	-3.35	1.02	54	-2.18	1.03	-1.17	1.08	(-2.96, 0.62)
12.0	56	-3.56	0.96	54	-3.24	0.98	-0.32	0.95	(-1.89, 1.26)
24.0	56	-2.54	1.08	54	-2.80	1.09	0.27	1.11	(-1.59, 2.12)

**Table 7: Analysis Results of  $\Delta QTcI$  and  $\Delta\Delta QTcI$  for Treatment Group = B:  
Flibanserin 100 mg tid**

Time(hr)	$\Delta QTcI$ : Flibanserin 100 mg tid			$\Delta QTcI$ : placebo			$\Delta\Delta QTcI$		
	N	Mean	SE	N	Mean	SE	Mean	SE	90% CI
0.5	54	-5.77	1.31	54	-5.66	1.31	-0.11	1.19	(-2.09, 1.87)
1.0	54	-5.22	1.07	54	-4.79	1.07	-0.43	1.34	(-2.66, 1.80)
1.5	54	-1.96	1.11	54	-4.00	1.11	2.04	1.90	(+0.06, 4.0)
2.0	54	-1.59	1.10	54	-3.26	1.10	1.67	1.19	(-0.30, 3.64)
3.0	54	-1.91	1.08	54	-1.99	1.08	0.09	1.10	(-1.74, 1.92)
4.0	54	-3.76	1.05	54	-1.03	1.05	-2.73	1.11	(-4.57, -0.88)
6.0	54	-3.57	1.03	54	-2.18	1.03	-1.39	1.08	(-3.18, 0.41)
12.0	54	-4.09	0.98	54	-3.24	0.98	-0.85	0.95	(-2.43, 0.73)
24.0	54	-2.77	1.09	54	-2.80	1.09	0.04	1.12	(-1.83, 1.90)

The largest upper bounds of the 2-sided 90% CI for the mean difference between flibanserin 50 mg bid and placebo, and between flibanserin 100 mg tid and placebo were 2.7 and 4.0, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. This analysis of QTcI included moxifloxacin data from Day 1 and placebo data from Day 5. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 10.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.6 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

**Table 8: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Moxifloxacin**

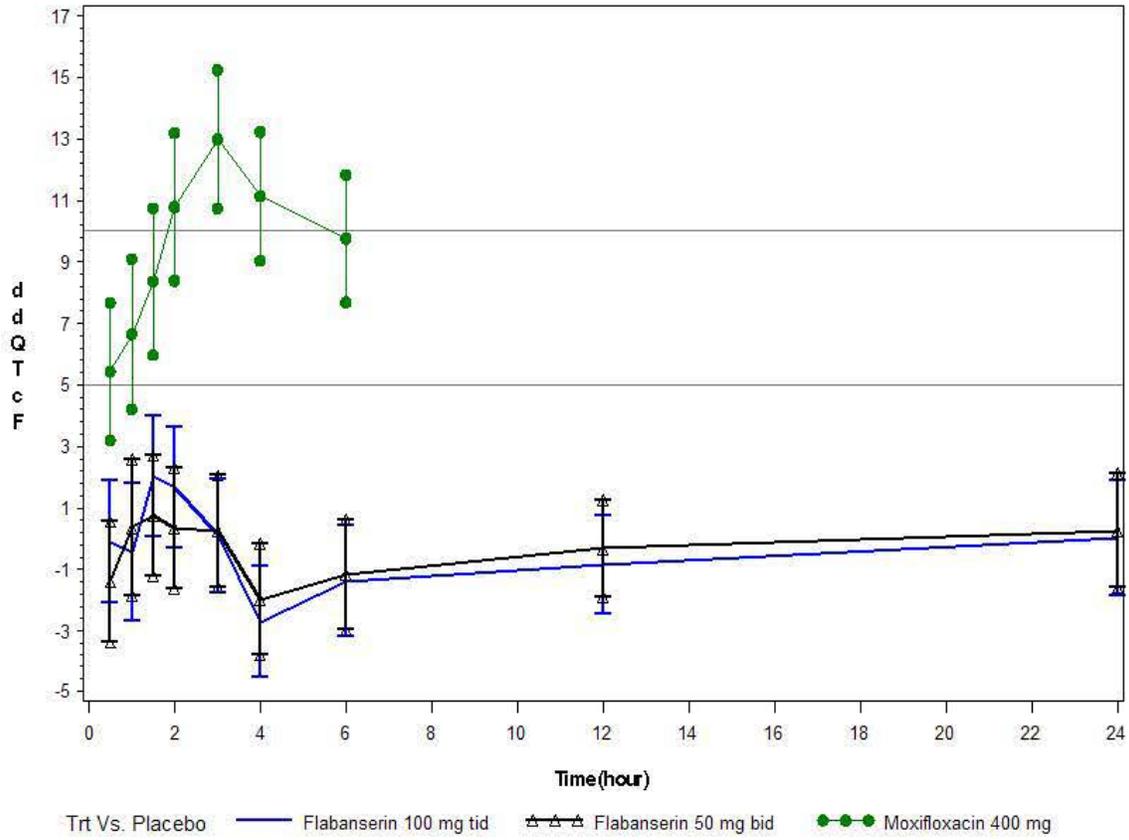
Time/ (hr)	$\Delta$ QTcI: moxifloxacin			$\Delta$ QTcI: placebo			$\Delta\Delta$ QTcI			
	N	Mean	SE	N	Mean	SE	Mean	SE	Unadjusted 90% CI	Adjusted* 90% CI
0.5	56	-0.14	1.36	54	-5.58	1.37	5.44	1.35	( 3.20, 7.68 )	(2.01, 8.80)
1	56	1.96	1.11	54	-4.70	1.13	6.66	1.47	( 4.22, 9.10)	(3.01, 10.31)
1.5	56	4.44	1.19	54	-3.93	1.21	8.37	1.44	(5.99, 10.75)	(4.81, 11.94)
2	56	7.49	1.15	54	-3.31	1.17	10.80	1.45	(8.40, 13.20)	(7.20, 14.40)
3	56	10.98	1.11	54	-2.02	1.13	13.00	1.36	(10.75, 15.25)	(9.63, 16.37)
4	56	10.08	1.02	54	-1.07	1.04	11.15	1.27	(9.05, 13.24)	(8.00, 14.28)
6	56	7.6	1.05	54	-2.17	1.06	9.77	1.25	(7.70, 11.84)	(6.67, 12.87)

