

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022526Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22526

SUPPL #

HFD # 580

Trade Name Addyi

Generic Name flibanserin

Applicant Name Sprout Pharmaceuticals

Approval Date, If Known August 18, 2015

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

511.71, 511.75, and 511.147

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

Investigation #3 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

Investigation #3 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

511.71, 511.75, and 511.147

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # (b) (4) YES  ! NO   
! Explain:

Investigation #2 !  
IND # (b) (4) YES  ! NO   
! Explain:

Investigation #3 !  
!

IND # (b) (4)

YES

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

!

!

YES

! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Jennifer Mercier

Title: Chief, Project Management Staff

Date: August 18, 2015

Name of Office/Division Director signing form: Hylton V. Joffe, M.D., M.M.Sc.  
Title: Director, Division of Bone, Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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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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JENNIFER L MERCIER  
08/18/2015

HYLTON V JOFFE  
08/19/2015

**1.3.3 DEBARMENT CERTIFICATION**

Certification Requirement Food, Drug and Cosmetic Act, Section 306(k)(1)

Sprout Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature:



Name of Applicant: Robert S. Whitehead  
Chief Executive Officer  
Sprout Pharmaceuticals, Inc.

Date:

1-30-2015

Mailing Address: Sprout Pharmaceuticals, Inc.  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 022526 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Addyi Established/Proper Name: flibanserin Dosage Form: 100 mg Tablet		Applicant: Sprout Pharmaceuticals Agent for Applicant (if applicable):
RPM: Jennifer Mercier		Division: DBRUP
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>August 18, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None CR 8-27-10 <input type="checkbox"/> CR 9-23-13
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) CR – 8-27-10 CR - 9-27-13
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
• Most recent draft labeling ( <i>if it is division-proposed labeling, it should be in track-changes format</i> )	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling ( <i>if it is division-proposed labeling, it should be in track-changes format</i> )	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) ( <i>indicate date(s)</i> )	2-12-10 (2)
• Review(s) ( <i>indicate date(s)</i> )	7-9-13 4-30-15
❖ Labeling reviews ( <i>indicate dates of reviews</i> ) <i>DMEPA: 8-14-13, 6-10-15</i> <i>DRISK: 2-25-10, 6-30-10, 9-16-13, 7-29-15, 8-17-15</i> <i>OPDP: 8-26-10, 10-4-13, 8-5-15</i> <i>SEALD: 8-19-13, 11-7-13, 4-21-15</i>	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None <b>See previous box</b> DMPP/PLT (DRISK): <input type="checkbox"/> None <b>see previous box</b> OPDP: <input type="checkbox"/> None <b>see previous box</b> SEALD: <input type="checkbox"/> None <b>see previous box</b> CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>8-22-13, 10-25-13, 6-4-14, 8-4-15</u> (<i>corrected to reflect the correct indication</i>) If PeRC review not necessary, explain:</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	X
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 1-15-15
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	June 18, 2010 June 4, 2015
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8-27-10 9-27-13, 8-18-15
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8-18-15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8-27-10 9-26-13, 8-18-15
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 8-18-15
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review 8-18-15 (CDTL review)
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	1-6-10, 8-27-10, 8-29-13, 5-16-14, 7-20-15
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See medical Officer Review dated 7-20-15, page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None QT: 5-3-10 DPP: 5-12-10, 1-23-15 Oph: 5-20-10

	Neuro: 7-31-13, 5-15-14 (2), 7-1-15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> N/A 7-28-10, 8-21-13, 8-23-13, 9-26-13, 6-24-15
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	9-3-13, 7-17-15, 7-20-15, 7-24-15, 7-24-15, 8-18-15 (5)  <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested <input checked="" type="checkbox"/> Included
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8-26-10, 8-30-13, 6-29-15
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 7-17-15
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12-15-09, 8-26-10(2), 5-2-13, 8-29-13, 5-28-14, 7-17-15, 8-14-15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 8-26-10
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 8-10-15
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7-7-10, 9-6-13, 7-16-15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T supervisory review, page 9
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review 7-28-10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 12-23-09, 7-1-10, 8-30-13, 9-10-13, 7-16-15
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None Biopharm: 6-2-10, 6-23-10, 8-7-13, 5-26-15
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		2-22-10
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>		Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/  
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JENNIFER L MERCIER  
08/19/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Friday, August 14, 2015 5:38 PM  
**To:** Amy Moore (AMoore@sproutpharma.com)  
**Cc:** josephine torrente (jtorrente@sproutpharma.com)  
**Subject:** Section 5.1 revisions  
**Attachments:** Revsied 5.1.doc

Amy,

Please see the attached revised section 5.1 for the label. We need your concurrence on this label and we also need for you to re-review the objective blood pressure data as well as search for interventions for every patient in the low-dose and high-dose alcohol groups and confirm that there is no-one else that was missed. We need this information by Monday morning.

Thanks,

Jen

The use of ADDYI and alcohol increases the risk of severe hypotension and syncope. In a dedicated alcohol interaction study conducted in 25 subjects (23 men and 2 premenopausal women), hypotension or syncope requiring therapeutic intervention (ammonia salts and/or placement in supine or Trendelenberg position) occurred in 4 (17%) of the 23 subjects co-administered ADDYI 100 mg and 0.4 g/kg alcohol (equivalent of two 12 ounce cans of beer containing 5% alcohol content, two 5 ounce glasses of wine containing 12% alcohol content, or two 1.5 ounce shots of 80-proof spirit in a 70 kg person, consumed over 10 minutes in the morning) (b) (4)

-[see *Clinical Pharmacology (12.2)*]. In these four subjects, all of whom were men, the magnitude of the systolic blood pressure reductions ranged from about 28 to 54 mmHg and the magnitude of the diastolic blood pressure reductions ranged from about 24 to 46 mmHg. 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. One of these subjects required therapeutic intervention (ammonia salts and placement supine with the foot of the bed elevated). There were no events requiring therapeutic intervention when ADDYI or alcohol were administered alone.

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/s/  
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JENNIFER L MERCIER  
08/14/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Friday, August 14, 2015 5:29 PM  
**To:** Amy Moore (AMoore@sproutpharma.com)  
**Cc:** josephine torrente (jtorrente@sproutpharma.com)  
**Subject:** Additional Information on the Alcohol

Amy,

Please see the additional clarification on the alcohol studies

- (1) Alcohol Challenge Study 1 be conducted prior to Alcohol Challenge Study 2 and Generalizable Study
- (2) Alcohol Challenge Study 2 and Generalizable Study can be conducted in parallel after the results of Alcohol Challenge Study 1 is analyzed and used to identify a dose for the two other studies
- (3) Include subjects with BMI lower than 18.5 (this is a follow-up to one AC member's (an ER physician) comment that patients who showed up in the ER for fainting had low BMI)

Please have the revised synopsis and new milestone dates (taking into account protocol review time for FDA/Sprout) to us by Monday morning.

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
08/14/2015

**Mercier, Jennifer L**

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**From:** Mercier, Jennifer L  
**Sent:** Friday, August 14, 2015 1:05 PM  
**To:** Amy Moore (AMoore@sproutpharma.com)  
**Cc:** josephine torrente (jtorrente@sproutpharma.com)  
**Subject:** Alcohol study - PMR

Amy.

Please see the revised synopsis for the alcohol study. We would also need your revised dates by Monday morning.

With regards to the design of the Alcohol Interaction Study, we have concerns [redacted] (b) (4)  
[redacted] if the study is conducted as it is currently designed. [redacted] (b) (4)  
[redacted] (b) (4)

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
08/14/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Friday, August 14, 2015 12:30 PM  
**To:** Amy Moore (AMoore@sproutpharma.com)  
**Cc:** josephine torrente (jtorrente@sproutpharma.com)  
**Subject:** Information Request - ASAP

Amy,

We cannot agree with label change to section 5.1 until we see this information.

Please clarify the treatment that was given to subject 108 (1009) during episode of pallor and somnolence (time of AE 5/25/12 at 11:06 AM) following administration of flibanserin + high dose alcohol? BP in this subject went from 117/76 (semi-recumbent) to 92/60 (standing), then 6 minutes later BP was 79/66 (semi-recumbent).

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
08/14/2015

**Mercier, Jennifer L**

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**From:** Mercier, Jennifer L  
**Sent:** Thursday, August 06, 2015 11:55 AM  
**To:** Amy Moore (AMoore@sproutpharma.com)  
**Cc:** josephine torrente (jtorrente@sproutpharma.com)  
**Subject:** PMR Comments

Amy,

Here are some PMR comments. We may have additional comments on PMR #2.

Thanks,

Jen

**PMR#1: enhanced pharmacovigilance**

1. Your proposed “draft program submission” and “final program submission” are both (b) (4), which does not allow time for review and finalization of your full proposal. We recommend revising the draft program submission to October 2015 and the final program submission to October 2020 to ensure adequate time for FDA’s review and your response.

**PMR#2: appendicitis**

1. Correct the milestone dates. Your proposed milestone dates indicate that the final protocol will be submitted by March 2016 and the study will be completed by March (b) (4). The proposal also states that the study duration is expected to be three years. (b) (4)

**PMR#3: pregnancy outcomes**

1. (b) (4)
2. Your agreement to conduct the second study in pregnant women is needed by COB 8/6/15. Submit a revised PMR proposal to include milestone dates and study synopsis by COB 8/10/15.

**PMR#4: alcohol interaction study**

1. We request that you study more than one dose in alcohol study 2. You should propose the second dose now. The dose selection will be finalized during the protocol review stage.

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/s/  
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JENNIFER L MERCIER  
08/06/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Tuesday, August 04, 2015 4:28 PM  
**To:** 'amy moore'  
**Cc:** josephine torrente (jtorrente@sproutpharma.com)  
**Subject:** RE: NDA 22-526  
**Attachments:** Summary of Requested Changes to Addyi REMS Materials.docx

Amy,

Please find attached the response to your REMS materials questions and the answer about dissemination.

Thanks,

Jen

---

**From:** amy moore [<mailto:amoore@sproutpharma.com>]  
**Sent:** Tuesday, August 04, 2015 1:59 PM  
**To:** Mercier, Jennifer L  
**Subject:** NDA 22-526

Jen,

Could you give us an update on timing for the PI both in terms of when you will get it to us and what our turnaround is to ensure that we maintain the PDUFA date?

In addition, we have begun implementing the revisions that were sent to us last night, however, we have a few points where we think the language is not optimized for patients/physician understanding. A summary of changes we propose is attached here. We'd be happy to have a call if you want to discuss and resolve the language quickly. We will then resubmit quickly to keep on timeline.

Also, on the REMS, the materials you sent to us state: "Note that REMS materials are not appropriate for use in a promotional manner." We intend to proactively disseminate this information to educate prescribers about the REMS. Proactive discussions or dissemination of material are often considered "promotional" by FDA. Please clarify that you are not objecting to proactive dissemination of the REMS materials by Sprout personnel or by Dear Healthcare Provider letters.

Best,

Amy

**amy moore** | director, regulatory affairs

Sprout Pharmaceuticals, Inc.

**p** 919.882.0850 x: 158

**f** 919.882.0855 **c** (b) (6)

**e** [amoore@sproutpharma.com](mailto:amoore@sproutpharma.com)

**w** [sproutpharma.com](http://sproutpharma.com)



*EMAIL CONFIDENTIALITY NOTICE*

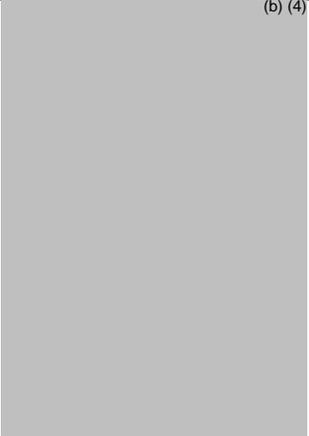
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*Sprout Pharmaceuticals, Inc.*

Sprout Pharmaceuticals is requesting consideration of the following changes to the Addyi REMS Program materials. The changes are annotated within each piece along with the rationale for the request. This document is provided as a means of calling-out the changes requested and simplify the review process.

Title	Requested changes based on Sprout’s review of FDA’s edits marked August 3, 2015	Rationale	DRISK comment
Addyi Patient-Provider Agreement	Remove the descriptor (b) (4) when describing low BP.	<ul style="list-style-type: none"> <li>The term (b) (4) is not descriptive (b) (4)</li> <li>There is no universal definition of (b) (4) low blood pressure.</li> </ul>	Revise the term (b) (4) to “severe”.
Addyi Patient-Provider Agreement	Replace the term “loss of consciousness” with fainting.	<ul style="list-style-type: none"> <li>The goal of the REMS program is to educate on hypotension and syncope due to an interaction with alcohol. The term “loss of consciousness” is not included within that goal.</li> <li>Loss of consciousness is not included in the current label therefore this statement as a standalone within the PPAF cannot be referenced to any data.</li> <li>Fainting is a more consumer-friendly term. Our enhanced PV efforts will determine if the fainting episode results in a loss of consciousness and it will be reported as appropriate.</li> </ul>	We do not agree.
Addyi Patient-Provider Agreement	Replace “healthcare provider” with (b) (4) in the patient portion of the agreement.	<ul style="list-style-type: none"> <li>This was recommended by clinicians in order to create clarity for the patient. (b) (4)</li> </ul>	We do not agree with this change. Patients may contact different healthcare providers in the healthcare system depending on their circumstances;

		<ul style="list-style-type: none"> <li>• (b) (4)</li> </ul>	(b) (4)
Prescriber Enrollment Form	(b) (4) Add Fax # Add DEA# (optional)	<ul style="list-style-type: none"> <li>• Changes being requested to simplify the enrollment process and enhance data gathering.</li> </ul>	These changes are acceptable.
Multiple Location Pharmacy Enrollment Form  Individual Location Pharmacy Enrollment Form  Inpatient Pharmacy Enrollment Form	Replace the attestation statement:  (b) (4)	<ul style="list-style-type: none"> <li>• In discussions with pharmacists this language more closely matches their current practice of reporting AEs.</li> <li>• The existing language is viewed by pharmacists as a significant barrier to pharmacy enrollment and, in turn, patient access.</li> </ul>	We do not agree with this change.
Prescriber and Pharmacy Training Program	Slide #6 FDA included a note about ensuring the content on slide #6 aligns with the PI.	<ul style="list-style-type: none"> <li>• Since the PI is undergoing changes this slide will be updated based upon final labeling.</li> </ul>	This is acceptable.
Inpatient Pharmacy Enrollment Form	Page #1, remove "outpatient" from prescriber	<ul style="list-style-type: none"> <li>• Inpatient prescribers can prescribe Addyi therefore the inclusion of outpatient is incorrect.</li> </ul>	Revise the statement on all 3 enrollment forms to the following: For inpatient use, Addyi is only available from certified

			inpatient pharmacies through the Addyi REMS Program. For outpatient use, Addy is only available from certified outpatient prescribers and certified outpatient pharmacies through the Addyi REMS Program.
Individual Location Pharmacy Enrollment Form	Page #1, remove "outpatient" from prescriber	<ul style="list-style-type: none"> <li>• Confusing, uncertain why this change is needed.</li> </ul>	See previous response
Multiple Location Pharmacy Enrollment	Add Chain ID to enrollment information	<ul style="list-style-type: none"> <li>• Enables better data capture</li> </ul>	This can be included as an optional field.
Prescriber and Pharmacy Training Program	Slide #7  (b) (4)	<ul style="list-style-type: none"> <li>•  (b) (4)</li> </ul>	We do not agree with this change.
Prescriber Enrollment form	Attestation #4, delete second sentence	<ul style="list-style-type: none"> <li>• Deleted to allow the e-attestation language and print attestation language to be consistent</li> </ul>	This is acceptable.
All REMS documents	<a href="http://www.AddyiREMS.com">www.AddyiREMS.com</a> will be upper-lower case	<ul style="list-style-type: none"> <li>• Consistent style</li> </ul>	This is acceptable.
Prescriber and Pharmacy Training Program	Slide #7 Replace 17% with 16% (4/25)	<ul style="list-style-type: none"> <li>• Correcting math</li> </ul>	This is acceptable.
Prescriber and Pharmacy	Slide #7 Change the content of the	<ul style="list-style-type: none"> <li>•  (b) (4)</li> </ul>	We do not agree

Training Program	<p>major bullet to:</p> <p>(b) (4)</p>	<p>(b) (4)</p> <ul style="list-style-type: none"> <li>Clinicians struggled with determining if there was a universal standard to classify the change in BP as (b) (4)</li> </ul>	with this change.
Prescriber and Pharmacy Training Program	<p>Slide #7</p> <p>Re-worded FDA’s description of alcohol comparisons from:</p> <p>Each beer serving contains 5% alcohol content and is equivalent to a 5 ounce glasses of wine containing 12% alcohol content, or a 1.5 ounce shots of 80-proof spirit in a 70 kg person.</p> <p>To</p> <p>(b) (4)</p>	<ul style="list-style-type: none"> <li>Greater comprehension, ease of reading.</li> </ul>	This must be aligned with final agreed upon labeling.
Prescriber and Pharmacy Training Program	<p>Slide #11</p> <p>Sprout is requesting changes to the PPAF (as noted above). If accepted those changes would be reflected on slide #11 of the Prescriber and Pharmacy Training Program deck.</p>	<ul style="list-style-type: none"> <li>Rationale for changes requested noted above.</li> </ul>	Please see comments above.
Knowledge	(b) (4)		



REMS Plan	Page 3, #4  This bullet was edited to align to Sprout's request to alter the verbiage for the pharmacy attestation statement regarding the reporting of hypotension and syncope.	<ul style="list-style-type: none"><li>For consistency between documents</li></ul>	We do not agree with this change.
REMS Plan	Page 5  [Redacted] (b) (4)	<ul style="list-style-type: none"><li>[Redacted] (b) (4)</li></ul>	We do not agree with this change.

		(b) (4)	
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Regarding the following clarification “We intend to proactively disseminate this information to educate prescribers about the REMS. Proactive discussions or dissemination of material are often considered “promotional” by FDA. Please clarify that you are not objecting to proactive dissemination of the REMS materials by Sprout personnel or by Dear Healthcare Provider letters.”

FDA Response: We do not have concerns with proactive dissemination of the REMS materials by Sprout after REMS approval.

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/s/  
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JENNIFER L MERCIER

08/05/2015

**PeRC Meeting Minutes  
May 20, 2015**

**PeRC Members Attending:**

Lynne Yao  
Rosemary Addy  
Jane Inglese  
Gregory Reaman  
Shrikant Pagay  
Hari Cheryl Sachs  
Wiley Chambers  
Daiva Shetty  
Olivia Ziolkowski (for Kristiana Brugger)  
Efe Eworuke  
Ruthanna Davi  
Lily Mulugeta  
Robert Nelson  
Dianne Murphy

**Agenda**

IND	NON RESPONSIVE		
IND			
IND			
IND			
NDA	22526	Addyi (flibanserin) Full Waiver	Treatment of hypoactive sexual desire disorder in premenopausal women
IND	NON RESPONSIVE		
IND			

NON RESPONSIVE

2 Page(s) have been Withheld in Full as Non Responsive immediately following this page

NON RESPONSIVE

**Addyi (flibanserin) Full Waiver**

- NDA 22526 seeks marketing approval for Addyi (flibanserin) for treatment of hypoactive sexual desire disorder in premenopausal women.
- The application triggers PREA as directed to a new active ingredient.
- The PDUFA goal date is August 18, 2015.
- *PeRC Recommendations:*
  - The PeRC agreed with the plan for a full waiver because studies would be impossible or highly impracticable.

NON RESPONSIVE

APPEARS THIS WAY ON ORIGINAL

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/s/  
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GEORGE E GREELEY  
08/04/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Thursday, July 30, 2015 3:32 PM  
**To:** Amy Moore (AMoore@sproutpharma.com)  
**Subject:** Information request  
**Attachments:** Flibanserin shell tables.xls

Amy,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, flibanserin, currently under review in the Division.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on [www.fda.gov/drugtrialsnapshot](http://www.fda.gov/drugtrialsnapshot).

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- "MORE INFORMATION" sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

We are requesting you submit this information no later than August 9, 2015.

Thank you in advance for your cooperation. Please feel free to respond with any questions.

Jen

**Table 7.5.3-a. Subgroup Analysis of Dizziness, Somnolence, and Nausea, Safety Population**

Subgroup	Treatment (N=50) n(%)		Con (N= n(%)
	x (%)**	Total, n	x (%)**
<b>AE*</b>	40 (80.0)	50	45 (90.0)
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Other			
Source:			

\*separate tables for each AE (dizziness,somnolence and nausea)

\*\* Percentages are calculated based on the number of subjects in the subgroup per arm. For example, percentage

\*\*\*Designated per review, other options are Risk Difference, Hazard Ratios, etc

Control 50) %)	Relative Risk***	95% CI	
		LL	UL
Total, n			
50			

3 of males with TEAEs in treatment group = 25/30

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JENNIFER L MERCIER  
07/30/2015



NDA 022526

**MEETING MINUTES**

Sprout Pharmaceuticals, Inc.  
Attention: Amy Moore  
Director, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Moore:

Please refer to your New Drug Application (NDA) dated October 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We also refer to your Complete Response submission dated February 18, 2015.

We also refer to the teleconference between representatives of your firm and the FDA on July 8, 2015. The purpose of the meeting was to discuss the status of the review of your proposed risk evaluation and mitigation strategy (REMS) and the review timeline for flibanserin.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier  
Chief, Project Management Staff  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Teleconference Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF TELECONFERENCE MINUTES**

**Meeting Date and Time:** July 8, 2015; 11:30 – 12:00 PM

**Application Number:** 022526  
**Product Name:** Flibanserin  
**Indication:** Hypoactive sexual desire disorder (HSDD) in premenopausal women  
**Applicant Name:** Sprout Pharmaceuticals, Inc.

**Meeting Chair:** Julie Beitz, M.D.  
**Meeting Recorder:** Jennifer Mercier

**FDA ATTENDEES**

Julie Beitz, M.D. – Director, Office of Drug Evaluation III (ODEIII)  
Amy Egan, M.D., M.P.H. – Deputy Director, ODEIII  
Hylton V. Joffe, M.D., M.M.Sc. – Director, Division of Bone, Reproductive and Urologic Products (DBRUP)  
Christina Chang, M.D., M.P.H. – Clinical Team Leader, DBRUP  
Jennifer Mercier – Chief, Project Management Staff, DBRUP

**APPLICANT ATTENDEES**

Josephine Torrente, J.D., M.S. – Executive Vice President, Corporate and Regulatory Affairs  
(b) (4) – Regulatory Consultant  
Amy Moore – Director, Regulatory Affairs  
Rich Franco – Executive Vice President, Strategy  
Stuart Apfel, M.D. – Vice President, Clinical Safety

**DISCUSSION**

With respect to labeling and the risk evaluation and mitigation strategy (REMS):

- The Agency stated that we are actively reviewing the proposed REMS with elements to assure safe use (ETASU).
- The Agency confirmed that there is Agency alignment with having an ETASU A (prescriber certification) and ETASU B (pharmacy certification), which have been discussed with senior FDA officials at the REMS Oversight Committee (ROC). The Agency is not pursuing ETASU D (informed consent) at this time.
- The Agency is aiming to send the first round of revised labeling and REMS documents to the Applicant on July 17, 2015. These documents will be heavily edited.

- The Agency also informed the Applicant that the package insert will have a Boxed Warning to align with the REMS/ETASU.

With respect to the timeline:

- The Agency is working on an aggressive timeline that includes rapid turnaround from every component within the Agency as well as from the Applicant.
- The timeline in place allows for up to three rounds of discussions with the Applicant.
- The Agency is working towards the original PDUFA goal date of August 18, 2015, but emphasized to the Applicant that there is a possibility of needing an extension of the clock to complete all the required activities surrounding the REMS. A clock extension does not necessarily mean that the Agency will need all 90 days to complete the action.
- The Applicant was concerned about a change in the PDUFA goal date and requested that the Agency notify them as soon as possible if that date was to be changed. The Agency agreed to do so.
- The Applicant requested a teleconference for July 20, 2015 for an opportunity to ask clarifying questions regarding FDA's comments and revisions to the label and REMS that will be conveyed on July 17, 2015. The Agency stated that we are still internally discussing the timelines for teleconference calls. In the meantime, the Applicant can submit clarifying questions for our consideration.

#### **ISSUES REQUIRING FURTHER DISCUSSION**

- Further discussion of the label and REMS for flibanserin.

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JENNIFER L MERCIER  
07/13/2015

**Mercier, Jennifer L**

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**From:** Mercier, Jennifer L  
**Sent:** Friday, June 26, 2015 12:49 PM  
**To:** 'amy moore'  
**Subject:** Information Request

Amy,

We have an information request that we need you to have back to us by COB Monday, June 29, 2015.

Submit all information you have pertaining to subject 13621 in study 511.130, including official autopsy report, laboratory data (including blood alcohol level if available), the rationale stated by the investigator/company determining that the event to not be related to the product.

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
06/26/2015

**PeRC Meeting Minutes  
May 20, 2015**

**PeRC Members Attending:**

Lynne Yao

Rosemary Addy

Jane Inglese

Gregory Reaman

Shrikant Pagay

Hari Cheryl Sachs

Wiley Chambers

Daiva Shetty

Olivia Ziolkowski (for Kristiana Brugger)

Efe Eworuke

Ruthanna Davi

Lily Mulugeta

Robert Nelson

Dianne Murphy

**Agenda**

IND	NON RESPONSIVE		
NDA	22526	Addyi (flibanserin) Full Waiver	Treatment of hypoactive sexual desire disorder (b) (4)
IND	NON RESPONSIVE		

NON RESPONSIVE

2 Page(s) have been Withheld in Full as Non Responsive immediately following this page

NON RESPONSIVE

**Addyi (flibanserin) Full Waiver**

- NDA 22526 seeks marketing approval for Addyi (flibanserin) for treatment of hypoactive sexual desire disorder [REDACTED] (b) (4).
- The application triggers PREA as directed to a new active ingredient.
- The PDUFA goal date is August 18, 2015.
- *PeRC Recommendations:*
  - The PeRC agreed with the plan for a full waiver because studies would be impossible or highly impracticable.

NON RESPONSIVE

APPEARS THIS WAY ON ORIGINAL

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/s/  
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GEORGE E GREELEY  
06/04/2015



NDA 022526

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Sprout Pharmaceuticals, Inc.  
4208 Six Forks Road  
Suite 1010  
Raleigh, NC 27609

ATTENTION: Robert S. Whitehead  
Chief Executive Officer

Dear Mr. Whitehead:

Please refer to your New Drug Application (NDA) resubmission dated February 14, 2015, received February 18, 2015, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Flibanserin Tablets, USP, 100 mg.

We also refer to your correspondence requesting review of your proposed proprietary name, Addyi.

We have completed our review of the proposed proprietary name, Addyi and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 14, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4952. For any other information regarding this application, contact Jennifer Mercier, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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KELLIE A TAYLOR on behalf of TODD D BRIDGES  
05/04/2015

**Mercier, Jennifer L**

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**From:** Mercier, Jennifer L  
**Sent:** Friday, April 17, 2015 3:50 PM  
**To:** 'anne tomalin'  
**Subject:** NDA 22526 IR - 4.17.15

Anne,

We request additional clarification on the responder analysis provided in your 4-13-15 response to the 3-30-15 request:

Please describe, in detail, the methodology you used to derive the PGI-I anchored responder rates for each efficacy endpoint. If this methodology is already submitted elsewhere in the NDA, clarify where we may be able to locate it. In addition, please provide your interpretation for each of the tables you presented in the 4-13-15 response (Tables 3, 4, 5 and 6 in the IR response to Questions II-1-4, pages 11-14 of 230).

Please provide your response by 4-21-15.

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
04/17/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Tuesday, April 14, 2015 10:44 AM  
**To:** 'Amy Moore'  
**Cc:** anne tomalin; josephine torrente  
**Subject:** NDA 22526 Information Request - Biopharmaceutics

Amy,

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

We request this information by COB April 23, 2015.

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
04/14/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Monday, March 30, 2015 9:27 AM  
**To:** atomalin@sproutpharma.com  
**Subject:** Information Request  
**Attachments:** NDA 22526 IR efficacy 3.30.15.doc

Anne,

Please see the attached information request. We would like to have the information in this request by April 13. Please let me know that you have received this email.

Thanks,

Jen

NDA 22526  
Flibanserin 100 mg qhs

Information Request

Please respond by April 13, 2015.

Reference is made to the March 13, 2015 submission in response to our Information Requests dated February 26, 2015 and March 2, 2015. After reviewing the information you provided, we have additional requests for Studies 511.71, 511.75, and 511.147.

- I. For each of the graphs submitted in your March 13, 2015 response:
  1. Clarify whether all your graphs display the subgroup analyses by quartiles, as requested. It is not obvious to us that you have done so.
  2. State the sample sizes for placebo and flibanserin groups in each subgroup.
  3. Explain whether any outliers were excluded from these analyses. If so, provide the rationale for excluding them.
  4. For each of your phase 3 studies (511.71, 511.75 and 511.147), provide a Forest plot of subgroup analyses for each of the following endpoints:
    - a. Satisfying sexual events (SSEs)
    - b. Sexual desire (as measured by the Female Sexual Function Index desire domain questions)
    - c. Distress (as measured by the Female Sexual Distress Scale-Revised, question 13).For each subgroup in these Forest plots, show the mean treatment difference between flibanserin and placebo, including 95% confidence interval and N's for flibanserin and placebo. Use the same subgroups that are used for your cumulative distribution curves.
  5. Explain how missing data were handled for the cumulative distribution curves and the newly requested Forest plots.
  6. For each pivotal study, summarize your overall interpretation of results from the subgroup analysis.
- II. Provide in tables the following responder analyses based on the Patient Global Improvement Index (PGI-I). Show results separately for Studies 511.71, 511.75, and 511.147:
  1. Number and percent of subjects (separately for placebo and flibanserin) at Week 24 reporting the change from baseline in satisfying sexual events (SSEs) to be:
    - a. Very much improved
    - b. Much improved
    - c. Minimally improved
  2. Number and percent of subjects (separately for placebo and flibanserin) at Week 24 reporting the change from baseline in sexual desire (as measured by the Female Sexual Function Index desire domain questions) to be:
    - a. Very much improved
    - b. Much improved
    - c. Minimally improved
  3. Number and percent of subjects (separately for placebo and flibanserin) at Week 24 reporting the change from baseline in distress (as measured by the Female Sexual Distress Scale-Revised, question 13) to be:
    - a. Very much improved
    - b. Much improved
    - c. Minimally improved
  4. Number and percent of subjects (separately for placebo and flibanserin) at Week 24 reporting the overall change from baseline to be:
    - a. Very much improved
    - b. Much improved

c. Minimally improved

5. Explain how missing data were handled for analyses 1-4 under bullet II.

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/s/  
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JENNIFER L MERCIER  
03/30/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Tuesday, March 10, 2015 9:33 AM  
**To:** atomalin@sproutpharma.com  
**Subject:** Information Request

Anne,

We did not see summary tables showing in a concise way the results of the pharmacodynamic endpoints from the driving study. Can you submit such tables? You can break the data into a number of tables - whatever seems to make sense, but perhaps one table for vehicle-related endpoints, one for the other objective endpoints, and one for the subjective endpoints. Each test should be a single row, with a column for the placebo value, and 1 column each for change vs. placebo for each drug treatment (mean value, unless makes more sense being median or some other measure), and another column for p-value vs. placebo.

Thanks,

Jen

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/s/  
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JENNIFER L MERCIER  
03/10/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Monday, March 02, 2015 9:32 AM  
**To:** atomalin@sproutpharma.com  
**Cc:** Mercier, Jennifer L  
**Subject:** NDA 022526 IR 2 27 15 v 2.doc  
**Attachments:** NDA 022526 IR 2 27 15 v 2.doc

Anne,

Please see the attached information request. There is some edits to the previous request.

Thanks,

Jen

NDA 022526

Flibanserin 100 mg tablet qHS for hypoactive sexual desire disorder in premenopausal women

Information Request:

Please submit the requested information by March 13, 2015.

Reference is made to the Information Request sent on 2/26/15. We are amending the requests for efficacy and safety as follows:

**Efficacy**

For requests 2-4 in the Information Request, in addition to excluding the 41 patients from Dr. Mucker's sites from analyses, also exclude the 28 patients enrolled by Dr. Elizabeth Houser in Study 511.75.

**Safety**

For question #5, also confirm that data from the 10 patients enrolled by Dr. Elizabeth Houser in Study 511.84 were not included in the integrated safety database.

For Question #6, in addition to providing a summary of each adverse event reported by the 41 patients enrolled by Dr. Richard Muckerman, please also summarize all adverse events reported by the 28 patients who were enrolled by Dr. Elizabeth Houser in Study 511.75. For these 28 patients, also include the verbatim and preferred terms for these reported adverse events, their start and end dates (relative to the date of randomization), whether the event was serious or led to discontinuation from the study, and the outcome of the event.

We refer to the letter from Boehringer Ingelheim to the FDA, dated February 25, 2009 (relating to Dr. Muckerman's site) and <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm306201.htm> (relating to Dr. Houser's site).

In addition, have you submitted scatterplots of morning drug levels vs. PD outcomes. If not, can you submit scatterplots for each of the drug treatments vs. placebo, i.e. 3 sets of scatterplots. For endpoints that were ordinal (e.g. safe/not safe to drive, KSS, etc) you can show results by outcome vs. binned drug level, e.g. for safe/not safe the percentage of patients in each bin reporting 'not safe'.

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/s/  
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JENNIFER L MERCIER  
03/02/2015

## **Mercier, Jennifer L**

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**From:** Mercier, Jennifer L  
**Sent:** Thursday, February 26, 2015 12:20 PM  
**To:** atomalin@sproutpharma.com  
**Subject:** Information Request  
**Attachments:** NDA 022526 IR 2-25-15.doc

Anne,

Please see the information request attached. The review team would like to have the information submitted to the NDA by March 13. Please let me know that you received this request.

Thanks,

Jen

NDA 022526

Flibanserin 100 mg tablet qHS for hypoactive sexual desire disorder in premenopausal women

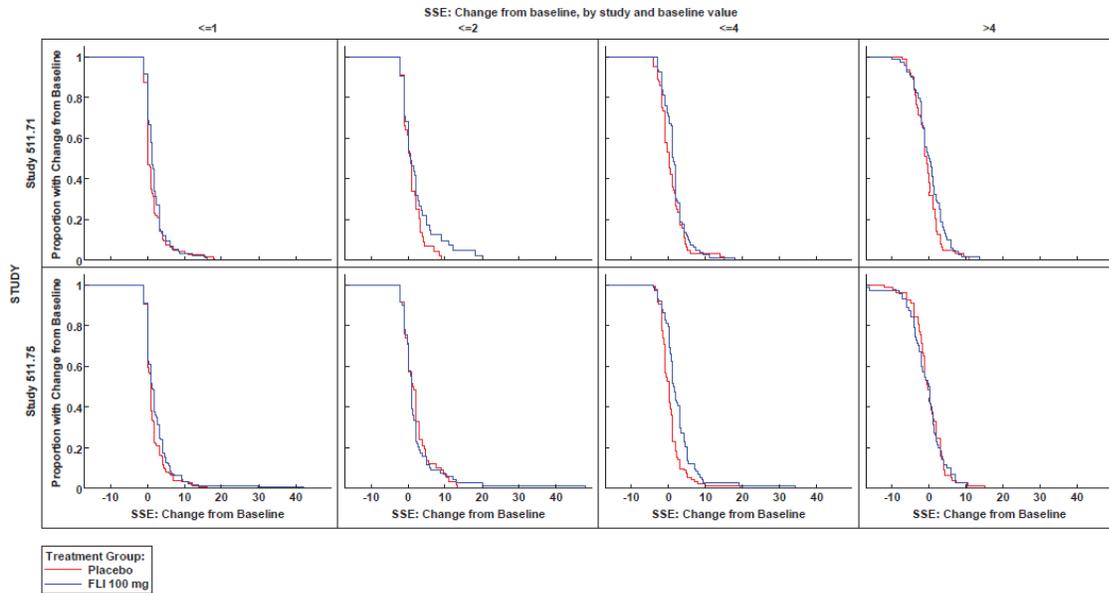
**Information Request:**

**Please submit the requested information by March 13, 2015.**

**Efficacy**

1. For requests 2-4 below, exclude from analyses the 41 patients enrolled by Dr. Richard Muckerman in Study 511.75.
2. Provide the following cumulative distribution curves. Show results separately for Studies 511.71, 511.75, and 511.147:
  - a. Change from baseline in satisfying sexual events (SSEs) for subjects in both flibanserin 100 mg qhs and placebo groups
    - i. By quartile of baseline SSEs
    - ii. By quartile of baseline FSFI desire domain score
    - iii. By quartile of baseline eDiary desire score (this does not apply to Study 511.147)
    - iv. By quartile of baseline distress (FSDS-R Q13) score
  - b. Change from baseline in FSFI desire domain score for subjects in both flibanserin 100 mg qhs and placebo groups
    - i. By quartile of baseline SSEs
    - ii. By quartile of baseline FSFI desire domain score
    - iii. By quartile of baseline eDiary desire score (this does not apply to Study 511.147)
    - iv. By quartile of baseline distress (FSDS-R Q13) score
  - c. Change from baseline in eDiary desire score for subjects in both flibanserin 100 mg qhs and placebo groups (this analysis does not apply to Study 511.147)
    - i. By quartile of baseline SSEs
    - ii. By quartile of baseline FSFI desire domain score
    - iii. By quartile of baseline eDiary desire score (this does not apply to Study 511.147)
    - iv. By quartile of baseline distress (FSDS-R Q13) score
  - d. Change from baseline in distress (FSDS-R Q13) score for subjects in both flibanserin 100 mg qhs and placebo groups
    - i. By quartile of baseline SSEs
    - ii. By quartile of baseline FSFI desire domain score
    - iii. By quartile of baseline eDiary desire score (this does not apply to Study 511.147)
    - iv. By quartile of baseline distress (FSDS-R Q13) score

For an example of what we are looking for, see below:



3. Graphically show the change from baseline over time (in monthly intervals) for flibanserin 100 mg qhs and placebo groups for the following endpoints. Show results separately for Studies 511.71, 511.75, and 511.147.
  - a. SSEs
  - b. FSFI desire domain score
  - c. eDiary desire score (this analysis does not apply to Study 511.147)
  - d. Distress (FSDS-R Q13) score
  
4. Analyze the following endpoints in two subgroups – those on hormonal contraceptives at baseline and those not on hormonal contraceptives at baseline. Show results for the change from baseline for both flibanserin 100 mg qhs and placebo groups and show results separately for Studies 511.71, 511.75, and 511.147. Provide updated efficacy datasets for these three studies that include a column indicating whether patients are on hormonal contraceptives.
  - a. SSEs
  - b. FSFI desire domain score
  - c. eDiary desire score (this analysis does not apply to Study 511.147)
  - d. distress (FSDS-R Q13) score

### **Safety**

5. Confirm that data from the 28 patients enrolled by Dr. Richard Muckerman in Study 511.84 were not included in the integrated safety database.
  
6. Summarize each adverse event reported by the 41 patients who were enrolled by Dr. Richard Muckerman in Study 511.75. Include the verbatim and preferred terms for these reported adverse events, their start and end dates (relative to the date of randomization), whether the event was serious or led to discontinuation from the study, and the outcome of the event.
  
7. Submit Case Report Forms for the following subjects:
  - 0511\_0077/036582
  - 0511\_0070/019081
  - 0511\_0075/027941
  - 0511\_0075/032413
  - 0511\_0071/025702

0511\_0075/030689  
0511\_0075/032050  
0511\_0075/033348  
0511\_0077/037779  
0511\_0147/040060  
0511\_0071/025198  
0511\_0071/025824  
0511\_0071/025935  
0511\_0071/026707  
0511\_0075/030396  
0511\_0075/030482  
0511\_0075/031735  
0511\_0077/037779  
0511\_0147/040090  
0511\_0147/044330

**Clinical Pharmacology**

On January 26, 2015 you asked for an example label that describes clinical implications and management instructions for use with sedative OTC drugs and/or foods/supplements with known CYP3A4 inhibitory properties. In the meeting minutes dated February 10, 2015, we offer the TIVICAY label for your consideration as a general example for the preparation of Section 7 and related sections of a Physician Labeling Rule-(PLR) formatted package insert for flibanserin. (NDA 204790 – dolutegravir, [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/204790s002lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204790s002lbl.pdf))

In your Complete Response submitted on February 14, 2015, you add labeling language to address pharmacokinetic drug-drug interactions with moderate and strong CYP3A4 inhibitors. However, you did not provide a label that addresses other significant drug interactions (e.g. over-the-counter medications, herbal products, dietary supplements, etc) that describes and decreases the likelihood of CNS depressive effects due to changes in flibanserin pharmacokinetics and/or due to pharmacodynamics changes from synergistic sedating mechanisms.

(b) (4)

Overall, we remind you that Section 7 should include clear and practical instructions for preventing or decreasing the likelihood of drug-drug, drug-food, drug-herbal and drug-OTC interaction(s).

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/s/  
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JENNIFER L MERCIER  
02/26/2015

## Mercier, Jennifer L

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**From:** Mercier, Jennifer L  
**Sent:** Thursday, February 26, 2015 2:23 PM  
**To:** 'anne tomalin'  
**Subject:** RE: Flibanserin NDA

Anne,

1. Clinical Pharmacology comment has been addressed in my previous.
2. In accordance to our comments in the meeting minutes dated February 10, 2015, submit additional analyses for Study SPR-14-01 (the driving study) by March 1, 2015.
3. As for the meeting minutes, we acknowledge receipt of your proposed change to the meeting minutes relating to additional discussion under question 9.

Please let me know if you are not going to be able to get the additional analysis by March 1.

Thanks,

Jen

---

**From:** anne tomalin [mailto:ATomalin@sproutpharma.com]  
**Sent:** Friday, February 20, 2015 2:31 PM  
**To:** Williamson, Charlene; Mercier, Jennifer L  
**Subject:** Flibanserin NDA

Dear Charlene and Jen,

Thank you for the NDA resubmission acknowledgement letter. We are looking forward to working with the Division through its review. We realize that the group is working under an abbreviated clock and will do our best to respond to any information requests as quickly as possible. Along those lines, I wanted to let you know that Josephine Torrente, (b) (4) has joined Sprout part-time as Executive Vice President of Corporate and Regulatory Affairs to help facilitate the review process from our side. I will continue to be the primary contact for correspondence.

We have also had a chance to review the February 10, 2015 minutes of the January 15 pre-submission meeting and wanted to comment on 3 aspects.

1. We appreciate the helpful suggestion from Clinical Pharmacology that we consider the TIVICAY package insert as a model. At the time we received the minutes, the proposed flibanserin package insert had been finalized and specific language from the draft PI had been included in other sections of the resubmission. As such we did not have time to fully consider learnings from the TIVICAY PI that might be helpful to flibanserin. We intend to better familiarize ourselves with the TIVICAY PI and consider its implications in advance of any flibanserin labeling discussions with the Division.
2. Regarding the driving study report, we appreciate the confirmation in the minutes that the symmetry analysis (already included in the study report) is appropriate. The post meeting comment also notes that responder graphs would be helpful. The final study report for the driving study was finalized prior to receipt of the minutes and so those graphs are not included in the resubmission. We would, however, be pleased to provide responder graphs as a separate submission to the NDA if that would be helpful. We will wait for your instruction before doing so since we are aware that sending in additional analyses post submission may cause confusion.

3. Finally, we wanted to seek a correction to the meeting discussion on Question 9. The minutes state  
The Sponsor understood that the Division’s analysis suggests an association, rather than definitive evidence of a causative effect, between accidents and sedation.”

This is not fully accurate. Sprout does not believe or understand that the Division’s analysis suggests an association. Sprout’s view was best captured in my January 14 pre-meeting email:

Regarding accidents and sedation, we were seeking agreement that the [Division’s] analysis does not demonstrate that sedation and accidental injury are necessarily associated. It was not our intent to say that the [Sponsor’s] analysis proved that sedation does not impact on accidental injury.

It would be correct to say

The Sponsor understood that the Division’s **believes its** analysis suggests an association, rather than definitive evidence of a causative effect, between accidents and sedation.

If you could ensure that objection to the current version of the Q9 discussion is noted in the record that would be great. If you need this request to be sent via formal channels please let me know and I would be happy to do so.

Please let me know if you have any questions.

Kind regards,

Anne

**anne tomalin** | acting vice president, global regulatory affairs

Sprout Pharmaceuticals, Inc

**p** 919.882.0850 x: 173

**f** 919.882.0855 **c** (b) (6)

**e** [ATomalin@sproutpharma.com](mailto:ATomalin@sproutpharma.com)

**w** [sproutpharma.com](http://sproutpharma.com)



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*Sprout Pharmaceuticals, Inc.*

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/s/  
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JENNIFER L MERCIER  
02/26/2015



NDA 022526

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

We acknowledge receipt on February 18, 2015, of your February 14, 2015, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We consider this a complete, class 2 response to our September 27, 2013 action letter. Therefore, the user fee goal date is August 18, 2015.

If you have any questions, call me at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier  
Chief, Project Management Staff  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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JENNIFER L MERCIER  
02/18/2015



IND (b) (4)

**MEETING MINUTES**

Sprout Pharmaceuticals, Inc.  
Attention: Anne E. Moore  
Manager, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Moore:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 15, 2015. The purpose of the meeting was to discuss your anticipated New Drug Application (NDA) resubmission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Mercier, Chief, Project Management Staff at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

Christina Chang, M.D., M.P.H.  
Clinical Team Leader  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
**Meeting Date and Time:** January 15, 2015; 1:00 PM – 2:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue, Bldg. 22, Room 1311  
Silver Spring, MD 20903

**Application Number:** (b) (4)  
**Product Name:** Flibanserin Tablets  
**Indication:** Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women  
**Sponsor:** Sprout Pharmaceuticals, Inc.  
**Meeting Chair:** Christine Chang, M.D., M.P.H.  
**Meeting Recorder:** Jennifer Mercier

**FDA ATTENDEES**

**Office of New Drugs**  
**Office of Drug Evaluation III**  
Julie Beitz, M.D. – Director

**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Hylton V. Joffe, M.D., M.M.Sc. – Director  
Christine Nguyen, M.D. – Deputy Director, Safety  
Christina Chang, M.D., M.P.H. – Clinical Team Leader  
Daniel Davis, M.D., M.P.H. – Medical Officer  
Catherine Sewell, M.D., M.P.H. – Medical Officer  
Olivia Easley, M.D. – Medical Officer  
Marcea Whitaker, M.D. – Medical Officer  
Alexander Jordan, Ph.D. – Pharmacology/Toxicology Team Leader  
Meredith Alpert, M.S. – Safety Regulatory Project Manager  
Charlene Williamson – Regulatory Health Project Manager  
Jennifer Mercier – Chief, Project Management Staff

**Office of New Drugs**  
**Office of Drug Evaluation I**  
**Division of Neurology**  
Ronald Farkas, M.D., Ph.D. – Clinical Team Leader

**Division of Psychiatry Products**

Lucas Kempf, M.D. – Medical Officer

**Office of Surveillance and Epidemiology (OSE)**

**Office of Medication Error Prevention and Risk Management**

**Division of Risk Management (DRISK)**

Reema Mehta, Pharm.D., M.P.H. – Acting Deputy Director

Kimberly Lehrfeld, Pharm.D., BCPS – Team Leader

Cathy Miller, M.P.H., BSN, – Risk Management Analyst

Joan E. Blair, R.N., M.P.H. – Health Communications Analyst

Shawnetta Jackson, M.S. – Regulatory Project Manager

**OSE, Office of Pharmacovigilance and Epidemiology**

**Division of Epidemiology II (DEPI-II)**

CDR David Moeny, M.P.H., RPh, USPHS – Deputy Director

Rita Ouellet-Hellstrom Ph.D., M.P.H. – Associate Director

Monique Falconer, M.D., M.S. – Drug Use Analyst

Jie Li, Ph.D. – Acting Team Leader

**Office of Translational Sciences**

**Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCPIII)**

Edward Dennis Bashaw, Pharm.D. – Director

Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader

LaiMing Lee, Ph.D. – Clinical Pharmacology Reviewer

**Office of Biostatistics (OB)**

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**Office of New Drug Quality Assessment**

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Mark Seggel, Ph.D. – Acting CMC Lead

**Study Endpoints and Labeling Development Team (SEALD)**

Ashley Slagle, Ph.D. – Endpoints Reviewer

**Controlled Substance Staff**

Katherine Bonson, Ph.D. – Pharmacologist

**SPONSOR ATTENDEES**

Robert Whitehead, Chief Executive Officer

Noel Kim, Ph.D., Vice President, Research and Development

Anne Tomalin, Vice President, Global Regulatory Affairs

James Yuan, M.D., Ph.D., M.B.A., Executive Director, Biostatistics/Business Intelligence

Amy Moore, Manager Regulatory Affairs

(b) (4) (Neurology Consultant)

(b) (4) (Clinical

Consultant)

(b) (4) (Clinical Psychology and Sexual

Medicine Consultant)

(b) (4) (Regulatory Consultant)

## 1. BACKGROUND

Sprout Pharmaceuticals, Inc. is developing flibanserin, a 5-HT<sub>1A</sub> agonist/5-HT<sub>2A</sub> antagonist, as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has received two Complete Response (CR) actions, with the second CR letter issued on September 27, 2013. On December 3, 2013, the Applicant filed a formal dispute resolution request (FDRR) to the Office of New Drugs (OND). OND issued an Appeal Denial on February 7, 2014, recommending that the Sponsor fully address the deficiencies identified in the second CR letter prior to resubmission. Key issues included the need for a driving study to assess next-day impairment and additional drug-drug interaction data to assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin.

In the pre-NDA meeting briefing document dated December 15, 2014, the Sponsor indicated that the NDA resubmission would include updated summaries of efficacy, safety and clinical pharmacology, an updated package insert, proposed Risk Evaluation and Mitigation Strategies (REMS) and Product Quality information regarding a new manufacturing site.

FDA sent Preliminary Comments to Sprout Pharmaceuticals, Inc. on January 14, 2015.

A summary of the discussion that took place at the meeting follows the Division's responses to Questions 8, 9, 12, 14, and 15. Neither the Sponsor nor the Division raised any additional issues pertaining to the remaining questions.

## 2. DISCUSSION

### Question 1

*Does the Division agree that the resubmission should present flibanserin efficacy data in a manner consistent with the pre-specified endpoints in the pivotal studies: that is, with SSEs and desire as the primary measures of efficacy and with distress the key secondary measure of efficacy?*

### FDA Response to Question 1

The resubmission should present flibanserin efficacy data from the pivotal trials already completed in a manner consistent with previous submissions, with the pre-specified and previously agreed-upon endpoints. Change from baseline in satisfying sexual events (SSEs) and sexual desire should remain the co-primary efficacy measures; change from baseline in distress should remain the key secondary efficacy measure.