\* Bonferroni method was applied for multiple endpoint adjustment for 7 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups. (Note: CIs are all unadjusted including moxifloxacin)

Figure 4: Mean and 90% CI  $\Delta\Delta Q_{TcI}$  Time-course



### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

**Table 9: Categorical Analysis for QTcI**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Baseline	56	1099	56	99.8%	2	3.6%
Placebo	14	260	14	100%	0	0%
Moxifloxacin	14	280	14	99.6%	1	7%
Flibanserin 50 mg bid	14	279	14	99.6%	1	7%
Flibanserin 100 mg tid	14	280	14	100%	0	0%

Table 10 lists the categorical analysis results for  $\Delta$ QTcI. No subject's change from baseline was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	14	568	14	567	1	1
Moxifloxacin	14	420	14	414	3	6
Fl banserin 50 mg bid	14	588	14	588	0	0
Fl banserin 100 mg tid	14	568	14	568	0	0

### 5.2.2 PR Analysis

The same statistical mixed model analysis was performed based the change from baseline in PR interval over to 0.5 to 24 hours. The point estimates and the 90% confidence intervals are presented in Table 11 and Table 12. The largest upper limits of 90% CI for the PR mean differences between flibanserin 50 mg bid and placebo and flibanserin 100 mg tid and placebo are 3.96 ms and 3.79 ms, respectively.

The outlier analysis results for PR are presented in Table 13. There are 2 (14%) and 3 (21%) subjects who experienced QRS interval greater than 200 ms in both flibanserin 50 mg bid and flibanserin 100 mg tid, respectively.

**Table 11: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = D:  
Flibanserin 50 mg bid**

Time(hr)	$\Delta$ PR: Flibanserin 50 mg bid			$\Delta$ PR: placebo			$\Delta\Delta$ PR		
	N	Mean	SE	N	Mean	SE	Mean	SE	90% CI
0.5	56	-0.94	1.13	54	-0.20	1.15	-0.74	1.46	(-3.16, 1.69)
1	56	-0.97	1.14	54	0.07	1.16	-1.04	1.30	(-3.19, 1.11)
1.5	56	-1.04	1.14	54	1.82	1.16	-2.86	1.34	(-3.43, 1.04)
2	56	-0.72	1.12	54	2.13	1.14	-2.85	1.41	(-5.19, -0.51)
3	56	0.99	1.18	54	2.28	1.20	-1.30	1.50	(-3.78, 1.19)
4	56	1.94	0.99	54	1.89	1.01	0.05	1.27	(-2.06, 2.16)
6	56	0.81	1.03	54	-1.09	1.05	1.90	1.24	(-0.15, 3.96)
12	56	0.16	1.04	54	-0.81	1.06	0.97	1.29	(-1.17, 3.10)
24	56	-0.56	1.15	54	-0.73	1.17	0.17	1.22	(-1.85, 2.20)