**Question 2**

*Consistent with discussion at the Patient-Focused Drug Development meeting, does the Division agree that desire and distress are the key symptoms in assessing HSDD severity and clinical meaningfulness of treatment effect?*

**FDA Response to Question 2**

We have always viewed desire and distress to be important symptoms to assess in clinical trials conducted for hypoactive sexual desire disorder (HSDD). As discussed in our response to Question 1, we will consider the efficacy data in accordance with the pre-specified and previously agreed-upon endpoints.

We are in the process of carefully reviewing the comments from the October 2014, Patient-Focused Drug Development (PFDD) meeting and the Scientific Workshop as well as the 110 comments received via the public docket, which only recently closed on December 29, 2014. Until we have reviewed all of these comments, it is premature to conclude that the perspectives shared at the workshops fully represent those of the larger HSDD population and the larger scientific community that has expertise in female sexual dysfunction.

**Question 3**

*Does FDA intend to present information and/or questions regarding the validity of the key PRO instrument, the FSFI, to the BRUDAC if a flibanserin advisory committee meeting is held?*

**FDA Response to Question 3**

At this point, it is premature to commit to the extent of information or the specific questions that we will present to the advisory committee. As we will need to take into account the risks of flibanserin in the context of the drug's benefits, we will be presenting the efficacy results. To place these efficacy results into context, we will need to explain how these efficacy results were generated, including, at a minimum, a description of the Female Sexual Function Index (FSFI) desire domain, its measurement properties, and challenges with the interpretation of meaningful efficacy findings. We believe that committee members with experience in the use of patient reported instruments in the regulatory setting can provide additional assistance with interpretation of findings using the FSFI desire domain.

**Question 4**

*Does the Division continue to view the DSDDS as a valid diagnostic tool for identifying patients with HSDD?*

**FDA Response to Question 4**

Yes. We view the DSDDS as a valid diagnostic tool for identifying patients with HSDD who are premenopausal, given that findings from Study 511.106 (a validation study) and Study 511.74 (a clinical trial) demonstrated a correlation between the DSDDS and standard, structured interviews in the proposed target population (i.e., pre-menopausal women).

We reserve comment on the use of DSDDS as a diagnostic tool in postmenopausal women. Per our Complete Response letter dated September 27, 2013, Study 511.156 was not extensively reviewed.

**Question 5**

*Recognizing that a complete review of the data can only occur in the context of a resubmission, does the Agency believe that the results of Study SPR-14-06 are sufficient to address concerns regarding CYP2C9 and CYP2C19 involvement in flibanserin metabolism? Are there additional analyses or presentations of the results that would aid your review?*

**FDA Response to Question 5**

Based upon your 7-page preliminary draft report, which did not include any safety data, Study SPR-14-06 appears to address CYP2C9 and CYP2C19 involvement in flibanserin metabolism. Our preliminary assessment of Study SPR-14-06 identified one subject who, as a CYP2C19 poor metabolizer, exhibited an approximately 3-fold increase in flibanserin exposure compared to those with normal CYP2C9 and CYP2C19 activity. The final study report of Study SPR-14-06 should include detailed safety data, pharmacokinetics, and genetic data for each subject as well as the analytical validation of genomic assay.

**Question 6**

*The 2013 CRL notes that “cumulative findings from the ketoconazole and fluconazole (strong and moderate CYP3A4 inhibitors) drug interaction studies and physiologically-based Pharmacokinetic modeling suggest that other CYP enzymes are involved in the metabolism of flibanserin” (emphasis added). What physiologically-based PK modeling does the Division believe is suggestive of the involvement of other enzymes in flibanserin metabolism?*

**FDA Response to Question 6**

By physiologically-based pharmacokinetic modeling, we refer to a study report entitled “Simulation of the effect of 200 mg itraconazole b.i.d. on the pharmacokinetics of flibanserin” submitted in the original NDA by Boehringer Ingelheim, which suggested potential metabolic pathways other than CYP3A4. The model includes unspecified metabolic pathways besides CYP3A4 to describe the effect of itraconazole on the pharmacokinetics of flibanserin observed in the clinical study entitled “A randomized, open study to investigate the influence of the cytochrome P450 3A4 inhibitor Itraconazole (200 mg q.d., oral administration) on the pharmacokinetics of a single tablet administration of 50 mg flibanserin and the influence of 50 mg tablets flibanserin b.i.d. as a putative cytochrome P450 3A4 inhibitor on the pharmacokinetics of oral administration of 40 mg Simvastatin in two independent two-fold cross-over designs in healthy female and male volunteers: Study 511.37.”

**Question 7**

*Recognizing that detailed comments on labeling can only be provided after all data are reviewed in the context of an NDA resubmission, please provide any comments or questions regarding the appropriateness and content of the following sections of the proposed package insert for inclusion in the resubmission:*

- *Section 7 (DDIs).*
- *Section 12.3 (Pharmacokinetics)*

**FDA Response to Question 7**

Detailed labeling recommendations will be provided following a full review of Study SPR-14-06 and NDA resubmission, if the NDA can be approved. Based upon our preliminary review of your meeting package, we have the following preliminary comments:

- a. In general, Section 7 should include practical instructions for preventing or decreasing the likelihood of drug interaction(s). This section can also provide advice regarding monitoring.
- b. You provide no recommendation to address the intermittent use of drugs that interact with flibanserin.
- c. You do not describe clinical implications and provide management instructions for nonprescription drugs with known sedative properties that may increase the central nervous system (CNS) depression effects of flibanserin.
- d. You do not describe clinical implications and provide management instructions for foods and herbal products with known CYP3A4 inhibitory properties that may increase the flibanserin exposure and adverse events.



- g. In Section 12.3 of your proposed label, you present the effect of fluconazole on flibanserin (b) (4) (b) (4).  
" Your proposed presentation of fluconazole and flibanserin interaction suggests (b) (4) this is inaccurate and misleading. As previously conveyed, fluconazole is considered a multi-enzyme inhibitor – moderate CYP3A4, moderate CYP2C9, and strong CYP2C19 inhibitor.
- h. (b) (4) Based upon the preliminary data from Study SPR-14-06 (a subject with poor CYP2C19 activity exhibiting approximately 3-fold increase in flibanserin exposure), the contribution from CYP2C19-mediated metabolism of flibanserin does not appear to be negligible.
- i. Pharmacokinetic data and a brief description of the study designs for the drug-drug interaction studies should be included in Section 12.3.

**General Clinical Pharmacology Comment:**

We recommend that you conduct an exposure-safety response analysis to define the relationship of adverse events to flibanserin exposure. A quantitative understanding of exposure and safety response can provide important insights for the risk of adverse events associated with increased plasma concentrations, and help further inform on the benefit/risk profile. Refer to the 2003 FDA Guidance for Industry: *Exposure-Response Relationships -Study Design, Data Analysis, and Regulatory Applications* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf>.

**Question 8**

*Does the Division's concern about "inappropriate use" extend to factors beyond:*

- *Use outside of the indicated population*
- *Concomitant use with contraindicated drugs*
- *Concomitant use with CNS depressants*
- *Daytime dosing?*

**FDA Response to Question 8**

Yes, our current concerns regarding "inappropriate use" relate to the factors you have cited – use outside of the indicated population, concomitant use with moderate and strong CYP3A4 inhibitors, concomitant use with CNS depressants, and daytime dosing. Additional safety concerns may or may not come to light based upon our review of the new safety information obtained since the second review cycle that will be included in your resubmission.

**Discussion during the meeting:**

*The Division clarified that the response to this question should start with the word "No" rather than "Yes," because our current concerns do not extend beyond the factors identified above. The Sponsor had no additional questions or comments relating to the remainder of the response.*

**Question 9**

*Does the Division agree that FDA's corrected analysis of accidental injuries associated with sedation does not raise concerns regarding a causative effect between "sedation" and "accident"?*

**FDA Response to Question 9**

No, we do not. One cannot exclude the possibility that sedation played a role in accidental injuries that occurred concurrently with sedation. We also have concerns that the findings from your Phase 3 trials, which enrolled relatively healthy women and excluded a large number of concomitant medications, may underestimate risk in the real-world setting.

You state that our calculations showing a three-fold higher incidence of accidental injury occurring concurrently with sedation simply reflects the overall three-fold higher incidence of sedation with flibanserin compared to placebo. However, this too does not exclude the possibility that sedation played a role in the accidental injury. Clarify why you consider our use of the denominator of total number of accidental injuries to be "only minimally informative" for

calculating accidental injury associated with sedation. If you continue to believe that sedation does not play a role in accidental injuries, submit detailed information in your NDA resubmission that you believe supports your conclusions. We will carefully review it.

**Discussion during the meeting:**

***The Sponsor understood that the Division's analysis suggests an association, rather than definitive evidence of a causative effect, between accidents and sedation.***

**Question 10**

*Recognizing that a complete review of the data can only occur in the context of a resubmission, does the Agency believe that the results of Study SPR-14-01 may be sufficient to address concerns regarding next-day driving impairment with flibanserin? Are there additional analyses or presentations of the results that would aid your review?*

**FDA Response to Question 10**

Based on your 10-page synopsis, the results of Study SPR-14-01 may be sufficient to address concerns regarding next-day driving impairment with flibanserin. The final study report of Study SPR-14-01 should include detailed safety data, pharmacokinetics, and pharmacodynamics assessments for each subject. Correlations of serum flibanserin levels to each pharmacodynamics measure evaluated (e.g., standard deviation of lateral position, lane exceedances and total collisions, cognitive testing, etc.) by treatment group should also be provided.

**Question 11**

*Recognizing that detailed comments on labeling can only be provided after all data are reviewed in the context of an NDA resubmission, please provide any comments or concerns regarding the appropriateness and content of the following documents for inclusion in the resubmission:*

- *The proposed package insert*
- *The proposed REMS*
- *The proposed additional risk management tools*

**FDA Response to Question 11**

It is premature for FDA to commit to specific risk mitigation strategies. If flibanserin is approved, risk management will need to take into account the risks of flibanserin in the context of the drug's benefits, the potentially large target population of healthy women, and the clinical setting of prescribing. You should propose in your NDA the necessary risk mitigation strategies that you believe would adequately address FDA's safety concerns. We expect to discuss your proposal at an advisory committee meeting and will carefully consider the committee's recommendations. Therefore, we will not be able to comment on the adequacy of the proposed insert labeling, REMS program, or additional risk management tools until after the submission of your Complete Response.

**Question 12**

*Please provide any comments regarding SPI's proposed approach to address concerns regarding rare events, such as appendicitis and neoplasms.*

**FDA Response to Question 12**

We do not have comments regarding your proposed approach at this time. We request that you submit study synopses or protocols addressing appendicitis and neoplasms separately as soon as possible, preferably by the time of the submission of the Complete Response. Submit justifications and supportive validation work in support of your proposed plans.

**Discussion during the meeting:**

*Based on the advice outlined in the September 27, 2013, Complete Response letter, the Sponsor was under the impression that these safety signals could be evaluated in a single study using a health claims database. FDA clarified that, in general, it is challenging to evaluate two very different safety outcomes such as appendicitis and neoplasms in a single study using a claims database. The Sponsor plans to confer with pharmacoepidemiology consultants prior to submitting the study synopses and protocols to FDA for review. The Sponsor was referred to FDA's Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data (May, 2013), which is available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatorinformation/guidances/ucm243537.pdf>*

**Question 13**

*Does the Agency agree that flibanserin is not considered a controlled substance under the Controlled Substances Act and will not be recommended for scheduling?*

**FDA Response to Question 13**

Flibanserin is not currently a controlled substance under the Controlled Substances Act (CSA). The final determination of whether flibanserin has abuse potential and will be recommended for scheduling under the CSA will occur after review of all preclinical and clinical data in the revised submission for flibanserin under NDA 022526. Thus, it is premature to determine the appropriate wording for Section 9.0 (Drug Abuse and Dependence) of the drug label, as proposed in the meeting package.

**Question 14**

*Is it the Agency's continued plan that a review of the safety and efficacy of flibanserin will include a discussion with and recommendation of the BRUDAC?*

**FDA Response to Question 14**

Yes, we plan to take your application to a Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee.

**Discussion during the meeting:**

*The Sponsor anticipates submitting the second Complete Response in February 2015, and is concerned about the timing of the deliverables for an advisory committee meeting in light of a 6-month review clock. The Division stated that the advisory committee meeting would likely take place around Month 4 of the review cycle. The Division is amenable to holding a teleconference call with the Sponsor prior to the Advisory Committee.*

**Post Meeting Comment:**

After the Sponsor submits their Complete Response to the September 27, 2014, action letter, the Advisory Committee Staff will provide the Sponsor with guidance regarding the logistics of the advisory committee meeting as well as the due dates for all the required items. The Sponsor's background package that is fully releasable to the public will be due 22 business days prior to the meeting. The specific dates and additional details will be provided by the Advisory Committee Staff after the resubmission has been received.

**Question 15**

*How can SPI remain apprised of FDA's thinking on topics discussed at the October 28, 2014 Scientific Workshop in advance of the flibanserin Advisory Committee meeting if one is conducted?*

**FDA Response to Question 15**

See our response to Question 2. We are still assessing the recommendations from the workshops as well as all of the public comments to the docket. If we have information that should be shared with you before the advisory committee meeting, we will do so.

**Discussion during the meeting:**

*The Division reiterated that any new information regarding FDA's position on broader topics related to female sexual dysfunction (FSD) that are not specific to flibanserin will be communicated publicly if and when this information becomes available.*

**Question 16**

*Does the Agency have any comment on the intended data for submission related to the new manufacturing site or the extension in expiry date?*

**FDA Response to Question 16**

We acknowledge your plan to provide information on the new manufacturing site, including Method Transfer Protocol, three executed batch records, specifications on a new bottle and cap size, and updated stability data. Refer to the Guidance for Industry: *Immediate Release Solid Oral Dosage Forms: Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979>).

.htm) for guidance on what additional information will need to be provided to support the manufacturing site change. In addition, the information provided in the package is not detailed enough for us to comment on extension of expiry.

We also recommend that you clarify the role of each manufacturing site and if you will use the original drug product manufacturing site as well as the (b) (4) manufacturing site for commercial production in your Complete Response. Please note that all facilities should be ready for inspection at the time of the NDA submission.

### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “*Guidance for Industry Assessment of Abuse Potential of Drugs*”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

### 3. ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting minutes due to the Applicant	FDA	February 14, 2015

### 4. POST MEETING COMMENTS

#### 4.1 Additional questions from the Sponsor (received via electronic mail on January 26, 2015)

##### Question 1

*The team at Sprout is putting together the flibanserin NDA and striving to facilitate the review by ensuring we fully address all comments that we have received. Along those lines we want to be sure that we are providing the responder analysis that you are looking for in the driving study.*

*Working with (b) (4) (our consultant), we have conducted a symmetry analysis comparing pair-wise within subject differences on Day 2 and Day 8 using the maximally selected McNemar test to determine whether the differences in SDLP between placebo and flibanserin (and between placebo and zopiclone) are symmetric around the zero point. Conclusions are summarized in the main body of the study report and results are presented in a post-text table in the study report.*

*Is this sufficient to address the requested analysis? We are more familiar with responder efficacy analyses in which bar graphs are employed to present cumulative percents of patients having a response above or below certain cut points and wanted to ensure that you were not also looking for that sort of presentation.*

##### FDA Response to Question 1

The symmetry test as you propose is acceptable. We also find helpful graphical presentations similar to what you propose that show a range of cut-points (for example, at 1 cm intervals).

##### Question 2

*Could the Agency suggest an example label of a drug that describes clinical implications and management instructions for use with sedative OTC drugs and/or with foods/supplements with known CYP3A4 inhibitory properties?*

##### FDA Response to Question 2

We offer the TIVICAY label for your consideration as a general example for the preparation of Section 7 and related sections of a Physician Labeling Rule-(PLR) formatted package insert for flibanserin. (NDA 204790 – dolutegravir, [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/204790s002lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204790s002lbl.pdf))

Section 7 of this label provides practical instructions for preventing or decreasing the likelihood of drug interactions with commonly used over-the counter medications, herbal products, and dietary supplements. However, due to differences in indication, target population, benefit-risk

profile, clinical development program, etc., the extent to which instructions to avoid drug-drug interactions as outlined in the TIVICAY label may be applicable to your product is unclear.

#### **4.2 Pregnancy and Lactation Labeling**

Revise the proposed labeling to ensure that the content and format of the pregnancy and lactation sections comply with the Final Rule. Refer to the following:

- Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling.  
(<https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for>)
- Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>)

#### **4.3 Proprietary Name**

Refer to our letter dated July 9, 2013, where we found your proposed proprietary name, Addyi, conditionally acceptable. Given the extended length of time that has elapsed since our previous review was conducted, a new request for proprietary name review will need to be submitted as part of your Complete Response.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or submitting a request for proprietary name review, we refer you to the following:

- Draft Guidance for Industry: Best Practices in Developing Proprietary Names for Drugs,  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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/s/  
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CHRISTINA Y CHANG  
02/10/2015



NDA 022526

## GENERAL ADVICE

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) for flibanserin submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We also refer to a segment of the Nightline program produced by the American Broadcast Company (ABC), entitled "Fight Over 'Little Pink Pill' Raises Sexism Questions," which aired on May 21, 2014 (<http://abcnews.go.com/Health/fight-pink-pill-boosting-womens-sex-drive-raises/story?id=23813586>). In this broadcast, a representative of your firm, Ms. Cindy Whitehead, was interviewed by Nightline.

We have reviewed the broadcast and found some of the information presented by ABC to be inaccurate and problematic. First, the claim that women in clinical trials who took flibanserin had "50% increase in sexual desire" is misleading, regardless of whether this refers to satisfying sexual events or sexual desire scores. The stated 50% increase erroneously inflated the treatment effects by failing to adjust for the effects observed in the placebo-treated subjects. Second, the only risks associated with taking flibanserin discussed on the broadcast were "sleepiness" and "dizziness." Significant safety concerns such as drug-drug interactions and accidental injuries were not mentioned. While we recognize that this misleading portrayal of flibanserin's benefit and risk profile was not personally conveyed by Ms. Whitehead in the broadcast, we are nevertheless concerned about the implications of these statements. We urge you to reach out to the network to correct these errors.

In addition, we note that Ms. Whitehead stated in the Nightline broadcast that there are "25 approved drugs for some forms of male sexual dysfunction, but still a great big zero for the most common form of FSD [female sexual dysfunction]." Ms. Whitehead has made similar statements to at least one other media outlet (<http://bigstory.ap.org/article/female-libido-drug-remains-limbo-0>). Such statements are misleading, erroneous, and deeply troubling. We ask that Sprout stop making such misleading statements. For example, when comparing the number of sexual dysfunction drugs approved for men and women, it is important to note that testosterone drugs are not actually approved for the treatment of male sexual problems. It is similarly misleading to count the male generic and innovator products separately when they have the identical active ingredient. Lastly, we note that the comparisons between men and women conspicuously fail to mention products, such as ospemifene, which is FDA-approved to treat

moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause that can result in sexual dysfunction.

We will continue to monitor statements made by, or on behalf, of your company related to flibanserin and will take necessary actions if we continue to identify misleading or inaccurate statements.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
06/13/2014



NDA 022526

**GENERAL ADVICE**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin.

We also refer to your April 17, 2014, submission, containing a clinical trial protocol SPR-14-06, titled, "*Pharmacokinetics of Flibanserin in Relation to CYP2C19 and CYP2C9 Genotypes.*"

We have reviewed the referenced material. The study design as outlined in protocol SPR-14-06 is acceptable except for the following:

- The CYP2C19\*17 allele is associated with enhanced enzyme activity, with an allele frequency ranging from approximately 3 to 21% depending on ethnicity. You define an individual carrying a CYP2C19\*17 allele as an ultra-rapid metabolizer. However, current data suggest that subjects heterozygous for CYP2C19\*17 (such as those genotyped as CYP2C19\*1\*17) may be considered either an extensive metabolizer or an ultra-rapid metabolizer. We recommend that you screen for the CYP2C19\*17 genotype and exclude subjects carrying either CYP2C19\*1\*17 or \*17\*17 alleles from the CYP2C19 extensive metabolizer group of the study.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
06/02/2014

From: LaiMing Lee, PhD

To: **DOCUMENT ROOM (LOG-IN and LOG-OUT)**  
Please log-in this consult and review action for the specified  
IND/NDA submission

DATE: 5/20/2014

NDA No.: **022526**  
Document No.: 061

NDA No.

DATE OF DOCUMENT  
4/17/2014

NAME OF DRUG: **flibanserin**

PRIORITY CONSIDERATION

Date of informal/Formal  
Consult:

NAME OF THE SPONSOR: Sprout Pharmaceuticals

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE**

- |   |   |  |
|---|---|--|
| <input type="checkbox"/> PRE-IND                          | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING          |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING          | <input type="checkbox"/> BIOAVAILABILITY STUDIES      | <input type="checkbox"/> LABELING REVISION               |
| <input type="checkbox"/> IN-VITRO METABOLISM              | <input type="checkbox"/> IN-VIVO WAIVER REQUEST       | <input type="checkbox"/> CORRESPONDENCE                  |
| <input checked="" type="checkbox"/> <b>PROTOCOL (DDI)</b> | <input type="checkbox"/> SUPAC RELATED                | <input type="checkbox"/> DRUG ADVERTISING                |
| <input type="checkbox"/> PHASE II PROTOCOL                | <input type="checkbox"/> CMC RELATED                  | <input type="checkbox"/> ADVERSE REACTION REPORT         |
| <input type="checkbox"/> PHASE III PROTOCOL               | <input type="checkbox"/> PROGRESS REPORT              | <input type="checkbox"/> ANNUAL REPORTS                  |
| <input type="checkbox"/> DOSING REGIMEN CONSULT           | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS    | <input type="checkbox"/> FAX SUBMISSION                  |
| <input type="checkbox"/> PK/PD- POPPK ISSUES              | <input type="checkbox"/> MEETING PACKAGE              | <input type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ): |
| <input type="checkbox"/> PHASE IV RELATED                 |   | [ ]  |

**REVIEW ACTION**

- |   |   |  |
|---|---|--|
| <input type="checkbox"/> NAI (No action indicated)  | <input type="checkbox"/> Oral communication with  | <input checked="" type="checkbox"/> <b>Formal Review/Memo (attached)</b> |
| <input type="checkbox"/> E-mail comments to:  | Name: [ ]   | <input type="checkbox"/> See comments below                              |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox    | <input type="checkbox"/> Comments communicated in | <input type="checkbox"/> See submission cover letter                     |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others | meeting/Telecon. see meeting minutes              | <input type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ):                 |
| (Check as appropriate and attach e-mail)  | dated: [ ]  | [ ]  |

**REVIEW COMMENT(S)**

- NEED TO BE COMMUNICATED TO THE SPONSOR**       **HAVE BEEN COMMUNICATED TO THE SPONSOR**

**Proposed Indication:** Treatment of Hypoactive Sexual Desire Disorder (HSDD) in Premenopausal Women.

**Background:** Sprout Pharmaceuticals is evaluating flibanserin for the treatment of HSDD. The proposed dose is 100 mg to be taken at bedtime due to sedation. The sponsor received two Complete Responses (August 27, 2010 and September 27, 2013) due to unfavorable risk/benefit assessment. The sponsor met with Dr. John Jenkins, Director of OND, on January 10, 2014 to petition the decision from DBRUP on a second Complete Response. As result of formal dispute resolution meeting, the sponsor submitted two protocols – one to assess driving impairment and one to assess potential DDI due to CYP2C9/CYP2C19-mediated metabolism of flibanserin. Ron Farkas, Clinical Team Leader, from the Division of Neurology Products is reviewing the driving protocol. This is a review of the DDI protocol. The sponsor indicated that they plan to resubmit the NDA at the completion of these two studies.

**Proposed Study SPR-14-06**

The proposed study is entitled “Pharmacokinetics of Flibanserin in Relation to CYP2C19 and CYP2C9 Genotypes”. This is an open-label, single dose, parallel, multi-center, Phase 1 to evaluate PK of flibanserin in healthy premenopausal women (18 to 50 years of age) characterized as either CYP2C9 or CYP2C19 poor metabolizers (PMs) or extensive metabolizers (EMs). The sponsor proposes to include 8 to 12 subjects with the genotypes CYP2C9 PM, CYP2C19 PM, and both CYP2C9 and CYP2C19 EM. PM genotypes will be exclusive of any other such that a subject who is wither a CYP2C9 PM cannot be a CYP2C19 PM or vice versa. No subject can have a PM genotype for either CYP3A4 or CYP2D6.

### Pharmacogenetic Screening (EM/PM Phenotype with Corresponding Genotyping)

CYP2C9 PM status: CYP2C9\*3\*3 and CYP2C19\*1\*1

CYP2C9 EM status: CYP2C9\*1\*1

CYP2C19 PM status: CYP2C19\*2\*2, \*2\*3, or \*3\*3 and CYP2C9\*1\*1

CYP2C19 EM status: CYP2C9\*1\*1

None of the subjects (whether EM or PM for CYP2C9 and/or CYP 2C19) can have a PM status genotype for either CYP3A4 or CYP2D6 (subjects identified as having one or more of the following variants will be excluded: CYP3A4\*22, CYP2D6\*3, CYP2D6\*4, CYP2D6\*5, or CYP2D6\*6).

Note: it appears that the sponsor is not screening for CYP2C19\*17, a known allele for CYP2C19 EM or UM status

### Primary Objective

- To evaluate single dose 100 mg flibanserin PK in healthy premenopausal women genotyped as CYP2C9 or CYP2C19 PMs compared to healthy premenopausal women genotyped as both CYP2C9 and CYP2C19 EMs.

### Secondary Objective

- To evaluate the safety and tolerability of flibanserin 100 mg in healthy premenopausal women genotyped as CYP2C9 or CYP2C19 PMs, compared to healthy premenopausal women genotyped as both CYP2C9 and CYP2C19 EMs.

### Pharmacokinetic Sampling

Blood samples for the determination of plasma flibanserin concentrations will be taken on Day 1 at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 12, 16, 24, 36, 48, 72, and 96 hrs following flibanserin administration, and at Follow-up visit on Day 7.

### Pharmacodynamic Measurements

Orthostatic vital signs will be measured at 1, 2, and 4 hrs after dosing, and at any time point thereafter at the discretion of the investigator.

### Safety Measurements

Safety and tolerability endpoints will include adverse events, vital signs (blood pressure, pulse rates, respiration rates), orthostatic vital signs, change from baseline in vital signs, blood and urine laboratory tests, and change from baseline in blood and urine laboratory tests.

### Pharmacokinetic Statistical Analysis Plan

For the comparison of PM vs. EM, a two-sided t-test will be performed separately for CYP2C9 and CYP2C19 on ln-transformed flibanserin AUC<sub>0-inf</sub>, AUC<sub>0-t</sub> and C<sub>max</sub> at the alpha level of 0.05. For each enzyme, the ratio of means (PM/EM) and a 90% CI for the ratio of means, based on the t-test of the ln-transformed data, will be calculated for the flibanserin AUC<sub>0-inf</sub>, AUC<sub>0-t</sub> and C<sub>max</sub>. In addition, for each enzyme, a 90% geometric CI (converting back to the original units) of the ratio (PM/EM) will be presented for flibanserin AUC<sub>0-inf</sub>, AUC<sub>0-t</sub> and C<sub>max</sub>.

### Reviewer's Comments:

- *T<sub>max</sub> and half-life of flibanserin are approximately 1 and 11 hrs, respectively. The PK sampling time frame from pre-dose, 0, 1, 2, and up to 96 hrs post-dose is acceptable as the proposed sampling time frame will cover the T<sub>max</sub> and more than 5 half-lives of flibanserin. The proposed times for measurement of orthostatic vital signs are acceptable as they cover the T<sub>max</sub>.*
- *The sponsor's proposed genotype groups comparing EMs to PMs for both CYP2C9 and CYP2C19 are acceptable as this study design is to assess the contribution of either enzyme on the metabolism of flibanserin.*
- *CYP2C19\*17 is a new allele variant is associated with enhanced enzyme activity with an allele frequency ranging from approximately 3 to 21%. Prevalence of the variant allele was typically <5% in Asians and about four times higher in White and African populations.*
- *The sponsor states that a CYP2C19\*17 allele is defined as an ultra-rapid metabolizer (UM); however, current data suggest subjects heterozygous for CYP2C19\*17 such as those genotyped as CYP2C19\*1\*17 may be considered either an EM or an UM. This reviewer recommends the sponsor genotype for CYP2C19\*17 allele and exclude subjects genotyped as CYP2C19\*1\*17 or \*17\*17 from the CYP2C19 EM group of the study.*

**Reference:**

Li-Wan-Po A, Girard T, Farndon P, et al. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19\*17 British journal of Clinical Pharmacology. 2009: 69(3); 222-230.

**Comments to the Sponsor:**

- *Your proposed study protocol SPR-14-06 is acceptable.*
- *CYP2C19\*17 is associated with enhanced enzyme activity with an allele frequency ranging from approximately 3 to 21%. You state that a CYP2C19\*17 allele is defined as an ultra-rapid metabolizer (UM); however, current data suggest subjects heterozygous for CYP2C19\*17 such as those genotyped as CYP2C19\*1\*17 may be considered either an EM or an UM. We recommend you genotype for CYP2C19\*17 and exclude subjects genotyped as CYP2C19\*1\*17 or \*17\*17 from the CYP2C19 EM group of the study.*

**SIGNATURE OF REVIEWER:** \_\_\_\_\_

Date \_\_\_\_\_

**SIGNATURE OF TEAM LEADER:** \_\_\_\_\_

Date \_\_\_\_\_

**CC.: TL: Kim; DD: Bashaw**

**Project Manager:** \_\_\_\_\_ **Date** \_\_\_\_\_

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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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LAI M LEE  
05/28/2014

MYONG JIN KIM  
05/28/2014



NDA 022526

**GENERAL ADVICE**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin.

We also refer to your submissions dated March 31, 2014 and April 2, 2014, containing respectively, Clinical Trial Protocol SPR-14-01 and an amended protocol entitled: "*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.*"

We have reviewed the referenced material and have the following comment:

- The study design as proposed in the revised protocol is acceptable. The interpretability of the study results will be a matter of review.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
05/23/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022526

**MEETING MINUTES**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin.

We also refer to the meeting between representatives of your firm and the FDA on March 12, 2014. The purpose of the meeting was to discuss a path forward for your drug product.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Williamson, Regulatory Project Manager at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Christina Chang, M.D., M.P.H.  
Clinical Team Leader  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** Other  
**Meeting Date and Time:** March 12, 2014; 9:30 AM – 10:30 AM  
**Meeting Location:** 10903 New Hampshire Avenue, Bldg. 22 Room 1311  
Silver Spring, MD 20903

**Application Number:** 022526  
**Product Name:** Flibanserin Tablets  
**Indication:** Hypoactive sexual desire disorder (HSDD) in premenopausal women  
**Applicant/Applicant Name:** Sprout Pharmaceuticals, Inc.  
**Meeting Chair:** Christina Chang, M.D., M.P.H.  
**Meeting Recorder:** Charlene Williamson

**FDA ATTENDEES**

**Office of Drug Evaluation III (ODE III)**

Julie Beitz, M.D., Director

Maria Walsh, R.N., M.S., Associate Director Regulatory Affairs

**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Hylton Joffe, M.D., M.M.Sc., Director

Christine Nguyen, M.D., Deputy Director of Safety

Christina Chang, M.D., M.P.H., Clinical Team Leader

Daniel Davis, M.D., M.P.H., Medical Officer

Olivia Easley, M.D., Medical Officer

Jennifer Mercier, Chief, Project Management Staff

Charlene Williamson, Regulatory Project Manager

**Division of Neurology Products (DNP)**

Ronald Farkas, M.D., Ph.D., Clinical Team Leader

**Office of Translational Sciences, Office of Clinical Pharmacology, Division of Clinical  
Pharmacology-3 (OTS/OCP/DCP-3)**

Myong-Jin Kim, Pharm.D., Clinical Pharmacology Team Leader

LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer

**Office of Translational Sciences, Office of Biostatistics**

**Division of Biometrics I (OTS/OB/DB I)**

Tristan Massie, Ph.D., statistics reviewer

**Division of Biometrics III (OTS/OB/DB III)**

Mahboob Sobhan, Ph.D., Statistical Team Leader

**Office of Surveillance and Epidemiology, Division of Risk Management (OSE/DRISK)**

Claudia Manzo, Pharm. D., Director  
Kimberly Lehrfeld, Pharm.D., BCPS, Team Leader  
Cathy Miller, M.P.H., BSN, Risk Management Analyst  
Amarilys Vega, M.D., M.P.H., Medical Officer  
Shawnetta Jackson, Regulatory Project Manager

**APPLICANT ATTENDEES**

Robert Whitehead, CEO  
Cindy Whitehead, President and Chief Commercial Officer  
James Symons, PhD, VP, Clinical Development  
Noel Kim, PhD, VP, Research & Development  
Karthi Natarajan, MPH, Director, Clinical Studies  
Anne Tomalin, VP, Regulatory Affairs  
Amy Moore, Manager, Regulatory Affairs

(b) (4), Regulatory Consultant, (b) (4)  
(b) (4), Pharmacokinetic Consultant, (b) (4)  
(b) (4)

**BACKGROUND**

Sprout Pharmaceuticals is developing flibanserin as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has received two Complete Response (CR) actions; the second CR letter was conveyed on September 27, 2013. On December 3, 2013, Sprout appealed to the Office of New Drugs (OND) with a request for formal dispute resolution (FDRR). Dr. John Jenkins, Director, OND denied Sprout's appeal on February 7, 2014. In his response to Sprout, Dr. Jenkins recommended that Sprout fully address the deficiencies identified in the second CR letter prior to resubmitting the application. Key among the issues to be addressed are a driving study to assess next-day impairment and drug-drug interaction studies to assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin.

**DISCUSSION**

**Question 1**

Does the Agency agree (b) (4) is an appropriate CYP2C19 inhibitor to investigate the metabolism of flibanserin by CYP2C19?

**FDA Response to Question 1**

No. (b) (4)  
(b) (4)

(b) (4)  
Another approach is to utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with CYP2C19 inhibitor. (b) (4)

(b) (4)  
**Discussion during the meeting**

- The Applicant (b) (4) requested clarification (b) (4). The Division clarified (b) (4).  
In the original NDA, *in vitro* data suggested CYP2D6 may be involved in the metabolism of flibanserin; this finding prompted the original NDA Applicant to conduct an *in vivo* study to evaluate flibanserin metabolism by CYP2D6.

- (b) (4)
- The Division reiterated that another approach to estimate the contribution of CYP2C19-mediated metabolism of flibanserin is to conduct a pharmacogenetics study. The Applicant requested examples of such pharmacogenetic data to address drug-drug interactions in currently approved products. The Division referred the Applicant to the labeling information for fesoterodine and tamsulosin.

**Post-Meeting Comment:**

(b) (4)  
(b) (4) The Division refers the Applicant to the product label of fesoterodine (section 7.4), tamsulosin (section 12.3), pantoprazole (section 12.4), celecoxib (section 12.5), and citalopram (Clinical Pharmacology/Pharmacokinetics) where dosing recommendations for the example drug were made based upon a pharmacogenetics study for CYP2D6, CYP2C9, or CYP2C19.

**Question 2**

*Does the Agency agree that the design of the proposed CYP2C19 study is appropriate to characterize the degree to which flibanserin is metabolized by CYP2C19 enzymes?*

**FDA Response to Question 2**

See response to Q#1. We recommend you utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with CYP2C19 inhibitor. (b) (4)

**Question 3**

*Does the Agency agree (b) (4) is an appropriate CYP2C9 inhibitor to investigate the metabolism of flibanserin by CYP2C9?*

**FDA Response to Question 3**

No. (b) (4)  
(b) (4)  
(b) (4) utilizing the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with CYP2C9 inhibitor may be a better alternative approach (b) (4)

**Discussion during the meeting**

- (b) (4)  
(b) (4)  
The Division reiterated that another approach to estimate the contribution of CYP2C9-mediated metabolism of flibanserin is to conduct a pharmacogenetics study.

**Question 4**

*Does the Agency agree that the design of the proposed CYP2C9 study is appropriate to characterize the degree to which flibanserin is metabolized by CYP2C9 enzymes?*

**FDA Response to Question 4**

See response to Q#3. We recommend you utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with CYP2C9 inhibitor. (b) (4)

**Question 5**

*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?*

**FDA Response to Question 5**

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.

(b) (4) 100 mg 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.

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 all patients be on concurrent oral contraceptives, and that both 100 mg and 150 mg be tested as described below.

The positive control should be included in all test periods. We recommend a full 4-way, 4-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
- Treatment D: Flibanserin 150 mg + zopiclone placebo, night 1 and 7; flibanserin 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) 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 final dose.

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 described by Laska et al.<sup>1</sup>

### **Discussion during the meeting**

- The Applicant noted that zopiclone is not approved for marketing in the United States and asked about FDA regulations guiding importation of the product for use in the driving study. The Division agreed to update the minutes with information regarding regulatory guidance for importation of non-approved drugs for use in an IND-sponsored study.
- The Applicant stated that requiring subjects to be on oral contraceptives would result in recruitment of a younger population, which may raise issues with generalizability of the results. The Applicant instead proposed including a higher dose of flibanserin to achieve the desired drug exposures. FDA expressed openness to the general approach, and asked the Applicant to submit a revised protocol for comment. The Applicant noted that a 50 mg dosage form is not available, and asked if a 200 mg dose (twice the dose planned for marketing) at the end of the week of flibanserin dosing would be adequate. FDA expressed openness to the general approach of using double the planned dose to understand safety, but stated that using the 200 mg dose only at the end of the dosing period was problematic because it would not provide information about acute effects of such exposures. FDA further stated that potentially it would be open to arguments that tolerance to impairing effects of flibanserin would develop after some period of use, but that if the Applicant was considering such an argument, the study would need to be designed carefully to understand the degree and timing of development of tolerance. FDA recommended that the Applicant submit a full protocol together with accompanying rationale for the key design features, for our review and comment prior to study implementation.

### **Post-Meeting Comment:**

While it was previously recommended that your driving study use zopiclone 7.5 mg tablet for the positive control, we recognize that zopiclone is not approved in the United States. An acceptable alternative would be eszopiclone 4 mg. However, since eszopiclone is available in 1, 2, or 3 mg tablets only, more than two eszopiclone tablets would be needed per dose. If you choose to use eszopiclone, we recommend that blinding be accomplished by overencapsulation so that both the subjects and study personnel can remain blinded to the assigned treatment.

### **Question 6**

*Does the Agency have any comments or concerns regarding the study design?*

### **FDA Response to Question 6**

See response to question 5.

### **Question 7**

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<sup>1</sup> Laska E, Meisner M, Wanderling J. A maximally selected test of symmetry about zero. Stat Med 2012;31:3178-91.

*Understanding that labeling and risk management considerations are inherently review issues, we would appreciate any reaction or feedback the Division has to the risk management activities outlined above.*

#### **FDA Response to Question 7**

We have determined that your proposed communication plan activities will not sufficiently assure that the benefits of flibanserin outweigh the risk of central nervous system (CNS) depression, hypotension and syncope, accidental injuries, drug-drug interactions with strong/moderate CYP3A4 inhibitors, and concomitant use of flibanserin with alcohol. Your proposal should include, at a minimum, strategies to ensure adequate prescriber expertise to safely prescribe flibanserin and appropriate patient selection.

#### **Additional Clinical Pharmacology Response:**

The clinical relevance and labeling implications of drug interactions between flibanserin with multiple CYP enzyme inhibitors, digoxin, oral contraceptives, grapefruit juice, and non-prescription drugs will be considered following the review of the proposed drug interaction studies. Genetic polymorphism for CYP2C9 and CYP2C19 enzymes may also be considered in the labeling and risk management assessment.

#### **Discussion during the meeting**

- The Applicant clarified that their currently proposed risk management strategy will include the following elements:
    - Providers will have training on selecting the appropriate patients for flibanserin.
    - Two additional concepts will be added to the Indications and Usage Section of the label to discourage off-label use:
      - Flibanserin has not been demonstrated safe or effective for forms of female sexual dysfunction (FSD) other than HSDD.
- (b) (4)
- 
- FDA clarified that multiple factors are considered when deciding upon and developing Risk Evaluation and Mitigation Strategies (REMS) including the clinical setting of drug use (e.g. inpatient as opposed to outpatient), the target patient and prescriber population and the severity of the product's risks. FDA considers the risks of flibanserin to be significant, particularly when factoring in the modest efficacy of the product, the potentially large target population of relatively healthy young women, and the clinical setting for prescribing (e.g., busy practitioner with time constraints in the outpatient setting). FDA indicated that in general, communication plans alone are limited in their effectiveness (e.g., with regard to tools, duration, intensity) to communicate risk messages to patients and prescribers. Given these considerations, a REMS with elements to assure safe use (ETASU) may be warranted, should FDA determine that flibanserin can be approved.
  - There was also discussion regarding use of the Decreased Sexual Desire Screener (DSDS) to diagnose women with HSDD. FDA noted that the instrument pre-dates the

Patient-Reported Outcomes guidance and stated that it is unclear as to how the DSDS has been studied in the clinical development program and how this supports use in clinical practice. The Applicant agreed to submit clarifying information with rationale for the use of the DSDS in the NDA resubmission.

**Question 8**

*Are there other areas that the Agency could suggest Sprout explore in terms of developing a risk management approach for flibanserin?*

**FDA Response to Question 8**

If you plan to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) with the application, it should include but not be limited to:

- Your rationale on how you determined a REMS is necessary and how the REMS will ensure that benefits outweigh the risks described above
- A clear characterization of the risk(s) and specific REMS messages
- REMS goals and objectives (program objectives must be specific and measurable, leading to achievement of the REMS goals)
- Proposed REMS elements including required actions for targeted stakeholders under any proposed element to assure safe use (e.g., prescribers, patients, pharmacists)
- All planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal
- REMS Supporting Document that includes REMS assessment activities and metrics to evaluate including but not limited to the impact of the REMS on patient and prescriber behavior and a description of the anticipated burden imposed by the proposed REMS on the healthcare system

**Discussion during the meeting**

See the discussion under Question 7.

**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

**ACTION ITEMS**

NDA 022526  
Meeting Minutes  
Type A

Office of Drug Evaluation III  
Division of Bone, Reproductive and Urologic Products

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Meeting minutes due to the Applicant	FDA	April 11, 2014

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/s/  
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CHRISTINA Y CHANG  
04/10/2014



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** A  
**Meeting Category:** Other  
**Meeting Date and Time:** March 12, 2014  
**Meeting Location:** White Oak, Building 22, Conference Room 1311

**Application Number:** 022526  
**Product Name:** Flibanserin  
**Indication:** Female sexual dysfunction  
**Applicant Name:** Sprout Pharmaceuticals, Inc.

**FDA ATTENDEES (tentative)**

Julie Beitz, M.D., Director, Office of Drug Evaluation III (ODE III)  
Amy Egan, M.D., Acting Deputy Director, ODE III  
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs, ODE III  
Hylton Joffe, M.D., M.M.Sc., Director, Division of Bone, Reproductive and Urologic Products (DBRUP)  
Christine Nguyen, M.D., Deputy Director, Safety, DBRUP  
Christina Chang, M.D., M.P.H., Clinical Team Leader, DBRUP  
Daniel Davis, M.D., Medical Officer, DBRUP  
Olivia Easley, M.D., Medical Officer, DBRUP  
Lynnda Reid, Ph.D., Pharmacology/Toxicology Supervisor, DBRUP  
Alexander Jordan, Ph.D., Pharmacology/Toxicology Team Leader, DBRUP  
Charlene Williamson, Regulatory Health Project Manager, DBRUP  
Jennifer Mercier, Chief, Project Management Staff, DBRUP  
Myong Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology-3 (DCP-3)  
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, OTS, OCP, DCP-3  
Ronald Farkas, M.D., Ph.D., Clinical Team Leader, Division of Neurology Products (DNP)  
Claudia Manzo, Pharm. D., Director, Division of Risk Management (DRISK)  
Kimberly Lehrfeld, Pharm.D., BCPS, Team Leader, DRISK  
Cynthia LaCivita, Pharm.D, Team Leader, DRISK  
Cathy Miller, M.P.H., BSN, Risk Management Analyst, DRISK  
Amarilys Vega, M.D., M.P.H., Medical Officer, DRISK

**SPONSOR ATTENDEES**

Robert Whitehead, CEO  
Cindy Whitehead, President and Chief Commercial Officer  
James Symons, PhD, VP, Clinical Development

Noel Kim, PhD, VP, Research & Development  
James Yuan, MD, PhD, Director, Biostatistics  
Karthi Natarajan, MPH, Director, Clinical Studies  
Anne Tomalin, VP, Regulatory Affairs  
Amy Moore, Manager, Regulatory Affairs

(b) (4), Regulatory Consultant, (b) (4)  
(b) (4), Pharmacokinetic Consultant, (b) (4)  
(b) (4), Consultant re Driving Study, (b) (4)

### **Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 12, 2014, 9:30 AM, EST, White Oak, Building 22, Conference Room 1311 between Sprout Pharmaceuticals, Inc. and the Division of Bone, Reproductive and Urologic Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

### **BACKGROUND**

Sprout Pharmaceuticals is developing flibanserin as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has received two Complete Response (CR) actions; the second CR letter was conveyed on September 27, 2013. On December 3, 2013, Sprout appealed to the Office of New Drugs (OND) with a request for formal dispute resolution (FDRR). Dr. John Jenkins, Director, OND denied Sprout's appeal on February 7, 2014. In his response to Sprout, Dr. Jenkins recommended that Sprout fully address the deficiencies identified in the second CR letter prior to resubmitting the application. Key among the issues to be addressed are studies to assess driving and next-day impairment, and drug-drug interactions involving CYP2C9 and/or CYP2C19 enzymes. On February 12, 2014, Sprout submitted a meeting request to discuss the path forward.

### **DISCUSSION**

1. **Does the Agency agree (b) (4) is an appropriate CYP2C19 inhibitor to investigate the metabolism of flibanserin by CYP2C19?**

FDA Response:

No. [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] Another approach is to utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with a CYP2C19 inhibitor. [REDACTED] (b) (4)

[REDACTED] (b) (4)

2. **Does the Agency agree that the design of the proposed CYP2C19 study is appropriate to characterize the degree to which flibanserin is metabolized by CYP2C19 enzymes?**

FDA Response:

See response to Q#1. We recommend you utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with a CYP2C19 inhibitor. [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]

3. **Does the Agency agree that [REDACTED] (b) (4) is an appropriate CYP2C9 inhibitor to investigate the metabolism of flibanserin by CYP2C9?**

FDA Response:

No. [REDACTED] (b) (4)

[REDACTED] (b) (4)

4. **Does the Agency agree that the design of the proposed CYP2C9 study is appropriate to characterize the degree to which flibanserin is metabolized by CYP2C9 enzymes?**

FDA Response:

See response to Q#3. We recommend you utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with a CYP2C9 inhibitor. [REDACTED] (b) (4)

5. **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.

[REDACTED] (b) (4) mg 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.

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 all patients be on concurrent oral contraceptives, and that both 100 mg and 150 mg be tested as described below.

The positive control should be included in all test periods. We recommend a full 4-way, 4-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
- Treatment D: Flibanserin 150 mg + zopiclone placebo, night 1 and 7; flibanserin 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) 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 the drug is then taken for the remainder of the week, with testing after chronic exposure the morning after the final dose.

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 Standard Deviation Lateral Position (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 that described by Laska et al.<sup>1</sup>

6. **Does the Agency have any comments or concerns regarding the study design?**

FDA Response:

See response to question 5.

7. **Understanding that labeling and risk management considerations are inherently review issues, we would appreciate any reaction or feedback the Division has to the risk management activities outlined above.**

FDA Response:

Your proposed communication plan activities will not sufficiently assure that the benefits of flibanserin outweigh the risk of central nervous system (CNS) depression, hypotension and syncope, accidental injuries, drug-drug interactions with strong/moderate CYP3A4 inhibitors, and concomitant use of flibanserin with alcohol. Your revised proposal for mitigating risk should include, at a minimum, strategies to ensure adequate prescriber expertise to safely prescribe flibanserin and appropriate patient selection. The Agency is discussing internally whether a Risk Evaluation and Mitigation Strategy (REMS) that includes elements to assure safe use (ETASU) can adequately mitigate the serious risks associated with flibanserin.

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<sup>1</sup> Laska E, Meisner M, Wanderling J. A maximally selected test of symmetry about zero. Stat Med 2012;31:3178-91.

We recommend that you consider a REMS that includes ETASU as part of your strategy.

Additional Clinical Pharmacology Response:

The clinical relevance and labeling implications of drug interactions between flibanserin with multiple CYP enzyme inhibitors, digoxin, oral contraceptives, grapefruit juice, and non-prescription drugs will be considered following the review of the proposed drug interaction studies. Genetic polymorphism for CYP2C9 and CYP2C19 enzymes may also be considered in the labeling and risk management assessment.

**8. Are there other areas that the Agency could suggest Sprout explore in terms of developing a risk management approach for flibanserin?**

FDA Response:

You should submit a proposed REMS with your Complete Response submission that includes but is not limited to:

- Your rationale on how the REMS will ensure that benefits outweigh the risks described above
- A clear characterization of the risks and specific REMS goals
- Program objectives that are specific and measurable, leading to achievement of the REMS goals
- Proposed REMS elements including required actions for targeted stakeholders under any proposed element to assure safe use (e.g., prescribers, patients, pharmacists)
- All planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal
- A REMS Supporting Document that includes REMS assessment activities and metrics to evaluate including, but not limited to, the impact of the REMS on patient and prescriber behavior and a description of the anticipated burden imposed by the proposed REMS on the healthcare system

Note that the adequacy and appropriateness of your proposed REMS will be determined in the context of all the available data in your Complete Response submission and would likely be presented at the advisory committee meeting. The adequacy and appropriateness of a REMS with ETASU would also involve further internal discussions with senior FDA officials.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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/s/  
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ZETA-MAE C WILLIAMSON  
03/11/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022526

**MEETING PRELIMINARY COMMENTS**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin.

We also refer to your February 12, 2014, correspondence, received February 12, 2014, requesting a meeting to discuss a path forward for your drug product.

Our preliminary responses to your meeting questions are enclosed.

You should provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Project Manager  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** A  
**Meeting Category:** Other  
**Meeting Date and Time:** March 12, 2014  
**Meeting Location:** White Oak, Building 22, Conference Room 1311

**Application Number:** 022526  
**Product Name:** Flibanserin  
**Indication:** Female sexual dysfunction  
**Applicant Name:** Sprout Pharmaceuticals, Inc.