**Table 12: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = C:  
Flibanserin 100 mg tid**

Time(hr)	$\Delta$ PR: Flibanserin 100 mg tid			$\Delta$ PR: placebo			$\Delta\Delta$ PR		
	N	Mean	SE	N	Mean	SE	Mean	SE	90% CI
0.5	54	1.12	1.15	54	-0.20	1.15	-1.32	1.47	(-1.11, 3.77)
1	54	-0.16	1.16	54	0.07	1.16	-0.23	1.30	(-2.40, 1.93)
1.5	54	0.63	1.16	54	1.82	1.16	-1.19	1.35	(-5.08, -0.64)
2	54	-0.17	1.14	54	2.13	1.14	-2.30	1.42	(-4.66, 0.06)
3	54	0.00	1.20	54	2.28	1.20	-2.28	1.51	(-4.78, 0.22)
4	54	1.22	1.01	54	1.89	1.01	-0.67	1.28	(-2.80, 1.45)
6	54	0.63	1.05	54	-1.09	1.05	1.72	1.25	(-0.35, 3.79)
12	54	0.63	1.06	54	-0.81	1.06	1.44	1.30	(-0.72, 3.59)
24	54	0.51	1.17	54	-0.73	1.17	1.25	1.23	(-0.79, 3.28)

**Table 13: Categorical Analysis for PR**

Treatment Group	Total N		PR $\geq$ 200 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Baseline	56	1099	9 (16%)	77 (7%)
Flibanserin 50 mg bid	14	279	2 (14%)	10 (3.6%)
Flibanserin 100 mg tid	14	280	3 (21%)	26 (9.3%)

### 5.2.3 QRS Analysis

The same statistical mixed model analysis was performed based on the change from baseline in QRS interval over to 0.5 to 24 hours. The point estimates and the 90% confidence intervals are presented in Table 14 and Table 15. The largest upper limits of 90% CI for the QRS mean differences between flibanserin 50 mg bid and placebo and flibanserin 100 mg tid and placebo are 0.41 ms and 0.57 ms, respectively. There are 1 (7.1%) and 0 (0%) subjects who experienced QRS interval greater than 110 ms in both flibanserin 50 mg bid and flibanserin 100 mg tid, respectively.

**Table 14: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = A:  
Flibanserin 50 mg bid**

Time(hr)	$\Delta$ QR: Flibanserin 50 mg bid			$\Delta$ QRS: placebo			$\Delta\Delta$ QRS		
	N	Mean	SE	N	Mean	SE	Mean	SE	90% CI
0.5	56	-0.61	0.25	54	-0.30	0.26	-0.31	0.32	(-0.84, 0.22)
1	56	-0.24	0.27	54	-0.10	0.27	-0.14	0.32	(-0.68, 0.40)
1.5	56	-0.34	0.29	54	-0.03	0.29	-0.31	0.35	(-0.88, 0.26)
2	56	-0.59	0.27	54	-0.29	0.28	-0.30	0.31	(-0.80, 0.21)
3	56	-0.72	0.27	54	-0.64	0.27	-0.08	0.30	(-0.57, 0.41)
4	56	-0.75	0.27	54	-0.39	0.28	-0.35	0.31	(-0.87, 0.17)
6	56	-0.77	0.25	54	-0.45	0.26	-0.32	0.29	(-0.80, 0.17)
12	56	-0.77	0.27	54	-0.39	0.28	-0.38	0.29	(-0.85, 0.10)
24	56	-0.30	0.26	54	-0.15	0.26	-0.15	0.27	(-0.61, 0.30)