**FDA ATTENDEES (tentative)**

Julie Beitz, M.D., Director, Office of Drug Evaluation III (ODE III)  
Amy Egan, M.D., Acting Deputy Director, ODE III  
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs, ODE III  
Hylton Joffe, M.D., M.M.Sc., Director, Division of Bone, Reproductive and Urologic Products (DBRUP)  
Christine Nguyen, M.D., Deputy Director, Safety, DBRUP  
Christina Chang, M.D., M.P.H., Clinical Team Leader, DBRUP  
Daniel Davis, M.D., Medical Officer, DBRUP  
Olivia Easley, M.D., Medical Officer, DBRUP  
Lynnda Reid, Ph.D., Pharmacology/Toxicology Supervisor, DBRUP  
Alexander Jordan, Ph.D., Pharmacology/Toxicology Team Leader, DBRUP  
Charlene Williamson, Regulatory Health Project Manager, DBRUP  
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Amarily Vega, M.D., M.P.H., Medical Officer, DRISK

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Sprout Pharmaceuticals is developing flibanserin as a treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA has received two Complete Response (CR) actions; the second CR letter was conveyed on September 27, 2013. On December 3, 2013, Sprout appealed to the Office of New Drugs (OND) with a request for formal dispute resolution (FDRR). Dr. John Jenkins, Director, OND denied Sprout's appeal on February 7, 2014. In his response to Sprout, Dr. Jenkins recommended that Sprout fully address the deficiencies identified in the second CR letter prior to resubmitting the application. Key among the issues to be addressed are studies to assess driving and next-day impairment, and drug-drug interactions involving CYP2C9 and/or CYP2C19 enzymes. On February 12, 2014, Sprout submitted a meeting request to discuss the path forward.

### **DISCUSSION**

1. Does the Agency agree (b) (4) is an appropriate CYP2C19 inhibitor to investigate the metabolism of flibanserin by CYP2C19?

FDA Response:

No. [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Another approach is to utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with a CYP2C19 inhibitor. (b) (4)

[REDACTED] (b) (4)

2. **Does the Agency agree that the design of the proposed CYP2C19 study is appropriate to characterize the degree to which flibanserin is metabolized by CYP2C19 enzymes?**

FDA Response:

See response to Q#1. We recommend you utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with a CYP2C19 inhibitor. (b) (4)

[REDACTED] (b) (4)

3. **Does the Agency agree that [REDACTED] (b) (4) is an appropriate CYP2C9 inhibitor to investigate the metabolism of flibanserin by CYP2C9?**

FDA Response:

No. [REDACTED] (b) (4)

[REDACTED] (b) (4)

4. **Does the Agency agree that the design of the proposed CYP2C9 study is appropriate to characterize the degree to which flibanserin is metabolized by CYP2C9 enzymes?**

FDA Response:

See response to Q#3. We recommend you utilize the pharmacogenetics data to estimate the magnitude of potential drug-drug interactions with a CYP2C9 inhibitor.

(b) (4)

(b) (4)

5. **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.

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In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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/s/  
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ZETA-MAE C WILLIAMSON  
03/11/2014



NDA 022526

**MEETING REQUEST GRANTED**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin.

We also refer to your February 12, 2014, correspondence requesting a Type A meeting to discuss the path forward for your drug development.

The meeting is scheduled as follows:

**Date:** March 12, 2014  
**Time:** 9:30 AM, EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1311  
Silver Spring, Maryland 20903

**Invited CDER Participants:**

Julie Beitz, M.D. – Director, Office of Drug Evaluation III (ODE III)  
Amy Egan, M.D. – Acting Deputy Director, ODE III  
Maria Walsh, R.N., M.S. – Associate Director for Regulatory Affairs, ODE III  
Hylton Joffe, M.D., M.M.Sc. – Director, Division of Bone, Reproductive and Urologic Products (DBRUP)  
Audrey Gassman, M.D. – Deputy Director, DBRUP  
Christine Nguyen, M.D. – Deputy Director, Safety, DBRUP  
Christina Chang, M.D. – Clinical Team Leader, DBRUP  
Daniel Davis, M.D. – Medical Officer, DBRUP  
Olivia Easley, M.D. – Medical Officer, DBRUP  
Lynnda Reid, Ph.D. – Pharmacology/Toxicology Supervisor, DBRUP  
Alexander Jordan, Ph.D. – Pharmacology/Toxicology Team Leader, DBRUP  
Charlene Williamson – Regulatory Health Project Manager, DBRUP  
Jennifer Mercier – Chief, Project Management Staff, DBRUP  
Donna Christner, Ph.D., CMC Lead, Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment (ONDQA)

Zhengfang Ge, Ph.D. – Chemist, ONDQA  
Tapash Gosh, Ph.D. – Biopharmaceutics Lead, ONDQA  
Mahboob Sobhan, Ph.D. – Team Leader, Division of Biometrics III (DBIII)  
Kate Dwyer, Ph.D. - Statistician  
Myong Jin Kim, Pharm.D. - Clinical Pharmacology Team Leader, Division of Clinical  
Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP) @ DRUP  
LaiMing Lee, Ph.D. – Clinical Pharmacology Reviewer, OCP @DRUP

Please e-mail me any updates to your attendees at [Jennifer.mercier@fda.hhs.gov](mailto:Jennifer.mercier@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Charlene Williamson at 301796-1025 or Kalesha Grayson at 301-796-2130.

If you have any questions, call me at (301) 796-0957.

Sincerely,

*{See appended electronic signature page}*

Jennifer Mercier  
Chief, Project Management Staff  
Division of Bone, Reproductive and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Foreign Visitor Data Request Form

### FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITIZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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JENNIFER L MERCIER  
02/13/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 22526

**MEETING MINUTES**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 10, 2014. The purpose of the meeting was to discuss the issues raised in your request for formal dispute resolution dated December 3, 2013.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1270.

Sincerely,

*{See appended electronic signature page}*

Khushboo Sharma, M.B.A, R.A.C  
Senior Regulatory Project Manager  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

**Meeting Date and Time:** January 10, 2014 3:00-4:30 pm EST  
**Meeting Location:** White Oak Campus, Building 22, Rm 1419

**Application Number:** NDA 22526  
**Product Name:** Flibanserin tablets  
**Sponsor/Applicant Name:** Sprout Pharmaceuticals, Inc.

**Meeting Chair:** John Jenkins, M.D.  
**Meeting Recorder:** Khushboo Sharma, M.B.A, RAC

### FDA ATTENDEES

#### Office of New Drugs

John Jenkins, M.D.	Office Director
Sandra L. Kweder, M.D., RADM (Retired)	Deputy Office Director
Beth Duvall	Associate Director, Regulatory Affairs Team
Khushboo Sharma, M.B.A.	Sr. Regulatory Health Project Manager, Regulatory Affairs Team
Ashley Slagle, Ph.D., M.S.	Endpoints Reviewer, SEALD

#### Office of Drug Evaluation III (ODE III)

Julie Beitz, M.D.	Office Director
Amy Egan, M.D.	Deputy Director (Acting)

#### ODE III/ Division of Bone Reproductive and Urologic Products (DBRUP)

Hylton V. Joffe, M.D., M.M.Sc.	Director
Christina Chang, M.D., M.P.H.	Clinical Team Leader
Daniel Davis, M.D.	Medical Officer
Olivia Easley, M.D.	Medical Officer
Charlene Williamson	Regulatory Health Project Manager

#### Office of Drug Evaluation I/ Division of Neurology Products

Ronald Farkas, M.D., Ph.D.	Clinical Team Leader
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#### Office of Translational Sciences/ Office of Clinical Pharmacology/ Division of Clinical Pharmacology-3

E. Dennis Bashaw, Pharm.D.	Division Director
Hae-Young Ahn, Ph.D.	Division Deputy Director
Myong-Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader
LaiMing Lee, Ph.D.	Clinical Pharmacology Reviewer

**Office of Translational Sciences/Office of Biostatistics**

Lisa LaVange, Ph.D.	Office Director
Mahboob Sobhan, Ph.D.	Statistical Team Leader
Kate Dwyer, Ph.D.	Statistician

**Center for Drug Evaluation and Research**

Robert Temple, M.D.	Deputy Center Director for Clinical Sciences
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**SPONSOR ATTENDEES**

Robert Whitehead	Chief Executive Officer
Cynthia Whitehead	President & Chief Commercial Officer
James Symons, Ph.D.	Vice President, Clinical Development
Noel Kim, Ph.D.	Vice President, Research & Development
Anne Tomalin	Vice President, Regulatory Affairs
James Yuan, M.D., Ph.D.	Director, Biostatistics
Karthi Natarajan, M.P.H.	Sr. Manager, Clinical Studies
Amy Moore	Manager, Professional Services
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(b) (4)	Regulatory Consultant, (b) (4)
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(b) (4)	(Consultant)

**BACKGROUND**

Sprout Pharmaceuticals submitted a request for formal dispute resolution (FDRR) to the Office of New Drugs (OND) on December 3, 2013, concerning the fundamental deficiency in the Complete Response letter dated September 27, 2013, specifically that the treatment benefits observed in flibanserin do not outweigh the substantial safety concerns. Dr. John Jenkins, Director, OND is the deciding authority. In Sprout Pharmaceutical's December 3, 2013 dispute resolution submission, the company requested a meeting with the deciding authority before he renders his decision on the matter. The meeting was granted and was held on January 10, 2014.

**MEETING OBJECTIVES**

The objective of this meeting was to discuss the issues surrounding the appeal.

## DISCUSSION

Sprout Pharmaceuticals presented several slides to open the meeting. The FDA and Sprout Pharmaceuticals then discussed issues surrounding the appeal, specifically the following:

- Sprout Pharmaceuticals stated that treatment of Hypoactive Sexual Desire Disorder (HSDD) represents an unmet medical need and believes that efficacy has been established based on data from three clinical studies (147, 71 and 75) that have assessed satisfying sexual events (SSE), sexual desire and distress due to HSDD. Sprout believes that these studies demonstrate a meaningful treatment effect size in the patient population studied and that another clinical study is not needed prior to approval. FDA questioned whether the data demonstrated a meaningful treatment effect size such that the benefit among responders will offset the risks among women who would use the product, if approved. FDA also asked the applicant to clarify the appropriateness of enrolling some women with a large number of SSEs at baseline. The applicant explained that SSEs are not ideal endpoints, nor are they used to diagnose HSDD, because a woman can have SSEs but might still have HSDD and associated distress.
- FDA questioned the key instruments used for the three clinical studies, including why the eDiary was not used to measure sexual desire in Study 147. The applicant stated that data collected via daily eDiary in Studies 51 and 75 are not ideal because women tire of entering data daily into the diary over the 6-month treatment period and because sexual desire is better assessed over weeks rather than days. FDA pointed out that an opportunity may have been lost in Study 147 by not comparing sexual desire data obtained via eDiary with those obtained via the Female Sexual Function Index (FSFI). The applicant stated that the FSFI is a better validated instrument for assessing female sexual dysfunction than the eDiary, and that there was no significant difference between using a 28-day vs. 7-day recall period with this instrument based on the nested cross-over study design of Study 147. FDA mentioned concerns with the cross-over study design and questioned whether women can accurately describe their desire using a 28-day recall period.
- FDA expressed the following safety concerns with flibanserin: overall tolerability, central nervous system depression, syncope, accidental injuries, drug-drug interactions (DDI, e.g., with co-administration of ethanol or CYP3A4 inhibitors), next-day sedation due to the drug's half-life of 11 hours, and the observation of mouse mammary gland carcinomas. Sprout stated that all safety concerns can be mitigated by prescribing the drug for bedtime dosing and through other labeling strategies. The FDA asked if the applicant is planning to conduct a driving study to assess the safety concerns related to the drug's long half-life. Sprout clarified that no driving studies were planned. The FDA also asked whether the applicant intends to further elucidate other metabolic pathways for flibanserin, as the fluconazole DDI study results suggest involvement of enzymes other than CYP3A4. Sprout stated that no additional studies were planned at this time.

- There was a broad discussion between FDA and Sprout regarding the overall benefit/risk profile of flibanserin for the treatment of HSDD. Sprout Pharmaceuticals presented a slide that showed the benefit/risk comparison of flibanserin versus silodosin, an approved alpha-adrenergic antagonist, which the applicant believes has a similar risk/benefit profile as flibanserin. FDA clarified some of the safety issues with silodosin and the reasons it believes that the profiles of the two drug products may not be comparable.

**DECISION (AGREEMENTS) REACHED:**

This meeting was not conducted with the expectation that decisions would be made or agreements would be reached at the meeting. The issues discussed will be taken into consideration when reaching a decision regarding the formal dispute resolution request, which will be made within 30 days from the meeting date.

**ATTACHMENTS/HANDOUTS:**

Slides from Sprout Pharmaceutical presentation

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/s/  
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KHUSHBOO SHARMA  
02/07/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 22526

**APPEAL DENIED**

Sprout Pharmaceuticals, Inc.  
Attention: Anne Tomalin  
Vice President, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We also refer to your December 3, 2013, request for formal dispute resolution received on December 3, 2013. You are disputing the Complete Response (CR) letter dated September 27, 2013, and take specific issue with FDA's conclusion that the treatment benefits observed with flibanserin do not outweigh the substantial safety concerns. We also refer to the meeting held between FDA and Sprout Pharmaceuticals on January 10, 2014, where the issues raised in your request for formal dispute resolution were discussed.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews, meeting minutes, and decision memoranda prepared by FDA staff, the CR letter, and other pertinent material (e.g., material and transcripts from the June 18, 2010, Reproductive Health Drugs Advisory Committee meeting). I have also consulted with staff in the Division of Bone, Reproductive, and Urologic Products (DBRUP), Office of Drug Evaluation III (ODE III), Office of Clinical Pharmacology, Office of Biostatistics (OB), Dr. Lisa LaVange, Director, OB, and Robert Temple, M.D., Deputy Center Director for Clinical Science.

I have completed my review of your request for formal dispute resolution and deny your appeal. Below I summarize the basis for my decision and provide my recommendations for a path forward.

The fundamental issue in dispute is whether the benefits of flibanserin observed in controlled clinical trials in pre-menopausal women with hypoactive sexual desire disorder (HSDD) outweigh the risks of the drug when used in the proposed patient population, should the drug be approved for marketing. You argue that ODE III/DBRUP erred in its assessment of the benefit-risk of flibanserin and state that the drug should be approved for the proposed use without requirement for additional data or analyses prior to approval.

As stated in FDA's draft implementation plan for its Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, the Agency's assessments of the benefits and risks of a product under review are "informed by science, medicine, policy, and judgment, in

accordance with applicable legal and regulatory standards. The intersection of these components constitutes the framework in which FDA makes its regulatory decisions.”<sup>1</sup> These decisions are often complex and invariably require application of judgment on the part of the FDA decision-maker as to whether the statutory standard for approval has been met.

After carefully reviewing the available data, I conclude that the benefit risk assessment made by ODE III/DBRUP was sound and did not deviate from Agency precedent for similar decisions. I agree with ODE III/DBRUP’s assessment that the benefits of flibanserin in HSDD do not outweigh the significant safety concerns that have been identified. I also agree with ODE III/DBRUP’s assessment that additional data are needed to further characterize the potential risks of flibanserin to better inform the benefit risk assessment (i.e., address uncertainty about the magnitude of the risk) and to assist in development of appropriate risk management strategies should the drug be approved for marketing. I briefly summarize my assessment of the benefits and risks below.

### Benefits of flibanserin in HSDD

The sponsor and ODE III/DBRUP are in agreement that statistically significant differences between flibanserin and placebo have been demonstrated in three Phase 3 trials<sup>2</sup> on the endpoints of satisfying sexual events (SSE)<sup>3</sup> and sexual desire as measured by the Female Sexual Function Index (FSFI) sexual desire score.<sup>4</sup> There is disagreement, however, on the clinical significance of the treatment differences observed in the Phase 3 trials as well as the interpretability of the results of the FSFI sexual desire domain given concerns expressed by ODE III/DBRUP in collaboration with OND’s Study Endpoints and Labeling Development Staff (SEALD) regarding the content validity of that instrument in accurately assessing sexual desire in patients with HSDD and the 28-day recall period employed in the Phase 3 trials. While the issues of content validity of the FSFI sexual desire domain as a measure of sexual desire in women with HSDD and the best recall period for a patient reported outcome measure of sexual desire in HSDD remain in dispute, I acknowledge that a numerically small and statistically significant difference has been observed on this endpoint across three Phase 3 trials. This finding, combined with the consistent numerically small but statistically significant effect on SSE, demonstrates a pharmacologic effect of flibanserin in the patients studied. While you argue that these findings are “robust” and ODE III/DBRUP argues that these effects are “modest,” it is clear that the clinical significance of these findings must be factored into the benefit risk assessment if there are significant safety concerns in the proposed patient population, which ODE III/DBRUP conclude is the case for flibanserin.

<sup>1</sup> <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>

<sup>2</sup> Studies 511.71 and Study 511.75 were submitted with the original NDA. Study 511.147 was submitted for review in response to the first Complete Response letter.

<sup>3</sup> SSE was a co-primary endpoint in each of the Phase 3 trials of flibanserin in HSDD. Across the three Phase 3 trials the mean increase from baseline in SSE per month in flibanserin-treated patients was 0.8-1.0, the median increase from baseline in SSE per month was 0.5-1.0.

<sup>4</sup> The FSFI sexual desire domain was a secondary endpoint in Studies 511.71 and 511.75 and a co-primary endpoint in Study 511.147. In Studies 511.71 and 511.75 an eDiary score of sexual desire, with a daily recall period, was a co-primary endpoint and was not statistically significant in either trial. Across the three Phase 3 trials, the mean increase from baseline for the FSFI sexual desire score was 0.3 – 0.4 in flibanserin-treated patients. The baseline mean FSFI sexual desire score in the Phase 3 trials was 1.8 -1.9 (the range of possible scores for the FSFI sexual desire instrument is 1.2 – 6.0).

### Risks of flibanserin

The most important risks identified for flibanserin from the clinical development program are central nervous system (CNS) depression and significant pharmacokinetic and pharmacodynamic interactions between flibanserin and alcohol and drugs that inhibit flibanserin's metabolism and clearance. You argue that these risks are similar to those seen for many approved CNS-active drugs and can be handled through appropriate labeling restrictions and warnings. ODE III/DBRUP have requested that you conduct additional clinical trials to better define these risks to help inform the benefit risk assessment and appropriate risk management strategies that could support approval.

With regard to CNS depression, women in the Phase 3 controlled clinical trials frequently reported adverse effects of fatigue, somnolence, and sedation. As you state, such adverse events are not uncommon for CNS-active drugs and are often reflected in product labeling to alert the prescriber and patient to monitor for and take appropriate action if such events occur in an individual patient. The significant concern raised by ODE III/DBRUP about these events in the case of flibanserin is linked to the drug's long half-life (11 hours), the observed dose-related increase in the incidence and severity of these adverse events, and the significant pharmacokinetic and pharmacodynamic interactions between flibanserin and alcohol and drugs that inhibit its metabolism, such as inhibitors of cytochrome P450 3A4 (CYP3A4), which also increase the incidence and severity of CNS depression.

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. This concern was not adequately addressed by the psychomotor impairment studies performed. For example, in Study 511.3, which evaluated psychomotor impairment due to flibanserin using Choice Reaction Time (CRT), flibanserin caused clinically significant mental impairment for up to 3.5 hours after dosing. However, the study was not adequately designed to exclude clinically significant impairment at later time points. The concern regarding next-day impairment of mental alertness is a significant safety issue for flibanserin since the drug is intended for chronic use in an active patient population that would be expected to engage in activities such as driving. The significant pharmacokinetic and pharmacodynamic interactions with alcohol and other drugs add to these concerns. ODE III/DBRUP, based on advice from experts in CDER's Division of Neurology Products, recommended that you conduct a driving impairment study to better explore this serious potential risk. I concur that such a study is necessary to define and characterize the risk of next-day impairment to inform the benefit risk assessment and to determine whether this potentially serious safety issue can be adequately addressed through label warnings and precautions.

The results of the interaction study between flibanserin and alcohol raised concerns regarding the potential for serious adverse events if flibanserin is taken together with alcohol. These concerns were not limited to the expected increase in sedation that is often seen when two CNS depressants are administered together, but also included significant episodes of orthostatic hypotension and syncope/near syncope. Given the prevalence of alcohol use in the target patient population for flibanserin, this represents a significant safety issue.

With regard to drug interactions, the available data demonstrate marked interactions between flibanserin and moderate to strong inhibitors of CYP3A4, including fluconazole and ketoconazole, and lesser, but potentially clinically significant interactions, between flibanserin and oral contraceptives and grapefruit juice. When administered with fluconazole (a moderate 3A4, moderate 2C9, and strong 2C19 inhibitor) and ketoconazole (a strong 3A4 inhibitor) the  $AUC_{0-inf}$  of flibanserin increased by 7.0 and 4.6 fold, respectively. These increases in flibanserin exposure were associated with a clinically significant increase in adverse events, including severe hypotension and syncope requiring medical intervention. The results of the drug interaction study with fluconazole, where the increase in flibanserin exposure was several fold higher than was seen after exposure to ketoconazole, raises concern that the metabolic pathways for flibanserin have not been fully investigated and suggests that inhibitors of CYP2C9 and/or CYP2C19 may also cause clinically significant interactions when taken with flibanserin.<sup>5</sup> If true, this would further expand the list of interacting drugs that would need to be avoided by patients to ensure the safe use of flibanserin. Given the magnitude of the increase in exposure observed in the drug interaction studies, the frequency and severity of the adverse reactions seen with the higher exposures to flibanserin, and the potentially long list of interacting drugs that would need to be avoided, it remains uncertain whether label warnings and precautions would be adequate to ensure the safe use of flibanserin. ODE III/DBRUP recommended that you address this concern and provide better understanding of the metabolic pathways of flibanserin, including potential interactions with CYP2C9 and/or CYP2C19 inhibitors, to further inform the benefit risk assessment. I concur that these additional investigations are important and should be conducted prior to approval.

ODE III/DBRUP identified other potentially serious safety concerns in the second CR letter. These included: 1) a greater incidence of appendicitis among patients treated with flibanserin, which may be a class effect of drugs with 5HT<sub>2A</sub> antagonism, 2) an increased incidence of mammary tumors in mice and uncertainty regarding the relevance of this finding to humans; and 3) the potential inhibition of P-gp by flibanserin, which raises the possibility of other clinically significant drug interactions beyond those discussed above. These additional safety concerns add further weight to the risk side of the benefit risk of flibanserin in HSDD.

#### Benefit risk assessment

In the second CR letter, ODE III/DBRUP concluded that the “modest” benefits of flibanserin in treatment of HSDD did not outweigh concerns about the “substantial” safety issues and provided advice regarding the additional data needed to better inform the benefit risk assessment. Some of the recommendations were focused on obtaining additional data to better describe the benefit of flibanserin; other recommendations focused on collection of additional safety information to better describe the potential risks. In your FDRR you argue that “ODEIII erred in refusing to approve flibanserin on the basis of the existing data” and ask that I agree that “the NDA should be resubmitted with no new data” so that you and ODEIII/DBRUP can reach agreement on appropriate labeling for marketing approval.

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<sup>5</sup> The entry criteria for the Phase 3 trials excluded many potential interacting drugs, thus the ability to rely on the adverse events reported in those trials to predict “real world” experience should the drug be approved is very limited.

As noted above, I do not believe that ODE III/DBRUP “erred” in its benefit risk assessment of flibanserin. They identified significant concerns regarding the clinical meaning of the improvements in SSE and FSFI sexual desire scores observed in women with HSDD treated with flibanserin and also identified significant safety concerns, which they concluded outweighed the observed benefit.

If there was any error in ODE III/DBRUP’s review of your NDA on the last cycle it was the decision not to present the application for discussion at a public advisory committee (AC) meeting. I understand that ODE III/DBRUP thought an advisory committee meeting would be premature given the issues they had identified in their review; however, I believe obtaining outside expert opinion on whether the observed benefits of flibanserin in HSDD outweigh its risks would have been very helpful to informing FDA’s benefit risk assessment. ODE III/DBRUP stated in the second CR that they planned to present this application to a public AC on the next review cycle, and I fully concur with that plan.

Benefit risk assessments require consideration and weighing of all available data on the demonstrated benefits of a drug and the known and potential risks. These are complex decisions and involve judgment based on an understanding of, among other things, the seriousness of the disease in question, the unmet medical need of the patients with the disease/disorder, an assessment of the clinical meaning/importance of the benefits demonstrated for the drug, careful consideration of the seriousness of the identified and potential risks associated with use of the drug, and the likely effectiveness of available strategies, such as label warnings, to mitigate/manage the risks to an acceptable level. In the current case you see HSDD as a serious/life-altering condition with a significant unmet medical need. You believe the demonstrated benefits of the drug are robust and clinically meaningful to patients. You also believe the safety profile of flibanserin is well-described and that the safety issues identified can be managed through label contraindications, warnings, and precautions and a responsible roll-out and marketing plan to educate prescribers and patients on the safe and effective use of flibanserin.

I agree that HSDD can cause significant distress and result in adverse consequences in women with the disorder. I also agree that there is an unmet medical need for safe and effective treatments for this disorder. However, I agree with ODE III/DBRUP that the demonstrated effects on SSE and sexual desire in women with HSDD are modest and of uncertain clinical benefit. I also agree with ODE III/DBRUP that the identified safety concerns are substantial and require further evaluation before a favorable benefit risk assessment and risk management plan to support approval can be reached.