**Table 15: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = B:  
Flibanserin 100 mg tid**

Time(hr)	$\Delta$ QR: Flibanserin 100 mg tid			$\Delta$ QR: placebo			$\Delta\Delta$ QR		
	N	Mean	SE	N	Mean	SE	Mean	SE	90% CI
0.5	54	-0.41	0.26	54	-0.30	0.26	-0.11	0.32	(-0.65, 0.42)
1	54	-0.07	0.27	54	-0.10	0.27	-0.02	0.33	(-0.52, 0.57)
1.5	54	-0.56	0.29	54	-0.03	0.29	-0.53	0.35	(-1.11, 0.04)
2	54	-0.75	0.28	54	-0.29	0.28	-0.46	0.31	(-0.97, 0.05)
3	54	-0.70	0.27	54	-0.64	0.27	-0.06	0.30	(-0.55, 0.43)
4	54	-1.13	0.28	54	-0.39	0.28	-0.74	0.32	(-1.26, -0.21)
6	54	-0.93	0.26	54	-0.45	0.26	-0.48	0.29	(-0.97, 0.00)
12	54	-0.64	0.28	54	-0.39	0.28	-0.25	0.29	(-0.73, 0.24)
24	54	-0.24	0.26	54	-0.15	0.26	-0.09	0.28	(-0.55, 0.36)

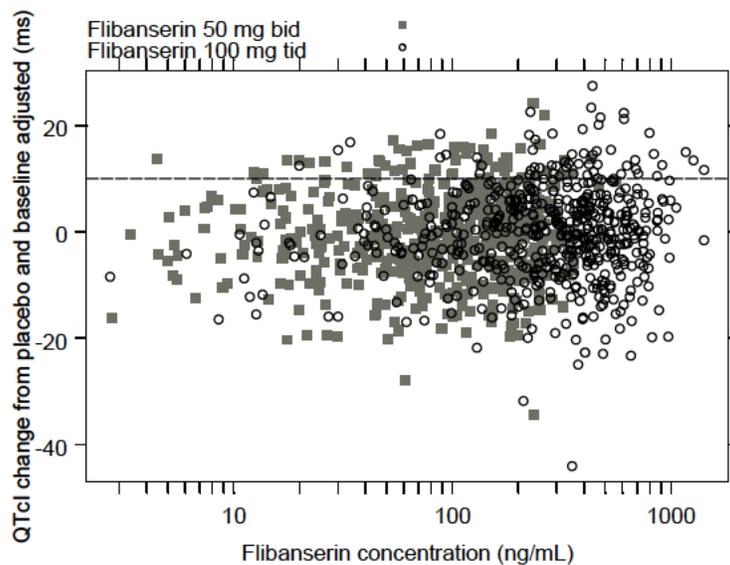
**Table 16: Categorical Analysis for QRS**

Treatment Group	Total N		QRS $\geq$ 110 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)
Baseline	56	1099	2 (3.6%)	18 (1.6%)
Fl banserin 50 mg bid	14	280	1 (7.1%)	7 (7.1%)
Fl banserin 100 mg tid	14	279	0 (0%)	0 (0%)

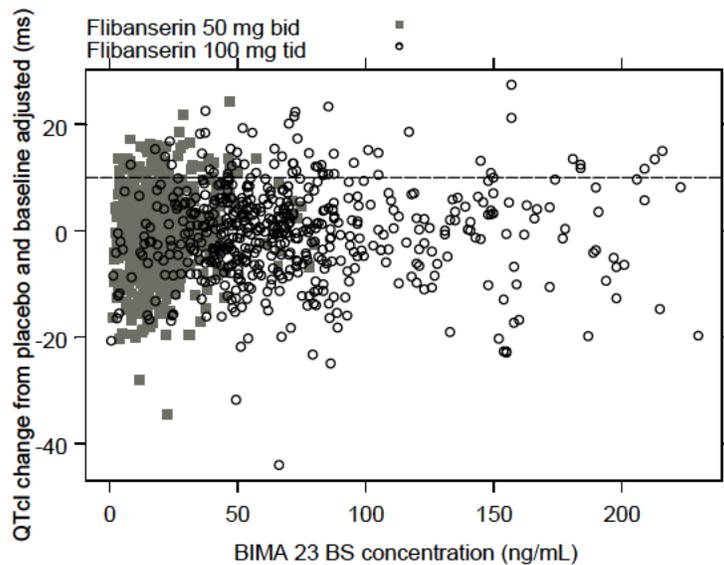
### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationships between  $\Delta\Delta\text{QTcI}$  and flibanserin (with the major metabolites) concentrations are visualized in Figure 5 to Figure 8 with no evident exposure-response relationship.

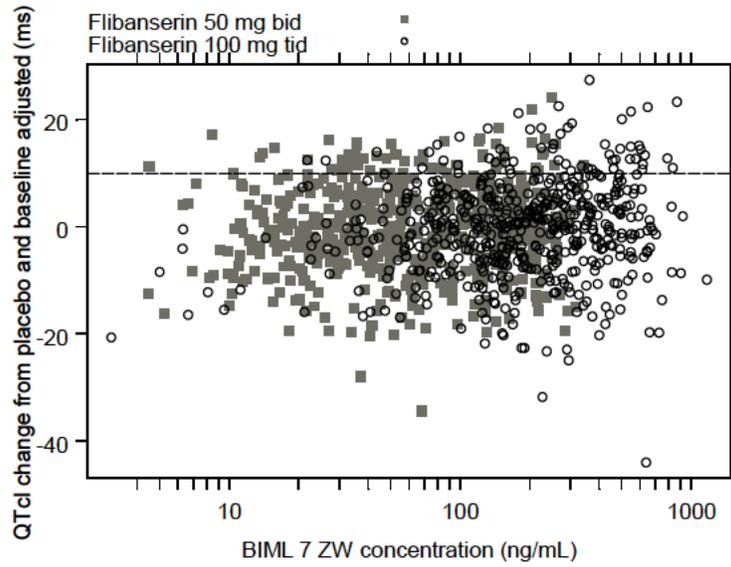
**Figure 5:  $\Delta\Delta$  QTcI vs. Flibanserin Concentration**



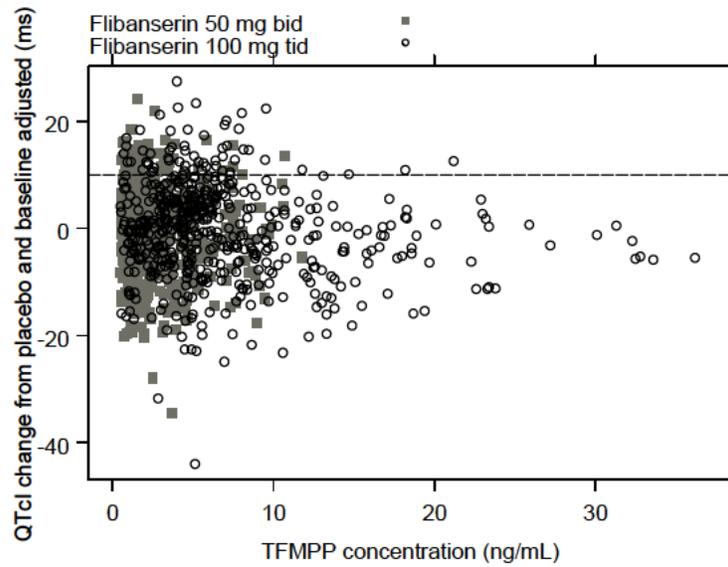
**Figure 6:  $\Delta\Delta$  QTcI vs. BIMA 23 BS Concentration**



**Figure 7:  $\Delta\Delta$  QTcI vs. BIML 7 ZW Concentration**



**Figure 8:  $\Delta\Delta$  QTcI vs. TFMPP Concentration**



## **5.4 CLINICAL ASSESSMENTS**

### **5.4.1 Safety assessments**

Three of the events identified to be of clinical importance per the ICH E 14 guidelines, i.e., seizure, significant ventricular arrhythmias or sudden cardiac death, did not occur in this study.

As mentioned earlier one subject in the high-dose flibanserin group experienced syncope but did not discontinue treatment. ECGs for this subject (#48) on the Day of the event, that were available in the warehouse were reviewed and found to be within normal limits.