While it is true, as you argue, that other drugs have been approved by FDA for symptomatic conditions despite “modest” efficacy and potentially serious safety concerns, the available data for flibanserin raise concerns that need to be addressed before approval. First, there remains substantial disagreement between you and FDA regarding the most appropriate means to assess the symptoms of decreased sexual desire and the benefit of the drug in women with HSDD. This disagreement on the assessment instruments used and the validity of their output serves to raise significant questions about the clinical significance of observed effects of flibanserin in the

Phase 3 clinical trials. Second, the observed frequency of CNS depression with flibanserin at the proposed dose, when combined with the significant and potentially life-threatening pharmacokinetic and pharmacodynamic interactions with alcohol and many drugs that are commonly used in the target population of patients, is of great concern and unlikely to be adequately managed by contraindications, warnings and precautions in drug labeling as you propose. Finally, given estimates of the prevalence of HSDD in pre-menopausal women, it is possible that millions of women could be eligible for treatment should flibanserin be approved, which raises significant questions of whether the net effect on public health would be positive. Before FDA makes a new decision on whether the benefits of flibanserin in HSDD outweigh its risks I believe it is important that there be discussion of these issues at a public advisory committee meeting, which will allow FDA to hear input from experts in the field as well as affected stakeholders such as patients with HSDD and patient safety advocates.

As to the path forward, I recommend that you fully address the issues raised by ODE III/DBRUP in the second CR letter, in particular the request that you conduct a driving study to assess next-day impairment and assess the effect of CYP2C9 and/or CYP2C19 enzymes on the metabolism of flibanserin, before resubmitting the application. Fully addressing the issues in the second CR letter will allow for a better informed review during the next review cycle and provide the basis for the most productive use of the public advisory committee meeting. That said; if you choose, against our strong advice, not to conduct additional clinical studies before resubmitting the application, we will accept the resubmission as a complete response provided you have responded to all of the issues raised by ODE III/DBRUP in the second CR letter. Such a resubmission will provide a weaker basis for the next review cycle and AC discussion; however, our willingness to accept such a resubmission indicates our openness to further considering your arguments in favor of approval of flibanserin and our desire to receive expert and public feedback at the planned AC meeting to better inform our benefit risk assessment. I must caution you, however, that while the latter course of action may result in a shorter time to resubmission of the application, not addressing the significant safety issues that have been identified by completion of new studies may result in another CR action on the next review cycle.

Questions regarding next steps as described in this letter should be directed to Charlene Williamson, Sr. Regulatory Project Manager, at (301) 796-1025.

This constitutes the final decision at the level of the Office of New Drugs. If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Khushboo Sharma at (301) 796-1270.

Sincerely,

*{See appended electronic signature page}*

John Jenkins, M.D.  
Director, Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration



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/s/  
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JOHN K JENKINS  
02/07/2014

**Food and Drug Administration (FDA)**  
**Center for Drug Evaluation and Research (CDER)**  
**Office of New Drugs (OND)**  
**Office of Drug Evaluation (ODE) III**  
**Division of Bone, Reproductive, and Urologic Products (DBRUP)**

**Clinical Memorandum**

**September 17, 2015**

To: NDA 022526

From: Christina Chang, M.D., M.P.H. – Clinical Team Leader, DBRUP

Through: Hylton Joffe, M.D., M.M.Sc. – Division Director, DBRUP

This memorandum serves to amend information contained in the September 27, 2013 Complete Response Letter (CRL), and related reviews.

In the CRL, item 1d under the **Clinical Safety** section documents the Division’s assessment concerning the incidences of accidental injuries temporally related to sedation that were observed in the Phase 3 clinical program for both flibanserin and placebo. Item 1d states:

“Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (74% vs. 37%).”

Based on further communication with the Applicant and re-analysis of the data, the Division determined that the two percentages stated in this paragraph and in the related reviews were incorrect. The paragraph should state:

“Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (**21% vs. 6%**).”

The revised percentages also apply to the corresponding text in the related reviews. The correct information is conveyed in the final, approved labeling.

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/s/  
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CHRISTINA Y CHANG  
09/17/2015

HYLTON V JOFFE  
09/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022526

**MEETING MINUTES**

Sprout Pharmaceuticals, Inc.  
Attention: Richard A. Davan  
Director, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Mr. Davan:

Please refer to your New Drug Application (NDA) dated April 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets 100 mg.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on November 18, 2013.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Christina Chang, M.D., M.P.H.  
Clinical Team Leader  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** End-of-Review

**Meeting Date and Time:** November 18, 2013 – 1:00 PM – 2:00 PM  
**Meeting Location:** 10903 New Hampshire, Bldg 22 Room 1315  
Silver Spring, MD 20903

**Application Number:** 022526  
**Product Name:** Flibanserin Tablets  
**Indication:** Treatment of hypoactive sexual desire disorder in premenopausal women  
**Sponsor/Applicant Name:** Sprout Pharmaceuticals, Inc.

**Meeting Chair:** Christina Chang, M.D., M.P.H.  
**Meeting Recorder:** Charlene Williamson

**FDA ATTENDEES**

Julie Beitz, M.D., Office Director, Office of Drug Evaluation III (ODE III)  
Amy Egan, M.D., Acting Deputy Director, ODE III  
Hylton V. Joffe, M.D., M.M.Sc., Director, Division of Bone, Reproductive and Urologic Products (DBRUP)  
Christina Chang, M.D., M.P.H., Clinical Team Leader, DBRUP  
Daniel Davis, M.D., M.P.H., Medical Officer, DBRUP  
Olivia Easley, M.D., Medical Officer, DBRUP  
Caren Kieswetter, M.D., M.P.H., Medical Officer, DBRUP  
Catherine Sewell, M.D., M.P.H., Medical Officer, DBRUP  
Ronald Farkas, M.D., Ph.D., Clinical Team Leader, Division of Neurology Products (DNP)  
Kate Dwyer, Ph.D., Statistician, Office of Biometrics III (OB III)  
Sonia Castillo, Ph.D., Statistician, OB III  
E. Dennis Bashaw, Pharm.D., Division Director, Office of Translational Sciences, Office of Clinical Pharmacology, Division of Clinical Pharmacology-3 (OTS/OCP/DCP-3)  
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, OTS/OCP/DCP-3  
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, OTS/OCP/DCP-3  
Katherine Bonson, Ph.D., Pharmacologist, Controlled Substance Staff (CSS)  
Elektra Papadopoulos, M.D., Team Leader, Study Endpoints and Labeling Development (SEALD)  
Charlene Williamson, Regulatory Project Manager, DBRUP

### SPONSOR ATTENDEES

Robert Whitehead, Chief Executive Officer  
Cynthia Whitehead, President & Chief Commercial Officer  
James Symons, Ph.D. Vice-President, Clinical Development  
Richard Davan, Director, Regulatory Affairs  
James Yuan, M.D., Ph.D., Director, Biostatistics  
Amy Moore, Manager, Professional Services

(b) (4) (Consultant)  
(b) (4) Regulatory Consultant (b) (4)  
(b) (4), Regulatory Consultant, (b) (4)

### BACKGROUND

Flibanserin is a post-synaptic 5-HT<sub>1A</sub> receptor agonist and 5-HT<sub>2A</sub> receptor antagonist that has been evaluated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The NDA was not approved in August 2010. On March 29, 2013, Sprout Pharmaceuticals, Inc. submitted a Complete Response to address the deficiencies outlined in the August 27, 2010, Complete Response Letter.

The Division issued a second Complete Response letter on September 27, 2013. The deficiencies cited include efficacy, safety, and clinical pharmacology issues. The Applicant requested an End-of-Review meeting on October 1, 2013, to discuss the path forward for the NDA. The meeting was held on November 18, 2013.

### GENERAL COMMENTS

We continue to believe that the efficacy of flibanserin, while statistically significant over placebo, is modest in the population of premenopausal women that was studied. We remain skeptical that the treatment benefit observed with flibanserin is sufficient to offset the substantial safety concerns. As we discussed in the September 27, 2013, Complete Response letter, should you choose to submit a Complete Response, we intend to bring your application to advisory committee for advice on whether the demonstrated benefits of treatment with flibanserin outweigh the risks associated with its use in the proposed target population. We also recognize that some of the individual safety issues with flibanserin that we have identified may have been managed with labeling for other products. However, our concerns for flibanserin are based on the totality of the safety data balanced against the modest efficacy findings. The other products you reference in your meeting package have different risk/benefit profiles (e.g., amenable to a PRN dosing regimen, indicated for a life-threatening clinical condition, shown to have substantial efficacy in the target population, etc.). Therefore, those labeling decisions cannot be used to conclude that similar labeling for flibanserin will ensure that the benefits of flibanserin outweigh its risks.

#### Discussion at the meeting:

The Sponsor asked why an Advisory Committee (AC) meeting was not held in the second review cycle. We believe that a more meaningful advisory committee meeting can take place

after the Sponsor has submitted a Complete Response addressing the deficiencies outlined in the Complete Response letter.

## **EFFICACY**

### **Question 1**

*Do the Office and Division agree that the NDA contains substantial evidence of the efficacy of flibanserin in the treatment of HSDD in premenopausal women?*

### **FDA Response to Question 1**

We acknowledge that your NDA contains clinical trials which demonstrated that flibanserin statistically outperformed placebo in the treatment of HSDD in premenopausal women. We also recognize that these trials indicated that, relative to placebo, more patients treated with flibanserin perceived their improvement to be clinically meaningful. However, we reiterate that the data in your NDA support only a modest effect of flibanserin on HSDD. A possible path forward would be to study a population of women with more severe HSDD in whom a more favorable benefit/risk profile can be demonstrated. Flibanserin should be assessed in such a population in a new placebo-controlled Phase 3 trial. Greater severity of the HSDD may be manifested either as profoundly reduced sexual desire or fewer episodes of satisfying sexual events (SSEs) at baseline. We recommend that you consider having an upper limit on the number of baseline satisfying sexual events as an enrollment criterion. In the three pivotal trials, we note that 10% of subjects reported > 6 SSEs/month at baseline, and 2.4% of subjects reported  $\geq 9$  SSEs/month at baseline. The maximum numbers of SSEs reported by any subject were 34, 16, and 23 per month, in Studies 511.147, 511.71, and 511.75, respectively. We are not convinced that a median increase of 1 or fewer SSEs/month (as shown across your phase 3 trials) is sufficient to offset the substantial safety concerns in all HSDD patients.

### **Discussion at the meeting:**

The Sponsor stated that the number of satisfactory sexual events (SSEs) at baseline is not a good measure of the severity of HSDD in women. The Sponsor stated that the level of distress and desire is a better measure of the HSDD severity.

The Division stated no predefined preference for measures for severity in HSDD at this time. However, the Division noted that, across the three pivotal trials, there was only a 10-15% treatment difference between flibanserin and placebo in the proportion of responders (subjects who considered their treatment response to be clinically meaningful for the three important efficacy endpoints of SSEs, sexual desire and distress). In light of the significant safety concerns, the Division encouraged the Sponsor to further characterize the responders, particularly those patients with more severe HSDD in whom a favorable risk/benefit profile can be more readily demonstrated.

### **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?*

**FDA Response to Question 2**

See the response to Question 1.

**Question 3:**

*Do the Office and Division agree that the FSFI is a validated PRO instrument that can be used to establish efficacy based on changes in desire?*

**FDA Response to Question 3**

We recommend that the selection or development of instruments be based upon the good principles of instrument development (outlined in the PRO Guidance). If an instrument without sufficient content validity is used and the observed treatment effects are modest, as demonstrated in the flibanserin trials, it is difficult to discern which element – the instrument or the product – contributed to the modest effects.

**Regarding establishing content validity of FSFI:**

We recognize that there are published studies which have attempted to assess content validity of the Female Sexual Function Index (FSFI) as well as the FSFI desire domain. However, we continue to believe that it is problematic to use the FSFI total score to evaluate female sexual function and to use FSFI desire domain to evaluate changes in desire.

Upon further review of the individual transcripts, it appears that in Revicki et al., 2011, a few open-ended questions were asked at the beginning of the cognitive debriefing interviews, prior to instrument administration. 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.

Based on your question, it appears that you are asking about the total FSFI score as a validated instrument for evaluating desire. Based on this understanding, our following comments pertain to the entire 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.

**Discussion at the meeting:**

We stated our continued concern that, in the literature provided (e.g., Revicki 2011), the concept elicitation for sexual desire is incomplete. We also expressed concern over the discrepant results from two validation studies reported in Revicki 2011. Specifically, when

subjects in these studies were asked whether the two FSFI desire domain items reflected all their problems with sexual desire or interest, only 67% of subjects in the first study and 53% of subjects in the second study replied yes. In addition, the FSFI desire domain items are “triple barreled” and may not distinguish among the three concepts embedded in each item (wanting to have a sexual experience, feeling receptive to a partner’s sexual initiation, and thinking or fantasizing about having sex). It is thus difficult to discern which of the three elements is most affected by the drug. For example, with a sedation-inducing product like flibanserin, we wonder whether it is possible that the improvement seen in FSFI desire domain scores may be primarily driven by women “feeling more receptive to the partner’s sexual initiation” due to increased sedation. If such factors are at play, it would be difficult to attribute the treatment effect to improvement in HSDD.

The sponsor asked whether FDA had looked at the concept elicitation in the Rosen 2000 publication. We agreed to review this publication and provide feedback as a post-meeting comment. The Sponsor was informed that irrespective of FDA’s interpretation of data from Rosen 2000, shortcomings in concept elicitation identified in Revicki 2011 and significant concerns about content validity cannot be discounted. Thus, review of Rosen 2000 would not likely change FDA’s conclusion.

**Post-meeting comment:**

We note that the 19-item FSFI questionnaire was developed primarily based on expert panel input and statistical considerations for patients with female sexual arousal disorder (FSAD), not HSDD. Concept elicitation interviews, using open-ended questions to explore patients’ experiences with HSDD as the basis for item generation were not used to develop the FSFI questionnaire. In addition, the methods used to obtain respondent input were not described in the Rosen article; therefore, it is not clear if the methods are adequate or appropriate.

After reviewing additional references that describe some qualitative research, our current view is that the content validity for the FSFI desire domain can be improved. Specifically, our concerns with the FSFI desire domain items include: the use of triple-barreled items (three concepts are included in each of the desire domain items); it is not clear that the desire items comprehensively assess the elements of desire that are important to women in the target population; and it is not clear that the response options are appropriate. Use of the FSFI desire domain, which is not clearly an optimized instrument, will likely increase the difficulty in detecting the true treatment benefit, if one exists. Therefore, we encourage the development of better assessments for use in this context. To further improve the instrument, we encourage evaluating individual components of desire separately, possibly building on the FSFI desire items (e.g., include individual items that specifically ask patients to report on their level of wanting to have a sexual experience, feeling receptive to a partner’s sexual initiation, and thinking or fantasizing about having sex).

**Regarding the appropriateness of the 28-day recall period:**

With respect to the FSFI desire domain items, we note that there is 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 make it more difficult to detect a treatment effect if one exists. Future studies to evaluate female sexual desire may be improved using a shorter recall period. We note that the developmental paradigm of the International Index of Erectile Function (IIEF) is not applicable to flibanserin. The IIEF is intended to measure events that are more discrete and less likely to be subject to issues related to recall. Additionally, we remain unconvinced that the embedded crossover study in Study 511.147 provided sufficient evidence to show that the 28-day and 7-day recalls are interchangeable. We note that the crossover occurred at the end of Study 511.147 such that patients in the crossover study already completed the 28-day recall version multiple times (at 4-5 clinic visits) before being given the modified 7-day version of the two FSFI desire domain items. Therefore, these patients are already familiar with the response options in the 28-day version. If the treatment response had plateaued after an initial improvement, it is possible that these patients may continue to select the same response options on the 7-day version due to habit or memory. This can result in a statistical finding of approximate equivalence on the two versions of the assessment. Consequently, the findings from Study 511.147 do not necessarily provide strong documentation of the appropriateness of using the 7-day and 28 day versions interchangeably.

**Discussion at the meeting:**

The Sponsor continues to believe that 28 day recall for measuring sexual desire is more accurate and meaningful than a shorter recall period. The Division acknowledged that there is uncertainty as to the optimal recall period to measure sexual desire. However, the Division continues to prefer a much shorter recall time frame than 28 days. The Division also noted that the majority of the 2010 Advisory Committee members considered some form of daily measurement to be of greater value than the 28-day recall in assessing desire. The Division stressed that all assertions made by the Sponsor (e.g., that desire is a "state") during the meeting be corroborated by scientific evidence when the Sponsor submits the Complete Response.

**Post-meeting comment:**

We reiterate our strong preference for the use of an electronic diary for the recording of all sexual events, satisfactory sexual events, and desire.

The selection of a recall period is based on many considerations, including: the phenomenon under study, how frequently this phenomenon changes over time, design of the trial intended to assess this phenomenon, dosing frequency of the product likely to affect this phenomenon, and how accurately the chosen efficacy endpoint can capture any changes in this phenomenon. With respect to measuring sexual desire, consider the following: 1) Is the recall period sufficiently short to adequately establish an interpretable relationship between any observed treatment effects and the administration/activity of the drug? 2) Do women conceptualize desire as a steady state with little to no change over a period of weeks or months, or does it change from day to day or over the course of a day?

Because item 1 of the FSFI asks how often a woman feels desire, the instrument itself appears to 1) encourage conceptualizing desire as a feeling that ebbs and flows and 2) imply that it is possible to count discrete occurrences/periods of desire. We acknowledge that it is not yet entirely clear whether “desire” is a discrete event, a steady state, or something in between. We strongly encourage the use of shorter recall periods (e.g., daily), as a longer recall period would likely increase the difficulty in detecting the true treatment benefit, if one exists. Also, importantly, a longer recall period and less frequent assessments would not allow for an understanding of the potential variability of a woman’s desire and how that variability may be impacted by drug treatment.

**Additional PRO instruments:**

If you wish to use an alternative method to capture patient-reported outcomes (use of a PRO instrument or different approach) to measure change in sexual desire, the new method will require validation. We encourage you to seek a separate meeting with the Division and the Study Endpoint and Labeling Development team (SEALD) to discuss any modification of an existing instrument or the design and validation of new instruments.

**Question 4:**

*Do the Office and Division agree that any reduction in efficacy with co-administration of flibanserin with CYP3A4 inducers can be managed via the flibanserin prescribing information?*

**FDA Response to Question 4**

Yes, the likely reduction in efficacy when flibanserin is co-administered with CYP3A4 inducers could be managed by labeling.

**SAFETY**

**Question 5**

*Do the Office and Division agree that any potential risks associated with alcohol co-administration can be adequately managed via the flibanserin prescribing information?*

**FDA Response to Question 5**

You propose labeling that states that “ (b) (4)

(b) (4) We question the practicality of having patients indefinitely avoid alcohol in the evening hours while chronically taking flibanserin. In addition, (b) (4), we note the concerning episodes of hypotension requiring medical intervention in the alcohol interaction study, which supports the possibility of such events occurring with widespread use of flibanserin.

**Question 6**

*Do the Office and Division agree that any potential risks associated with the co-administration of flibanserin with strong or moderate CYP3A4 inhibitors can be adequately managed via the flibanserin prescribing information?*

**FDA Response to Question 6**

At this time, in light of the overall risk/benefit profile, we believe the risk of concerning adverse events (e.g., hypotension) associated with the flibanserin-CYP3A4 interaction is significant enough in light of the modest benefit of flibanserin such that labeling alone is insufficient to ensure that the benefits outweigh the risk. We note your comment about these adverse events in Studies 511.111 and SPR-12-01 not being consistent with the phase 3 program and have the following additional comments:

- We acknowledge that 30 subjects in study 511.147 took a CYP3A4 inhibitor of some type during the course of the study, and that adverse events occurring in those subjects were not significantly different between flibanserin and placebo subjects. However, CYP3A4 administration was topical in four of those subjects and in those receiving oral administration, treatment duration was brief (single dose up to 10 days). Therefore, there are insufficient clinical safety data at this time to mitigate our concerns over flibanserin co-administered with CYP3A4 inhibitors.
- In the four Phase 3 studies conducted by the previous NDA holder (Boehringer Ingelheim), CYP3A4 inhibitors were prohibited except in rare circumstances. Therefore, the absence of adverse events related to interaction with CYP3A4 inhibitors in the Phase 3 trials does not obviate the findings of studies SPR-12-01 and 511.111.
- Other products you reference in your briefing package that address interaction with CYP3A4 inhibitors in labeling have different overall risk/benefit profiles than flibanserin. We cannot conclude that applying the same labeling decisions for those drug products to flibanserin will ensure that the benefits of flibanserin outweigh its risks. Refer to our General Comments.

**Discussion at the meeting:**

The Sponsor referenced two products, the alpha-1-antagonists alfuzosin and silodosin, both approved by the Division and indicated for a non-life-threatening indication (benign prostatic hyperplasia), that contain a contraindication for concomitant use with CYP3A4 inhibitors in their respective labels. Furthermore, alfuzosin and silodosin are also associated with hypotension and syncope. The Sponsor asserted that, approval of both drugs was based on a patient-reported outcome efficacy measure (the International Prostate Symptom Score or IPSS) and placebo-adjusted efficacy results appeared modest. Therefore, in the Sponsor's opinion, the Division's conclusion that "flibanserin-CYP3A4 interaction is significant enough in light of the modest benefit of flibanserin such that labeling alone is insufficient to ensure that the benefits outweigh the risk" does not seem consistent with the action taken for silodosin and alfuzosin, two drugs considered by the Sponsor to have a similar risk/benefit profile as flibanserin. The Division stated that the CYP3A4 interaction and the risk of hypotension were not the only safety concerns identified for flibanserin. Furthermore, unlike silodosin and alfuzosin, flibanserin is a new molecular entity (NME) for a novel indication, and if approved, would be the first in its class. The Sponsor was asked if consideration had been given to a Risk Evaluation Mitigation Strategy (REMS) or restricted distribution. In response, the Sponsor stated that they plan on a limited product launch and a communication plan directed at potential prescribers, and do not believe that any form of a restricted distribution is warranted.

**Post-meeting comment:**

With regard to the comparison made of flibanserin to the approved alpha-1-adrenergic receptor blockers alfuzosin and silodosin, we note the following:

- Flibanserin has numerous additional safety concerns, including a significant interaction with alcohol, a risk of central nervous system depression and accidental injury, and a possible association with appendicitis.
- Use of silodosin and alfuzosin is contraindicated with strong CYP3A4 inhibitors only. In contrast, the co-administration of flibanserin with a strong or moderate CYP3A4 inhibitor resulted in a significant increase in flibanserin exposure and, in turn, was associated with considerably more adverse events such as fatigue and hypotension, compared with flibanserin alone.
- Hypotension associated with alpha-1 adrenergic antagonists such as silodosin is primarily related to postural changes following the initial doses.
- Alfuzosin and silodosin were not NMEs when they were approved. The adverse event profiles of alpha-1 adrenergic antagonists in general were already well-recognized by both prescribing clinicians and patients.
- The increased incidence of adverse events when flibanserin and hormonal contraceptives are co-administered suggests there is an interaction with mild CYP3A4 inhibitors as well. Given the number of products with any CYP3A4 inhibitory activity (mild, moderate, or strong), we believe that the potential for a clinically significant drug interaction with flibanserin is great and may not be easily avoided (for example, practitioners may be unfamiliar with metabolic pathways of drugs they are prescribing).
- As indicated in our Complete Response letter, the Sponsor has not fully elucidated the metabolic pathways for flibanserin; therefore, the extent of drug-drug interactions with flibanserin is likely to be more significant and will involve drugs other than CYP3A4 inhibitors.
- To ensure that appropriate patients are treated and adequately informed of the risks, administration of the product could be proposed as one component of a comprehensive psychological intervention by healthcare professionals trained in HSDD or sex therapy. The sponsor is encouraged to develop such a proposal and provide it in the Complete Response.

**Question 7**

*Do the Office and Division agree that any potential risks associated with hormonal contraceptive co-administration can be adequately managed via the flibanserin prescribing information?*

**FDA Response to Question 7**

It is likely that many premenopausal women using flibanserin would also be taking hormonal contraceptives. It is possible that labeling may address the risks in this setting but one concern would be the potential for additive adverse effects in the setting of other intrinsic/extrinsic factors that further increase flibanserin exposures.

**Question 8**

*Do the Office and Division agree that the any potential risk of accidental injury and/or next-day impairment have been adequately characterized? Do the Office and Division agree that such potential risks can be adequately managed via the flibanserin prescribing information?*

**FDA Response to Question 8**

No. We do not believe that next-day impairment has been adequately characterized and have the following comments:

- We acknowledge your reference to Study 511.3, which assessed the pharmacokinetics, pharmacodynamics, and safety of flibanserin using Choice reaction Time (CRT). However, as we noted in the Complete Response letter, Study 511.3 was not adequately designed to exclude impairment at time points beyond 4 hours post-dose.
- We do not believe that results of Study 511.10 adequately support your conclusion that flibanserin does not affect CRT at later time points (i.e. beyond 4 hours post-dose). Regarding the 74% vs. 37% difference for sedation reports in association with reports of injury mentioned in the Complete Response letter, we used the following analysis method:
- We searched the Phase 3 placebo-controlled pre-menopausal HSDD database for adverse events coding to the MedDRA version 11.1 *Accidents and Injury* SMQ.
- We then searched for adverse event preferred terms of *dizziness, somnolence, fatigue, hypotension, circulatory collapse, or sedation* and noted the start and end dates of these adverse events. Where there was overlap between the event of accidental injury and one of the “sedation” preferred terms, we considered a possible association between the two events. In other words, the injury had to occur between the onset date and end date of the “sedation” preferred terms. At this time, we do not believe that labeling for accidental injury will ensure that the benefit of flibanserin outweighs its risks.