### **5.4.2 ECG assessments**

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 99% of the ECGs were annotated in the primary lead II, with less than 0.4% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

As indicated in the statistical assessments, there were no clinically relevant effects on the PR and QRS intervals.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	100 mg q.d.	
Maximum tolerated dose	100 mg single dose, 100 mg t.i.d. (20 mg and 20 mg b.i.d. are the no adverse event level dose & regimen)	
Principal adverse events	At 150 mg single dose, several AEs per subject; the most common were somnolence, fatigue, pallor, slurred speech, nausea; dose-limiting were orthostasis and mild tachycardia.	
Maximum dose tested	Single Dose	150 mg
	Multiple Dose	100 mg tid
Exposures Achieved at Maximum Tested Dose	Single Dose	gMean (range) of study 511.1: $C_{max}$ : 510 (321-710) ng/mL $AUC_{0-\infty}$ : 2412 (1184-3880) ng·h/mL
	Multiple Dose	gMean (%gCV) of study 511.90: $C_{max,ss}$ : 565 ng/mL (41.6) $AUC_{\tau,ss}$ : 2670 ng·h/mL (49.1)
Range of linear PK	0.1 to 150 mg (single dose), study 511.1 20 tid to 100 tid (steady state), study 511.2	
Accumulation at steady state	gMean (%gCV) for 100 mg qd, study 511.105 $RA_{AUC}$ : 1.44 (63.5) $RA_{C_{max}}$ : 1.36 (58.0)	
Metabolites	Sorted by exposure relative to flibanserin, given with $C_{max,ss}$ for 100 mg q.d. and lowest $K_i$ value from receptor screening, where applicable: CD 11760 SE (M25) –no receptor binding <10000 nM BIML 7 ZW (M38) – $C_{max,ss}$ : 1.32 $\mu$ M – $K_i$ 207 nM, 5-HT <sub>2A</sub> BI 400301 SE (M31b) –no receptor binding <10000 nM BI 401703 ZW (M2) –no receptor binding <10000 nM BI 400296 ZW (M8) –no receptor binding <10000 nM BIMA 23 BS (M35) – $C_{max,ss}$ : 105 nM – $K_i$ 42.1 nM, H <sub>1</sub> TFMPP (M30a) – $C_{max,ss}$ : 27.8 nM – $K_i$ 32 nM, 5-HT <sub>1B</sub> BI 404016 ZW (M26)– no receptor binding <10000 nM	

Metabolites (continued)	At least 27 further metabolites were detected. Of those metabolites that were structurally identified, the metabolites were only present in urine or in negligible concentrations in plasma (study 511.15)	
Absorption	Absolute/Relative Bioavailability	<p>Oral solution vs. i.v. infusion, gMean (%gCV) of study 511.15: 33.2% (18.8)</p> <p>Capsule vs. oral solution gMean ratio (90% CI) of AUC from study 511.17: 0.83 (0.73-0.96)</p> <p>Tablet vs. capsule gMean ratio (90% CI) of AUC from study 511.33: 1.065 (0.985-1.152)</p>
	T <sub>max</sub>	<p>Median (range) ( study, 511.105, 100 mg q.d., steady-state)</p> <ul style="list-style-type: none"> <li>• Flibanserin: 1.00 (0.500–3.00) h</li> <li>• BIML 7 ZW: 1.00 (0.750–3.00) h</li> <li>• BI 401703 ZW: 3.00 (3.00–4.00) h</li> <li>• BI 400296 ZW: 3.00 (2.00–3.00) h</li> <li>• BIMA 23 BS: 0.750 (0.500–3.00) h</li> <li>• TFMPP: 2.00 (0.750–6.00) h</li> <li>• BI 404016 ZW: 0.750 (0.500–1.50) h</li> </ul> <p>Median (range) ( Metaanalysis PK2, 100 mg single dose)</p> <ul style="list-style-type: none"> <li>• CD 11760 SE: 1.02 (0.75–1.50) h</li> </ul> <p>Exploration of pooled plasma at two time points (study 511.15 )</p> <ul style="list-style-type: none"> <li>• BI 400301 SE: 1h</li> </ul>
Distribution	V <sub>ss</sub>	gMean (%gCV) (Metaanalysis PK1): 183 L (37.9)
	% bound	98%