**Discussion at the meeting:**

The Sponsor stated that they were still unable to duplicate the Division’s findings regarding events of sedation overlapping with accidental injury. The Division stated that the purpose of the analysis was to try to determine the reason for the numerically greater incidence of accidental injury in flibanserin-treated subjects. Nevertheless, the Division’s and the Sponsor’s analyses showed a similar magnitude of imbalance (about a two-fold difference) between the flibanserin 100 mg and placebo-treated subjects with respect to accidental injuries related to sedation. Incidences of injuries related to sedation in the Phase 3 program, as seen in Table 3 in the Sponsor’s briefing package were 18.2% and 10.4% in subjects treated with 100 mg flibanserin and placebo, respectively.

The Sponsor asked whether flibanserin would remain a viable product should a driving study indicate impairment. The Division replied that a positive study would not necessarily preclude approval of the drug. However, the results of such a study would be factored into the overall risk/benefit analysis and, should the drug be approved, would inform final labeling. The Division recommended that the Sponsor submit a protocol for the driving study for FDA review and comment.

**Question 9**

*Do the Office and Division agree that cases of appendicitis can be presented in the flibanserin prescribing information and further information gathered post approval? We note the statement that such risks may be a class effect. What information can you share to help us better understand the basis for this statement?*

**FDA Response to Question 9**

We believe that the reports of appendicitis may represent a class effect of drugs with 5HT2A receptor antagonist properties. Should flibanserin be approved in the future, and in the absence of new data addressing this risk, we will request inclusion of the appendicitis data in the prescribing information. We agree that further information could be gathered post-approval.

**Question 10**

*Do the Office and the Division concur* (b) (4)

(b) (4)

**FDA Response to Question 10**

(b) (4)

No, we do not agree. (b) (4)

(b) (4)

**CLINICAL PHARMACOLOGY**

**Question 11**

*Do the Office and Division agree that the drug interaction studies described can be appropriately reflected in the flibanserin approved prescribing information with warning/precaution to prescribers to not use flibanserin in patients prescribed strong or*

*moderate CYP3A4 inhibitors as previously suggested? If no, can the Division discuss other language that would be sufficient?*

**FDA Response to Question 11**

See our response to Question 6. In addition, information on drug interactions with flibanserin is incomplete because you have not identified enzymes other CYP3A4 that may contribute to the metabolism of flibanserin. We are unclear as to how you are conducting a cross-study comparison of Studies 511.111 and SPR-12-01. Generally, a fold change due to a drug-drug interaction is calculated based upon a comparison to a control group within the same study, not between studies. As we noted earlier, fluconazole is identified as an inhibitor of multiple enzymes - CYP3A4 (moderate), CYP2C9 (moderate) and CYP2C19 (strong) - according to the FDA Draft Guidance for Industry: Drug Interactions – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations (February 2012). The *in vivo* study results suggest that CYP2C9 and/or CYP2C19 may be involved in the metabolism of flibanserin. You should identify enzymes other than CYP3A4 that potentially contribute to the metabolism of flibanserin.

**Discussion at the meeting:**

The Sponsor indicated that they have not decided on their approach to addressing the Division's concern of other metabolizing enzymes.

**Question 12**

*Do the Office and Division agree that the digoxin/flibanserin drug interaction study provides adequate information to inform the flibanserin labeling?*

**FDA Response to Question 12**

Yes, the interaction between digoxin and flibanserin may be conveyed in the product label. However, we disagree with your interpretation of the data. Digoxin exposure increased by 46%, 25%, 62% and 96% for C<sub>max</sub>, AUC<sub>0-24</sub>, AUC<sub>0-72</sub>, and AUC<sub>0-inf</sub>, respectively, following multiple doses of flibanserin 100 mg co-administered with a single dose of digoxin 0.5 mg. A 2-fold increase in digoxin AUC suggests flibanserin may be a P-gp inhibitor. Due to the narrow margin for efficacy and safety, this increase in digoxin systemic exposure can result in digoxin toxicity from the same digoxin dose that had previously maintained appropriate digoxin concentrations. You claim that the shape of the digoxin plasma concentration-time profiles were similar for both treatment groups and conclude that the increase in digoxin exposure is moderate based upon digoxin AUC<sub>0-24</sub> (25% increase). You state that flibanserin transport is not mediated via P-gp because an 8% reduction in digoxin renal clearance (CL<sub>R,0-24</sub>) was observed and was considered not relevant. We do not agree that digoxin clearance is unaffected by flibanserin. Although the shapes of the pharmacokinetic profiles are similar, there is clearly an increase in digoxin exposure when flibanserin is administered with digoxin. Based upon digoxin AUC<sub>0-inf</sub>, not AUC<sub>0-24</sub>, digoxin exposure increases by 96% with flibanserin administration. Digoxin C<sub>max</sub> increased by 46%. The 8% reduction in digoxin renal clearance is based upon urine samples calculated from 0 to 24 hours. Based upon figure 11.5.2.2:1 of Study 511.158, the reduction in digoxin renal clearance with flibanserin administration appears to be greater at 72 hours. Finally, use of C<sub>max</sub> and AUC ratios are a more direct and sensitive assessment of the clinical drug interaction between flibanserin and digoxin compared to the renal clearance ratio due to the

nature of the sample collection (plasma versus urine). In summary, the *in vivo* study with flibanserin + digoxin co-administration suggests that P-gp is involved with flibanserin transport.

### PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

### ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting minutes to Sponsor	FDA	December 18, 2013

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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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CHRISTINA Y CHANG  
12/21/2013



NDA 22526

**ACKNOWLEDGE –  
FORMAL DISPUTE RESOLUTION REQUEST  
AND MEETING GRANTED**

Sprout Pharmaceuticals, Inc.  
Attention: Richard Davan  
Director, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Mr. Davan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We acknowledge receipt on December 3, 2013, of your December 3, 2013, request for formal dispute resolution concerning the Complete Response letter dated September 27, 2013, specifically that the treatment benefits observed in flibanserin do not outweigh the substantial safety concerns.

Your appeal has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. In your appeal, you requested a meeting to discuss the matter. We are granting your meeting request. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type A.

**The meeting is scheduled as follows:**

**Date:** January 10, 2014  
**Time:** 3:00-4:30 pm EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1419  
Silver Spring, Maryland 20903  
Or  
**Phone Arrangements:** 1-866-833-9224  
Passcode: (b) (4)

**Invited CDER Participants**

**Center for Drug Evaluation and Research**

Robert Temple, MD Deputy Center Director for Clinical Sciences

**Office of New Drugs**

John Jenkins, MD Office Director  
RADM Sandra L. Kweder, MD Deputy Office Director  
Amy Bertha Formal Dispute Resolution Project Manager

Khushboo Sharma, MBA	Sr. Regulatory Health Project Manager, Regulatory Affairs Team
Elektra Papdopoulos, MD, MPH	Endpoint Reviewer, Study Endpoint and Labeling Development Team (SEALD)
Ashley Slagle, Ph.D., MS	ORISE Fellow, SEALD

**Office of Drug Evaluation III (ODE III)**

Julie Beitz, MD	Office Director
Maria R. Walsh, RN, MS	Associate Director for Regulatory Affairs
Giuseppe Randazzo, MS	Regulatory Scientist

**ODE III/ Division of Bone Reproductive and Urologic Products**

Hylton V. Joffe, MD, MMSc	Director
Audrey Gassman, MD	Deputy Director
Christina Change, MD, MPH	Clinical Team Leader
Daniel Davis, MD	Medical Officer
Olivia Easley, MD	Medical Officer
Alex Jordan, PhD	Toxicology Team Leader
Jennifer Mercier	Chief, Project Management Staff
Charlene Williamson	Regulatory Health Project Manager

**Office of Drug Evaluation I/ Division of Neurology Products**

Ronald Farkas, MD	Clinical Team Leader
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**Office of Translational Sciences/ Office of Clinical Pharmacology**

Edward Bashaw, Ph.D.	Division Director
Hae Young, Ahn, Ph.D.	Supervisory Pharmacologist
Myong-Jin Kim, Pharm.D.	Pharmacology Team Leader
LaiMing Lee, Ph.D.	Clinical Pharmacology Reviewer

**Office of Translational Sciences/Office of Biostatistics**

Lisa LaVange, PhD	Office Director
Stephen Wilson, PhD	Division Director
Mahboob Sobhan, PhD	Statistical Team Leader
Kate Dwyer, PhD	Statistician

**Office of Center Director/ Control Substance Staff**

Katherine Bonson, PhD	Pharmacologist
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Please e-mail Khushboo Sharma any updates to your attendees at [Khushboo.sharma@fda.hhs.gov](mailto:Khushboo.sharma@fda.hhs.gov) at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Khushboo Sharma at x6-1270.

A response will be provided within 30 days of the meeting date (February 9, 2014). We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796-1647.

Sincerely,

*{See appended electronic signature page}*

Amy Bertha  
Formal Dispute Resolution Project Manager  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form



**FOREIGN VISITOR DATA REQUEST FORM**

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Khushboo Sharma Sr. Regulatory Project Manager, OND Bldg 22, Rm 1419 301-796-1270
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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AMY E BERTHA  
12/17/2013

**Food and Drug Administration (FDA)**  
**Center for Drug Evaluation and Research (CDER)**  
**Office of New Drugs (OND)**  
**Office of Drug Evaluation (ODE) III**  
**Division of Bone, Reproductive, and Urologic Products (DBRUP)**

**Clinical Memorandum**

**September 17, 2015**

To: NDA 022526

From: Christina Chang, M.D., M.P.H. – Clinical Team Leader, DBRUP

Through: Hylton Joffe, M.D., M.M.Sc. – Division Director, DBRUP

This memorandum serves to amend information contained in the September 27, 2013 Complete Response Letter (CRL), and related reviews.

In the CRL, item 1d under the **Clinical Safety** section documents the Division’s assessment concerning the incidences of accidental injuries temporally related to sedation that were observed in the Phase 3 clinical program for both flibanserin and placebo. Item 1d states:

“Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (74% vs. 37%).”

Based on further communication with the Applicant and re-analysis of the data, the Division determined that the two percentages stated in this paragraph and in the related reviews were incorrect. The paragraph should state:

“Flibanserin 100 mg nightly appears to be associated with an increased frequency of adverse events of hypotension, syncope and accidental injury, including reports of severe events. Although the phase 3 program is not large enough to assess the risk of major injury (e.g., motor vehicle accidents), sedation was reported more commonly in association with reports of injury in flibanserin-treated subjects as compared to placebo-treated subjects (**21% vs. 6%**).”

The revised percentages also apply to the corresponding text in the related reviews. The correct information is conveyed in the final, approved labeling.

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/s/  
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CHRISTINA Y CHANG  
09/17/2015

HYLTON V JOFFE  
09/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022526

**MEETING PRELIMINARY COMMENTS**

Sprout Pharmaceuticals, Inc.  
Attention: Richard A. Davan  
Director, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Mr. Davan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets 100 mg.

We also refer to your October 1, 2013, correspondence, requesting an End-of-Review/Post-Action meeting to discuss your Complete Response letter dated September 27, 2013.

Our preliminary responses to your meeting questions are enclosed.

You should provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Project Manager  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** A  
**Meeting Category:** End-of Review/Post-Action Meeting

**Meeting Date and Time:** November 18, 2013 – 1:00 PM – 2:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue, Bldg. 22 Room 1315  
Silver Spring, MD 20993

**Application Number:** 022526  
**Product Name:** Flibanserin Tablets  
**Indication:** Treatment of hypoactive sexual desire disorder in premenopausal women

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

**INTRODUCTION:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 18, 2013, 1:00 PM – 2:00 PM, 10903 New Hampshire Avenue, Bldg. 22 Room 1315, Silver Spring, MD 20993 between Sprout Pharmaceuticals, Inc., and the Division of Bone, Reproductive and Urologic Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

**BACKGROUND**

Flibanserin is a post-synaptic 5-HT<sub>1A</sub> receptor agonist and 5-HT<sub>2A</sub> receptor antagonist that has been evaluated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women. The first NDA submission was not approved. On March 29, 2013, Sprout Pharmaceuticals, Inc. submitted a Complete Response to address the deficiencies outlined in the August 27, 2010 Complete Response Letter.

The Division issued a second Complete Response on September 27, 2013. The deficiencies cited include efficacy, safety, and clinical pharmacology issues. The Applicant requested an End-of-

Review/Post-Action meeting on October 1, 2013, to discuss the path forward for the NDA. The meeting is scheduled for November 18, 2013.

## **GENERAL COMMENTS**

We continue to believe that the efficacy of flibanserin, while statistically significant over placebo, is modest in the population of premenopausal women that was studied. We remain skeptical that the treatment benefit observed with flibanserin is sufficient to offset the substantial safety concerns. As we discussed in the September 27, 2013, Complete Response letter, should you choose to submit a Complete Response, we intend to bring your application to advisory committee for advice on whether the demonstrated benefits of treatment with flibanserin outweigh the risks associated with its use in the proposed target population.

We also recognize that some of the individual safety issues with flibanserin that we have identified may have been managed with labeling for other products. However, our concerns for flibanserin are based on the totality of the safety data balanced against the modest efficacy findings. The other products you reference in your meeting package have different risk/benefit profiles (e.g., amenable to a PRN dosing regimen, indicated for a life-threatening clinical condition, shown to have substantial efficacy in the target population, etc.). Therefore, those labeling decisions cannot be used to conclude that similar labeling for flibanserin will ensure that the benefits of flibanserin outweigh its risks.

## **EFFICACY**

### **Question 1**

*Do the Office and Division agree that the NDA contains substantial evidence of the efficacy of flibanserin in the treatment of HSDD in premenopausal women?*

### **FDA Response to Question 1**

We acknowledge that your NDA contains clinical trials which demonstrated that flibanserin statistically outperformed placebo in the treatment of HSDD in premenopausal women. We also recognize that these trials indicated that, relative to placebo, more patients treated with flibanserin perceived their improvement to be clinically meaningful. However, we reiterate that the data in your NDA support only a modest effect of flibanserin on HSDD.

A possible path forward would be to study a population of women with more severe HSDD in whom a more favorable benefit/risk profile can be demonstrated. Flibanserin should be assessed in such a population in a new placebo-controlled Phase 3 trial. Greater severity of the HSDD may be manifested either as profoundly reduced sexual desire or fewer episodes of satisfying sexual events (SSEs) at baseline. We recommend that you consider having an upper limit on the number of baseline satisfying sexual events as an enrollment criterion. In the three pivotal trials, we note that 10% of subjects reported > 6 SSEs/month at baseline, and 2.4% of subjects reported  $\geq 9$  SSEs/month at baseline. The maximum numbers of SSEs reported by any subject were 34, 16, and 23 per month, in Studies 511.147, 511.71, and 511.75, respectively. We are not convinced that a median increase of 1 or fewer SSEs/month (as

shown across your phase 3 trials) is sufficient to offset the substantial safety concerns in all HSDD patients.

**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?*

**FDA Response to Question 2**

See the response to Question 1.

**Question 3:**

*Do the Office and Division agree that the FSFI is a validated PRO instrument that can be used to establish efficacy based on changes in desire?*

**FDA Response to Question 3**

We recommend that the selection or development of instruments be based upon the good principles of instrument development (outlined in the PRO Guidance). If an instrument without sufficient content validity is used and the observed treatment effects are modest, as demonstrated in the flibanserin trials, it is difficult to discern which element – the instrument or the product – contributed to the modest effects.

**Regarding establishing content validity of FSFI:**

We recognize that there are published studies which have attempted to assess content validity of the Female Sexual Function Index (FSFI) as well as the FSFI desire domain. However, we continue to believe that it is problematic to use the FSFI total score to evaluate female sexual function and to use FSFI desire domain to evaluate changes in desire.

Upon further review of the individual transcripts, it appears that in Revicki et al., 2011, a few open-ended questions were asked at the beginning of the cognitive debriefing interviews, prior to instrument administration. 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.

Based on your question, it appears that you are asking about the total FSFI score as a validated instrument for evaluating desire. Based on this understanding, our following comments pertain to the entire 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.

**Regarding the appropriateness of the 28-day recall period:**

With respect to the FSFI desire domain items, we note that there is 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 make it more difficult to detect a treatment effect if one exists. Future studies to evaluate female sexual desire may be improved using a shorter recall period.

We note that the developmental paradigm of the International Index of Erectile Function (IIEF) is not applicable to flibanserin. The IIEF is intended to measure events that are more discrete and less likely to be subject to issues related to recall. Additionally, we remain unconvinced that the embedded crossover study in Study 511.147 provided sufficient evidence to show that the 28-day and 7-day recalls are interchangeable. We note that the crossover occurred at the end of Study 511.147 such that patients in the crossover study already completed the 28-day recall version multiple times (at 4-5 clinic visits) before being given the modified 7-day version of the two FSFI desire domain items. Therefore, these patients are already familiar with the response options in the 28-day version. If the treatment response had plateaued after an initial improvement, it is possible that these patients may continue to select the same response options on the 7-day version due to habit or memory. This can result in a statistical finding of approximate equivalence on the two versions of the assessment. Consequently, the findings from Study 511.147 do not necessarily provide strong documentation of the appropriateness of using the 7-day and 28 day versions interchangeably.

**Additional PRO instruments:**

If you wish to use an alternative method to capture patient-reported outcomes (use of a PRO instrument or different approach) to measure change in sexual desire, the new method will require validation. We encourage you to seek a separate meeting with the Division and the Study Endpoint and Labeling Development team (SEALD) to discuss any modification of an existing instrument or the design and validation of new instruments.

**Question 4:**

*Do the Office and Division agree that any reduction in efficacy with co-administration of flibanserin with CYP3A4 inducers can be managed via the flibanserin prescribing information?*

**FDA Response to Question 4**

Yes, the likely reduction in efficacy when flibanserin is co-administered with CYP3A4 inducers could be managed by labeling.

## **SAFETY**

### **Question 5**

*Do the Office and Division agree that any potential risks associated with alcohol co-administration can be adequately managed via the flibanserin prescribing information?*

### **FDA Response to Question 5**

You propose labeling that states that (b) (4)

(b) (4) We question the practicality of having patients indefinitely avoid alcohol in the evening hours while chronically taking flibanserin. In addition, (b) (4) we note the concerning episodes of hypotension requiring medical intervention in the alcohol interaction study, which supports the possibility of such events occurring with widespread use of flibanserin.

### **Question 6**

*Do the Office and Division agree that any potential risks associated with the co-administration of flibanserin with strong or moderate CYP3A4 inhibitors can be adequately managed via the flibanserin prescribing information?*

### **FDA Response to Question 6**

At this time, in light of the overall risk/benefit profile, we believe the risk of concerning adverse events (e.g., hypotension) associated with the flibanserin-CYP3A4 interaction is significant enough in light of the modest benefit of flibanserin such that labeling alone is insufficient to ensure that the benefits outweigh the risk.

We note your comment about these adverse events in Studies 511.111 and SPR-12-01 not being consistent with the phase 3 program and have the following additional comments:

- We acknowledge that 30 subjects in study 511.147 took a CYP3A4 inhibitor of some type during the course of the study, and that adverse events occurring in those subjects were not significantly different between flibanserin and placebo subjects. However, CYP3A4 administration was topical in four of those subjects and in those receiving oral administration, treatment duration was brief (single dose up to 10 days). Therefore, there are insufficient clinical safety data at this time to mitigate our concerns over flibanserin co-administered with CYP3A4 inhibitors.
- In the four Phase 3 studies conducted by the previous NDA holder (Boehringer Ingelheim), CYP3A4 inhibitors were prohibited except in rare circumstances. Therefore, the absence of adverse events related to interaction with CYP3A4 inhibitors in the Phase 3 trials does not obviate the findings of studies SPR-12-01 and 511.111.
- Other products you reference in your briefing package that address interaction with CYP3A4 inhibitors in labeling have different overall risk/benefit profiles than flibanserin. We cannot conclude that applying the same labeling decisions for those drug products to flibanserin will ensure that the benefits of flibanserin outweigh its risks. Refer to our General Comments.

**Question 7**

*Do the Office and Division agree that any potential risks associated with hormonal contraceptive co-administration can be adequately managed via the flibanserin prescribing information?*

**FDA Response to Question 7**

It is likely that many premenopausal women using flibanserin would also be taking hormonal contraceptives. It is possible that labeling may address the risks in this setting but one concern would be the potential for additive adverse effects in the setting of other intrinsic/extrinsic factors that further increase flibanserin exposures.

**Question 8**

*Do the Office and Division agree that the any potential risk of accidental injury and/or next-day impairment have been adequately characterized? Do the Office and Division agree that such potential risks can be adequately managed via the flibanserin prescribing information?*

**FDA Response to Question 8**

No. We do not believe that next-day impairment has been adequately characterized and have the following comments:

- We acknowledge your reference to Study 511.3, which assessed the pharmacokinetics, pharmacodynamics, and safety of flibanserin using Choice reaction Time (CRT). However, as we noted in the Complete Response letter, Study 511.3 was not adequately designed to exclude impairment at time points beyond 4 hours post-dose.
- We do not believe that results of Study 511.10 adequately support your conclusion that flibanserin does not affect CRT at later time points (i.e. beyond 4 hours post-dose).

Regarding the 74% vs. 37% difference for sedation reports in association with reports of injury mentioned in the Complete Response letter, we used the following analysis method:

- We searched the Phase 3 placebo-controlled pre-menopausal HSDD database for adverse events coding to the MedDRA version 11.1 *Accidents and Injury* SMQ.
- We then searched for adverse event preferred terms of *dizziness, somnolence, fatigue, hypotension, circulatory collapse, or sedation* and noted the start and end dates of these adverse events. Where there was overlap between the event of accidental injury and one of the “sedation” preferred terms, we considered a possible association between the two events. In other words, the injury had to occur between the onset date and end date of the “sedation” preferred terms.

At this time, we do not believe that labeling for accidental injury will ensure that the benefit of flibanserin outweighs its risks.

**Question 9**

*Do the Office and Division agree that cases of appendicitis can be presented in the flibanserin prescribing information and further information gathered postapproval? We note the statement that such risks may be a class effect. What information can you share to help us better understand the basis for this statement?*

**FDA Response to Question 9**

We believe that the reports of appendicitis may represent a class effect of drugs with 5HT<sub>2A</sub> receptor antagonist properties.

Should flibanserin be approved in the future, and in the absence of new data addressing this risk, we will request inclusion of the appendicitis data in the prescribing information. We agree that further information could be gathered post-approval.

**Question 10**

*Do the Office and the Division concur*

(b) (4)

(b) (4)

**FDA Response to Question 10**

(b) (4)

No, we do not agree.

(b) (4)

(b) (4)

**CLINICAL PHARMACOLOGY**

**Question 11**

*Do the Office and Division agree that the drug interaction studies described can be appropriately reflected in the flibanserin approved prescribing information with warning/precaution to prescribers to not use flibanserin in patients prescribed strong or moderate CYP3A4 inhibitors as previously suggested? If no, can the Division discuss other language that would be sufficient?*

**FDA Response to Question 11**

See our response to Question 6. In addition, information on drug interactions with flibanserin is incomplete because you have not identified enzymes other than CYP3A4 that may contribute to the metabolism of flibanserin. We are unclear as to how you are conducting a cross-study comparison of Studies 511.111 and SPR-12-01. Generally, a fold change due to a drug-drug interaction is calculated based upon a comparison to a control group within the same study, not between studies.

As we noted earlier, fluconazole is identified as an inhibitor of multiple enzymes - CYP3A4 (moderate), CYP2C9 (moderate) and CYP2C19 (strong) - according to the FDA Draft Guidance for Industry: Drug Interactions – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations (February 2012). The *in vivo* study results suggest that CYP2C9 and/or CYP2C19 may be involved in the metabolism of flibanserin. You should identify enzymes other than CYP3A4 that potentially contribute to the metabolism of flibanserin.

**Question 12**

*Do the Office and Division agree that the digoxin/flibanserin drug interaction study provides adequate information to inform the flibanserin labeling?*

**FDA Response to Question 12**

Yes, the interaction between digoxin and flibanserin may be conveyed in the product label. However, we disagree with your interpretation of the data. Digoxin exposure increased by 46%, 25%, 62% and 96% for C<sub>max</sub>, AUC<sub>0-24</sub>, AUC<sub>0-72</sub>, and AUC<sub>0-inf</sub>, respectively, following multiple doses of flibanserin 100 mg co-administered with a single dose of digoxin 0.5 mg. A 2-fold increase in digoxin AUC suggests flibanserin may be a P-gp inhibitor. Due to the narrow margin for efficacy and safety, this increase in digoxin systemic exposure can result in digoxin toxicity from the same digoxin dose that had previously maintained appropriate digoxin concentrations.

You claim that the shape of the digoxin plasma concentration-time profiles were similar for both treatment groups and conclude that the increase in digoxin exposure is moderate based upon digoxin AUC<sub>0-24</sub> (25% increase). You state that flibanserin transport is not mediated via P-gp because an 8% reduction in digoxin renal clearance (CL<sub>R,0-24</sub>) was observed and was considered not relevant.