Elimination	Route	<ul style="list-style-type: none"> <li>• Flibanserin itself is almost completely metabolized</li> <li>• 44.1% of radioactivity dose via urine</li> <li>• 50.9 % of radioactivity dose via feces</li> </ul>
	Terminal t <sub>1/2</sub>	<p>gMean (%gCV) ( study, 511.105, 100 mg q.d., steady-state)</p> <ul style="list-style-type: none"> <li>• Flibanserin: 11.4 h (24.3)</li> <li>• BIML 7 ZW: 12.6 h (35.6)</li> <li>• BI 401703 ZW: 11.9 h (32.0)</li> <li>• BI 400296 ZW: 12.1 h (29.2)</li> <li>• BIMA 23 BS: 13.3 h (40.2)</li> <li>• TFMPP: 9.49 h (47.3)</li> <li>• BI 404016 ZW: 15.5 h (83.3)</li> </ul> <p>Median (range) (Metaanalysis PK2, 100 mg single dose)</p> <ul style="list-style-type: none"> <li>• CD 11760 SE: 14.3 h (38.7)</li> </ul>
	CL	gMean (%gCV) (Metaanalysis): 425 mL/min (26.6)
Intrinsic Factors	Age	Not applicable
	Sex	Not applicable
	Race	Metaanalysis PK1: 57% higher C <sub>max,ss</sub> in Asians compared to Whites
	Hepatic & Renal Impairment	<p>Flibanserin GMR in % (90% CI), studies 511.67, 511.96</p> <p><u>Mild-to-moderate and severe renal impairment:</u></p> <p>C<sub>max</sub>: 92.7 (69.1-124) and 131 (91.4-188)</p> <p>AUC<sub>0-∞</sub>: 109 (74.5-159) and 120 (94.4-153)</p>

Extrinsic Factors	Drug interactions	<u>Effect of itraconazole 200mg q.d.:</u> flibanserin C <sub>max</sub> : 1.69-fold increased flibanserin AUC: 2.57-fold increased  <u>Effect of paroxetine:</u> No change in flibanserin C <sub>max</sub> & AUC  <u>Effect of rifampicin:</u> flibanserin AUC: 95% decreased flibanserin C <sub>max</sub> : 90% decreased  <u>Effect of ketoconazole 400 mg q.d.:</u> flibanserin AUC: 4.5-fold increased flibanserin C <sub>max</sub> : 1.8-fold increased
	Food Effect	Study 511.26: Light breakfast: AUC: 18% increased, C <sub>max</sub> no change Medium breakfast: AUC 43% increased, C <sub>max</sub> 12% increased High fat & caloric breakfast: AUC 56% increased, C <sub>max</sub> 15% increased  Study 511.33: High fat & caloric breakfast: AUC 37% increased, C <sub>max</sub> 34% decreased
Expected High Clinical Exposure Scenario	The use of flibanserin is not recommended in patients with impaired liver function and in patients receiving potent inhibitors of CYP3A4.  There was only one other factor causing a significant increase in C <sub>max</sub> : Asians would have a 57% higher C <sub>max</sub> .  For AUC, a maximal increase in 56 % is anticipated when flibanserin is taken directly after a high fat, high caloric meal	

## 6.2 TABLE OF STUDY ASSESSMENTS

Table 6.2.2: 1 Triplicate ECG measurements during treatment periods

Visit	Day	Relative time [h]									
		-1:00	0:30	1:00	1:30	2:00	3:00	4:00	6:00	12:00	24:00
2/5	-1	x	x	x	x	x	x	x	x	x	x
2/3/4/5 <sup>a</sup>	1	x									
	5	x	x	x	x	x	x	x	x	x	x
	6										
2/3/4/5 <sup>b</sup>	1	x	x	x	x	x	x	x	x		

<sup>a</sup> When fibanserin or placebo is administered

<sup>b</sup> When moxifloxacin is administered

### Study Flow chart

Trial phase	Scr.	Treatment periods 1 and 4 with preceding baseline day with a washout of at least 14 days						Treatment periods 2 and 3 with a washout of at least 14 days						E.o.s.	
Visit	1	2 and 5						3 and 4						6	
Day		-1	1	2	3	4	5	6	1	2	3	4	5	6	
Informed Consent	x														
Physical examination	x														x
Demographics	x														
Medical history	x														
Drug/virus screening	x														
In-exclusion criteria	x														
Laboratory tests	x	x <sup>1</sup>	(x <sup>1</sup> )				x <sup>1</sup>		(x <sup>1</sup> )				x <sup>1</sup>		x
Urine pregnancy test	x	x <sup>2</sup>	(x <sup>2</sup> )				x <sup>2</sup>		(x <sup>2</sup> )				x <sup>2</sup>		x
12-lead-ECG	x	x <sup>3</sup>	(x <sup>3</sup> )				x <sup>3</sup>		(x <sup>3</sup> )				x <sup>3</sup>		x
HR, BP	x	x <sup>4</sup>	(x <sup>4</sup> )				x <sup>4</sup>		(x <sup>4</sup> )				x <sup>4</sup>		x
Randomisation <sup>5</sup>		x													
Drug administration <sup>6</sup>			x	x	x	x	x		x	x	x	x	x		
Pharmacokinetics <sup>6</sup>			x			x	x		x			x	x		
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tolerability							x							x	

<sup>1</sup> Safety laboratory tests: complete laboratory analysis on day -1 of visit 2, electrolytes only on ECG profile days

<sup>2</sup> ECG profile pre-dose (-1:00 h), as well as 0:30 h, 1:00 h, 1:30 h, 2:00 h, 3:00 h, 4:00 h, 6:00 h, 12:00 h and 24 h post-dose (fibanserin and placebo).

<sup>3</sup> ECG baseline on day -1 until 12:00 h "post-dose", for moxifloxacin (in brackets) on day 1 until 6:00 h post-dose

<sup>4</sup> On day 5 for fibanserin and placebo, on day 1 for moxifloxacin: pre-dose (-1:00 h), as well as 2:00 h and 6:00 h post-dose

<sup>5</sup> Only at visit 2

<sup>6</sup> Single moxifloxacin dose on day 1, only morning dose on day 5 for fibanserin and placebo

<sup>6</sup> PK sampling for fibanserin/placebo treatments only: pre-dose on day 1 (morning dose) and day 4. PK time-points on day 5 equal to time-points of ECG profile

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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/s/

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JOANNE ZHANG  
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HAO ZHU  
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**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: February 25, 2010

To: Scott Monroe, MD  
Director, Division of Reproductive and Urologic Products

Through: Todd Bridges, RPh, Team Leader  
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Subject: Label and Labeling Review

Drug Name(s): Giosa (Flibanserin) Tablets  
100 mg

Application Type/Number: NDA 022526

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2009-2280

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## 1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urologic Products for assessment of labels and labeling for Girosa (Flibanserin) Tablets for their vulnerability to medication errors.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis<sup>1</sup> (FMEA) to evaluate the labels and labeling that were submitted on October 27, 2009 (Appendix A through D; no image of insert labeling).

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the labels and labeling can be clarified and improved on to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 (*Comments to the Division*) for discussion during the review team's label and labeling meetings. Section 3.2 (*Comments to the Applicant*) contains our recommendations for the container label, [REDACTED] (b) (4). We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Maria Wasilik, OSE Project Manager, at 301-796-0567.

### 3.1 COMMENTS TO THE DIVISION

#### A. *General Comment*

DMEPA recommends the Division contact the Division of Drug Marketing, Advertising, and Communications (DDMAC), to determine [REDACTED] (b) (4).

#### B. *Insert Labeling*

Include the route of administration (orally) in the Highlights of Prescribing, Dosage and Administration section.

### 3.2 COMMENTS TO THE APPLICANT

#### A. *Container Label (100 mg)*

1. The established name does not have a prominence commensurate to that of the proprietary name. Revise the established name per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

2. The dosage form should be presented in the same size and font as the active ingredient, flibanserin. Flibanserin tablets is the established name of this product.
3. Relocate the statement (b) (4) to the side panel in order to allow room to revise and increase the prominence of established name. Additionally, revise to read: “Usual Dosage: See package insert for dosage information”.



**C. Professional Sample Carton Labeling (100 mg)** (b) (4)

1. Although the established name appears to be at least half as large as the proprietary name, it does not have a prominence commensurate to that of the proprietary name because of the font type used. Revise the established name per 21 CFR 201.10(g)(2) which states: The established name ... shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. Ensure the presentation of the strength indicates 100 mg per tablet on the carton labeling to clarify that the strength represents per tablet and not the total strength of the entire carton.

This will minimize the potential for patients inadvertently taking the entire contents of the package as one dose. This could be accomplished through either of the following statements: “100 mg per tablet”, “100 mg/tablet” and/or inclusion of a prominent statement stating “Each tablet contains 100 mg”.

3. Relocate the product strength so that it appears immediately below the established name and dosage form. Thus, the presentation of the proprietary name, established name, dosage form and product strength will appear as follows:

Girosa  
(Flibanserin) tablets  
100 mg/tablet

4. The proprietary name and established name appear on the side panel without the product strength. Revise to include the product strength wherever this information appears on the carton.
5. Relocate the graphic that appears in front of the proprietary name away from the proprietary name. (b) (4)  

6. Revise the (b) (4) statement to read: “Professional Sample: Not for Sale”.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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/s/

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