We do not agree that digoxin clearance is unaffected by flibanserin. Although the shapes of the pharmacokinetic profiles are similar, there is clearly an increase in digoxin exposure when flibanserin is administered with digoxin. Based upon digoxin AUC<sub>0-inf</sub>, not AUC<sub>0-24</sub>, digoxin exposure increases by 96% with flibanserin administration. Digoxin C<sub>max</sub> increased by 46%. The 8% reduction in digoxin renal clearance is based upon urine samples calculated from 0 to 24 hours. Based upon figure 11.5.2.2:1 of Study 511.158, the reduction in digoxin renal clearance with flibanserin administration appears to be greater at 72 hours. Finally, use of C<sub>max</sub> and AUC ratios are a more direct and sensitive assessment of the clinical drug interaction between flibanserin and digoxin compared to the renal clearance ratio due to the nature of the sample collection (plasma versus urine). In summary, the *in vivo* study with

flibanserin + digoxin co-administration suggests that P-gp is involved with flibanserin transport.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

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ZETA-MAE C WILLIAMSON  
11/15/2013

**PeRC PREA Subcommittee Meeting Minutes  
August 7, 2013**

**PeRC Members Attending:**

Wiley Chambers  
Robert "Skip" Nelson  
Patricia Dinndorf  
Tom Smith  
Shrikant Pagay  
William J. Rodriguez  
Martha Nguyen  
Peter Starke  
Ruthanna Davi  
Dianne Murphy  
Kevin Krudys  
Rosemary Addy  
Gilbert Burckart  
Maura O'Leary  
Gregory Reaman  
George Greeley

NON-RESPONSIVE

Karen Davis-Bruno  
Hari Cheryl Sachs

**Guests Attending:**

Amy Taylor (PMHS)	Erica Wynn (PMHS)
Nichella Simms (PMHS)	Julie Bullock (DCPV)
Courtney Suggs (OCP)	Gerold Wharton (OPT)
Melissa Tassinari (PMHS)	Millie Wright (PMHS)
Vicki Moyer (PMHS)	Theresa Finn (CBER)
Philantha Bowen (DPARP)	Susan Limb (DPARP)
Jennifer Pippins (DPARP)	Jianmeng Chen (OCP)
George Shashaty (DHP)	Janet Higgins (DHP)
Janice Brown (CMC)	Kathy Robie Suh (DHP)
Ethan Hausman (PMHS)	Erica Radden (PMHS)

**Agenda**

NON-RESPONSIVE

NDA 22526                      Addyi Tablets (Flibanserin) Full Waiver

NON-RESPONSIVE

**Addyi Full Waiver**

- NDA 22526, Addyi (flibanserin) tablet, was studied for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.
- The application was submitted on March 29, 2013 and has a PDUFA goal date of September 29, 2013.
- The application triggers PREA as a new indication.
- A full waiver is being requested because the disease/condition does not exist in pediatric patients.

*PeRC Recommendations:*

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because the disease/condition does not exist in pediatric patients.

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JANE E INGLESE  
10/25/2013



NDA 22526

**MEETING REQUEST GRANTED**

Sprout Pharmaceuticals, Inc.  
Attention: Richard A. Davan  
Director, Regulatory Affair  
4608 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Mr. Davan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flibanserin Tablets.

We also refer to your October 1, 2013, correspondence requesting an End-of-Review/Post-Action meeting to discuss the Complete Response letter dated . Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

**Date:** November 18, 2013  
**Time:** 1:00 PM – 2:00 PM  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22 Conference Room: 1315  
Silver Spring, Maryland 20903

**Invited CDER Participants:**

Julie Beitz, M.D., Office Director, Office of Drug Evaluation III  
Hylton Joffe, M.D., M.M.Sc., Director, Division of Bone, Reproductive and Urologic  
Products (DBRUP)  
Christina Chang, M.D., M.P.H., Clinical Team Leader, DBRUP  
Daniel Davis, M.D., Medical Officer, DBRUP  
Olivia Easley, M.D., Medical Officer, DBRUP  
Alex Jordan, Ph.D., Toxicology Team Leader, DBRUP  
Myong-Jin Kim, Pharm.D., Pharmacology Team Leader, Office of Clinical Pharmacology  
(OCP)  
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, OCP

Donna Christner, CMC Lead, Office of New Drug Quality Assessment (ONDQA)  
Zhengfang Ge, Ph.D., Chemist, ONDQA  
Mahboob Sobhan, Ph.D., Statistical Team Leader, Division of Biostatistics III, (OB III)  
Kate Dwyer, Ph.D., Statistician, OB III  
Katerine Bonson, Ph.D., Pharmacologist, Controlled Substance Staff  
Jennifer Mercier, Chief, Project Management Staff, DBRUP  
Charlene Williamson, Regulatory Project Manager, DBRUP

Please e-mail me any updates to your attendees at [Charlene.williamson@fda.hhs.gov](mailto:Charlene.williamson@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Charlene Williamson – 301-796-1025.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 20 desk copies to me) at least 1 month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by October 18, 2013, we may cancel or reschedule the meeting.

Submit the 20 desk copies to the following address:

Charlene Williamson  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 5332  
10903 New Hampshire Avenue  
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

NDA 22526

Page 3

If you have any questions, call me at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Project Manager  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:

Foreign Visitor Data Request Form

### FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

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ZETA-MAE C WILLIAMSON  
10/15/2013

**PeRC PREA Subcommittee Meeting Minutes  
August 7, 2013**

**PeRC Members Attending:**

Wiley Chambers  
Robert "Skip" Nelson  
Patricia Dinndorf  
Tom Smith  
Shrikant Pagay  
William J. Rodriguez  
Martha Nguyen  
Peter Starke  
Ruthanna Davi  
Dianne Murphy  
Kevin Krudys  
Rosemary Addy  
Gilbert Burckart  
Maura O'Leary  
Gregory Reaman  
George Greelev

NON-RESPONSIVE

Karen Davis-Bruno  
Hari Cheryl Sachs

**Guests Attending:**

Amy Taylor (PMHS)	Erica Wynn (PMHS)
Nichella Simms (PMHS)	Julie Bullock (DCPV)
Courtney Suggs (OCP)	Gerold Wharton (OPT)
Melissa Tassinari (PMHS)	Millie Wright (PMHS)
Vicki Moyer (PMHS)	Theresa Finn (CBER)
Philantha Bowen (DPARP)	Susan Limb (DPARP)
Jennifer Pippins (DPARP)	Jianmeng Chen (OCP)
George Shashaty (DHP)	Janet Higgins (DHP)
Janice Brown (CMC)	Kathy Robie Suh (DHP)
Ethan Hausman (PMHS)	Erica Radden (PMHS)

**Agenda**

NON-RESPONSIVE

NDA 22526

Addyi Tablets (Flibanserin) Full Waiver

NON-RESPONSIVE

**Addyi Full Waiver**

- NDA 22526, Addyi (flibanserin) tablet, was studied for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.
- The application was submitted on March 29, 2013 and has a PDUFA goal date of September 29, 2013.
- The application triggers PREA as a new indication.
- A full waiver is being requested because the disease/condition does not exist in pediatric patients.

*PeRC Recommendations:*

- The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies are impossible or highly impractical because the disease/condition does not exist in pediatric patients.

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/s/  
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GEORGE E GREELEY  
08/22/2013

From: Williamson, Charlene  
Sent: Wednesday, July 10, 2013 9:08 AM  
To: rick davan  
Cc: Williamson, Charlene  
Subject: FW: Flibanserin NDA

Rick,

Please submit the final complete protocol (dated 9-16-10) for Study 511.147, preferably as a Word document.

Thanks

Charlene

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/s/  
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ZETA-MAE C WILLIAMSON  
07/10/2013



NDA 022526

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Sprout Pharmaceuticals, Inc.  
4208 Six Forks Road  
Suite 1010  
Raleigh, NC 27609

ATTENTION: Richard A. Davan  
Director, Regulatory Affairs

Dear Mr. Davan:

Please refer to your New Drug Application (NDA) resubmission dated March 28, 2013, received March 29, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Flibanserin Tablets, 100 mg.

We also refer to your correspondence, dated and received April 10, 2013, requesting review of your proposed proprietary name, Addyi. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Addyi, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 10, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Marcus Cato, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application contact Z. Charlene Williamson, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796- 1025.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
07/09/2013

**From:** [rick davan](#)  
**To:** [Jennings, Kerri-Ann](#)  
**Subject:** RE: NDA 22526 (flibanserin)  
**Date:** Tuesday, June 11, 2013 12:01:33 PM

---

Ms. Jennings,

Just to confirm that I have received the request. We are in the process of responding to a request for additional dissolution data regarding these same batches and anticipate submitting this information by the end of this week. Is it acceptable to include the information to respond to this request in that submission or is it preferred to submit this in a separate sequence?

Best regards,  
Rick

**rick davan** | **director, regulatory affairs**

Sprout Pharmaceuticals, Inc

**p** 919.882.0850 x: 135

**f** 919.882.0855 (b) (6)

**e** [RDavan@sproutpharma.com](mailto:RDavan@sproutpharma.com)

**w** [sproutpharma.com](http://sproutpharma.com)



---

**From:** Jennings, Kerri-Ann [mailto:Kerri-Ann.Jennings@fda.hhs.gov]  
**Sent:** Tuesday, June 11, 2013 11:49 AM  
**To:** rick davan  
**Subject:** NDA 22526 (flibanserin)

Good morning Mr. Davan,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets.

We are reviewing the application and have the following comments and information requests. We request a prompt written response in order to continue evaluation of your NDA.

- Please provide Certificate of Analysis (COA) for drug product batches No. 4001397 (b) (4), including all the tests required in the drug product specification.

Submit an amendment to NDA 22526.

Please confirm receipt of this email.

Thank you.

Regards,

*Kerri-Ann E. Jennings, MS, BSN, RN*  
LT, United States Public Health Service  
Regulatory Health Project Manager  
FDA/CDER/OPS/ONDQA  
Division of New Drug Quality Assessment II  
Phone (301) 796-2919

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/s/  
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KERRI-ANN JENNINGS  
06/11/2013

# REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Neurology Products (DNP)**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Division of Bone, Reproductive and Urologic Products**  
**Attn: Charlene Williamson**

DATE  
May 22, 2013

IND NO.

NDA NO.  
22526

TYPE OF DOCUMENT  
EDR

DATE OF DOCUMENT  
March 29, 2013

NAME OF DRUG  
Flibanserin Tablets

PRIORITY CONSIDERATION  
Priority

CLASSIFICATION OF DRUG  
Antidepressant

DESIRED COMPLETION DATE  
July 15, 2013

NAME OF FIRM: **Sprout Pharmaceuticals, Inc**

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                   |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                          |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                               |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                     |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                              |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER): <b>Class II Resubmission</b> |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

#### COMMENTS / SPECIAL INSTRUCTIONS:

DBRUP has received a resubmission for flibanserin, a 5-HT<sub>1A</sub> agonist and 5-HT<sub>2A</sub> antagonist intended for the treatment of hypoactive female sexual disorder (HSDD) in pre-menopausal women. 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 state is approximately 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 your responses 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?

Please do not hesitate to contact Olivia Easley (primary MO for safety, 6-0884) or Christina Chang (TL, 6-2078) should you have any questions.

SIGNATURE OF REQUESTOR

Charlene Williamson

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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ZETA-MAE C WILLIAMSON  
05/22/2013

**From:** Williamson, Charlene  
**Sent:** Thursday, May 16, 2013 4:36 PM  
**To:** rick davan  
**Cc:** Williamson, Charlene  
**Subject:** RE: Flibanserin Abuse Potential Information Request

Rick,

In current datasets, QSSEQ is the only available related to sequence. For example, the value of QSSEQ is from 1 to 5508 in qsar.xpt. There are 6 sequences in the study (See Table 1 on page 25 in the sponsor's report). The sponsor should include two variables for the treatment sequences. One is SEQ for the sequence number, and the other is TRTSEQ which includes the treatment sequence. For example, a subject took sequence number 3 (CDBEAF), SEQ should be 3, and TRTSEQ should be CDBEAF or list real name of treatments in the sequence. Use the same way to present the data from Qualification Phase.

About treatment period, the information is included in the variable VISIT in the datasets. However, please add a variable PERIOD to indicate the numeric portion of the treatment period. For example, VISIT="Period 1, Day 1", Period=1.

Data submission for future studies, please use ADaM format. Here is a CDISK Analysis Data Model (ADaM) implementation guidance.

<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/Drugs/ComputationalScienceCenter/UCM211175.pdf>

---

**From:** rick davan [mailto:RDavan@sproutpharma.com]  
**Sent:** Thursday, May 16, 2013 11:54 AM  
**To:** Williamson, Charlene  
**Subject:** RE: Flibanserin Abuse Potential Information Request

Charlene,

The data sets for study SPR-12-05 that are referred to in the e-mail are in SDTM format and do not have the treatments included consistent with applicable standards. To respond to this request we will need to submit the following analysis data sets (SAS transport files) for the study:

ADQSAR.XPT  
ADQSDE.XPT  
ADQSHL.XPT  
ADQSSD.XPT

These data sets will be submitted to the NDA as Sequence 0042 by end Monday (5/20/2013). Please do not hesitate to contact me or Jim if there are any questions regarding the information.

Best regards,  
Rick

Reference ID: 3310602

file:///C:/Documents and Settings/williamsonc/Desktop/RE Flibanserin Abuse Potential Information Request htm[5/17/2013 1:30:00 PM]

**rick davan** | director, regulatory affairs

Sprout Pharmaceuticals, Inc

**p** 919.882.0850 x: 135

**f** 919.882.0855 (b) (6)

**e** RDavan@sproutpharma.com

**w** [sproutpharma.com](http://sproutpharma.com)



---

**From:** Williamson, Charlene [mailto:Charlene.Williamson@fda.hhs.gov]

**Sent:** Wednesday, May 15, 2013 7:45 PM

**To:** rick davan

**Cc:** Williamson, Charlene

**Subject:** Flibanserin Abuse Potential Information Request

Rick,

An information request from the Control Substance Staff. Please respond to this request within 3 business days.

Please acknowledge receipt of this email.

Thanks

Charlene

For study SPR-12-05, there are four datasets directly related to the abuse potential measures. These datasets are qsar.xpt, qsde.xpt, qshl.xpt and qssd.xpt. However, two important variables SEQ for indicating 6 sequences used in the study, and TRTNAME for treatments in the study, are not included in these datasets. Please either resubmit these datasets including the variables, SEQ and TRTNAME, or locate the analysis datasets in the submission.

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/s/  
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ZETA-MAE C WILLIAMSON  
05/17/2013

**From:** Williamson, Charlene  
**Sent:** Tuesday, April 30, 2013 5:15 PM  
**To:** rick davan  
**Cc:** Williamson, Charlene  
**Subject:** NDA 22-526 - Information Request  
Rick,

For study 511-114, please provide a summary of treatment-emergent adverse events according to treatment at onset (i.e. shown in Table below).

Frequency [N(%)] of patients with adverse events according to initial treatment

	Placebo	Fli 50 qhs → 100 qhs	Fli 100 qhs
Total N (%)	38 (100)	45 (100)	28 (100)
Preferred term:			

Thanks

Charlene

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/s/  
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ZETA-MAE C WILLIAMSON  
05/05/2013

**From:** Williamson, Charlene  
**Sent:** Wednesday, May 01, 2013 2:37 PM  
**To:** 'rick davan'  
**Cc:** Williamson, Charlene  
**Subject:** NDA 22526 FLIBANSERIN Information Request

Rick,

An statistical Information Request.

Please respond to the following request ASAP, and please acknowledge receipt.

For Study 511.147, please provide all the SAS programs related to your efficacy analyses. These programs should be sufficient to duplicate your study results.

Thanks  
Charlene

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/s/  
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ZETA-MAE C WILLIAMSON  
05/05/2013



NDA 22526

**ACKNOWLEDGE – CLASS 2 RESPONSE**

Sprout Pharmaceuticals, Inc.  
Attention: Richard A. Davan  
Director, Regulatory Affairs  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear Mr. Davan:

We acknowledge receipt on March 29, 2013, of your March 28, 2013, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flibanserin Tablets.

We consider this a complete, class 2 response to our August 27, 2010, action letter. Therefore, the user fee goal date is September 29, 2013.

If you have any questions, call me at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Health Project Management  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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ZETA-MAE C WILLIAMSON  
04/12/2013



NDA 22526

**ACKNOWLEDGE TRANSFER NDA OWNERSHIP**

Sprout Pharmaceuticals, Inc.  
Attention: James Symons, M.S., Ph.D.  
Vice President, Clinical Development  
4208 Six Forks Road, Suite 1010  
Raleigh, NC 27609

Dear: Dr. Symons

We acknowledge the January 23, 2012, receipt of your January 20, 2012, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product:            Flibanserin Tablets 100 mg  
NDA Number:                        22526  
Name of New Applicant:            Sprout Pharmaceuticals, Inc.  
Name of Previous Applicant:       Boehringer Ingelheim Pharmaceuticals, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Sprout Pharmaceuticals, Inc. as the applicant of record for this application.

**DRUG MASTER FILE LOA**

If your NDA references any Drug Master Files (DMF), we request that you notify your suppliers and contractors who have DMFs referenced by your NDA of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s) and send you a copy of the new LOAs. Please submit these copies of the LOAs to this NDA.

**REPORTING REQUIREMENTS**

All changes to the information in the NDA from that described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. However, changes in the name of the manufacturer, packer, or distributor in the drug product's label or labeling may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you

notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new LOA to their DMFs.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 21 CFR 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

CC: Boehringer Ingelheim Pharmaceuticals, Inc.  
Attention: Alexander Rochefort  
Director, Drug Regulatory Affairs  
900 Ridgebury Road, P.O. Box 368  
Ridgefield, CT 06877

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/s/

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ZETA-MAE C WILLIAMSON  
02/17/2012

3 Page(s) have been Withheld in Full  
as b4 (CCI/TS) immediately  
following this page



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022526

MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.  
Attention: Alex Rochefort  
Director, Drug Regulatory Affairs  
900 Ridgebury Road, P.O. Box 368  
Ridgefield, CT 06877

Dear Mr. Rochefort:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets 100 mg.

We also refer to the meeting between representatives of your firm and the FDA on July 22, 2010. The purpose of the meeting was to obtain a clear understanding of the Division's thinking on key issues following the June 18, 2010 meeting of the Advisory Committee for Reproductive Health Drugs that focused on the flibanserin NDA submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Charlene Williamson, Regulatory Project Manager at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** A  
**Meeting Category:** Post-Advisory Committee Meeting  
**Meeting Date and Time:** July 22, 2010  
**Meeting Location:** 10903 New Hampshire Avenue, Bldg. 22 Room 1315  
Silver Spring, MD 20903  
**Application Number:** NDA 022526  
**Product Name:** Flibanserin Tablets 100 mg  
**Indication:** Hypoactive Sexual Desire Disorder in premenopausal women  
**Sponsor/Applicant Name:** Boehringer Ingelheim Pharmaceuticals, Inc.  
**Meeting Chair:** Lisa Soule, M.D.  
**Meeting Recorder:** Charlene Williamson

**FDA ATTENDEES**

Julie Beitz, M.D., Office Director, Office of Drug Evaluation III (ODE III)  
Scott Monroe, M.D., Division Director, Division of Reproductive and Urologic Products (DRUP)  
Lisa Soule, M.D., Clinical Team Leader, DRUP  
Daniel Davis, M.D., Medical Officer, DRUP  
Olivia Easley, M.D., Medical Officer, DRUP  
Jonathan Jarow, M.D., Medical Officer, DRUP  
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology  
Lisa Kammerman, Ph.D., Statistician, Office of Biometrics  
Elisabeth Piau-Louis, Pharm. D., Study Endpoints and Labeling (SEALD)  
Giuseppe Randazzo, R.Ph., Regulatory Scientist, (ODE III)  
Charlene Williamson, Regulatory Project Manager, DRUP

**SPONSOR ATTENDEES**

David Brill, Ph.D., Director, Drug Regulatory Affairs  
Christopher Corsico, M.D., Senior V.P. Medicine and DRA  
Arne Froemder, Ph.D., International Project Management  
Lutz Hilbrich, M.D., Executive Director, General Medicine  
Juergen Reess, M.D., Vice President, Therapeutic Area Head, CNS/General Medicine  
Alexander Rochefort, Director, Drug Regulatory Affairs  
Michael Sand, Ph.D., MPH, Director, Clinical Research, General Medicine

## **BACKGROUND**

The Sponsor requested a Type A Meeting following the discussion at the June 18, 2010 Advisory Committee meeting. The Sponsor would like to obtain an understanding of the Division's thoughts on:

- The acceptability of the FSFI- sexual desire domain to serve as the primary regulatory efficacy endpoint for the desire component of HSDD
- Safety concerns related to flibanserin and possible strategies to address those concerns.

## **SPONSOR'S QUESTIONS AND THE DIVISION'S COMMENTS**

### **Question 1**

*Can the Division accept the FSFI-desire as the primary regulatory endpoint to assess the desire component of HSDD?*

### **Division Response:**

For the current NDA submission, the Division does not accept the FSFI desire items as the primary regulatory endpoint for desire, in accord with the recommendations of the Advisory Committee for Reproductive Health Drugs.

Although the measurement properties of the FSFI sexual desire (FSFI SD) domain using a one-month recall period have been described in the literature using data from the Sponsor's clinical trials with women diagnosed with HSDD, the measure's performance should be evaluated and confirmed in any future studies and in exploratory analyses of the currently ongoing trial.

Additional issues remain unresolved, including:

- Recall period: The validity of data collected using a four-week recall period was not documented.
- Response options: The validity of the FSFI SD response options was not demonstrated. We are not convinced that women can validly report whether they have "always" felt sexual desire or interest over the past four weeks. In addition, examination of the recently submitted cross-tab analyses suggest that patients have difficulties deciphering among options such as "most times," "sometimes," and a "few times."
- Impact of setting and timing of the assessment of sexual desire frequency and intensity: It appears that the FSFI SD was completed during the office visits, after the Beck Depression Inventory questionnaire and the Female Sexual Distress Scale were administered; therefore, it is unclear whether the setting and timing of the completion of the FSFI SD items might have influenced patients' feedback on sexual desire as opposed to similar rating on the eDiary answered privately at home.
- Whether the optimal treatment population has been studied, or whether future studies should be limited to more severely affected subjects

Some other issues might be resolved through analyses of existing trial data. At a minimum, the Division recommends exploring:

- The impact of missing data and the use of LOCF on the results of the FSFI SD analysis

- Exploratory Rasch/IRT analysis of FSFI SD data to determine whether the range of patient experience is adequately captured, and use of other means to assess the properties of the FSFI SD, including its appropriateness for the population of interest, the domain's scoring algorithm, the properties of the scale, and the definition and ordering of the response categories for the items
- Whether other endpoint definitions using data from the eDiary desire item, such as area under the curve (AUC), might be more appropriate compared to the total monthly desire score and whether this would better document patients' experience of sexual desire over the course of a month and within the clinical trial timeframe
- A comparison of FSFI-SD data with eDiary distress data to explore the results of daily recording vs. seven-day recall on evaluation of a mental/emotional state

**Additional Discussion at the Meeting:**

The Sponsor acknowledged that the FSFI SD would not be accepted as the regulatory endpoint for desire in the current NDA submission, but asked for clarification on the path forward for ongoing studies. The Division does not have any *a priori* conclusion as to the optimal instrument for assessing desire. Contingent upon the Applicant demonstrating that the FSFI-SD is a well-developed and reliable instrument with adequate content validity including recall validity, and acceptable measurement properties, the FSFI-SD could be accepted as the co-primary efficacy endpoint for measurement of desire.

The Sponsor noted that the FSFI content validity had been evaluated in two qualitative studies submitted to the current NDA, and asked for guidance as to what specific deficiencies the Division noted. One issue is that it is not clear that the response options "most of the time" and "half the time" are interpreted by subjects in a consistent manner; the cross-tabs analysis provided by the Sponsor indicates that some subjects interpret these responses differently or do not consistently apply these response options. Use of the Rasch analysis may aid in evaluating whether items appropriately capture desire at all response options and for subjects at different baseline severity. In addition, cognitive debriefing about the recall period did not provide empirical data to document that women accurately recall desire after four weeks. The Sponsor proposed including a seven-day recall option in Study 511.147 and evaluating how well desire data based on this recall period correlated with those obtained using a 28-day recall period.

**Post-Meeting Comment:**

The Division understood the Sponsor's question to relate only to the co-primary efficacy endpoint that relates to desire, and this interpretation formed the basis of the Division's response. The Division continues to require that the second co-primary efficacy endpoint of change in satisfactory sexual events (SSEs) be evaluated to support a marketing application for an HSDD product.

An additional question regarding recall period is whether having women assess their level of desire more frequently (e.g., weekly) provides more valid data than a once-monthly query, in which women are asked to recall over the past 28 or 7 days.

**Question 2**

*If the Division accepts the FSFI-desire as the primary regulatory endpoint to assess desire,*

*could data from the ongoing premenopausal study 511.147 potentially address the efficacy concerns raised by the Division?*

*If no, what additional data would be required?*

**Division Response:**

See response to Question 1; the Division has not yet accepted the FSFI-desire items as the appropriate regulatory endpoints to assess desire.

The Sponsor should address the issues in Question 1, and, following review of this information, the Division may be able to provide further guidance as to the value of Study 511.147 in supporting a regulatory submission.

The Division does recommend incorporating the following modifications and additional features to Study 511.147 and/or future efficacy trials:

- Follow all subjects for the full trial duration, even if they discontinue study drug
- Minimize the exclusion criteria and prohibited medications in order to provide data on a study population that will easily generalize to the target market
- Analyze all collected data without linking to study visits
- Evaluate daily recording of desire, but allowing a longer lock-out period (e.g., allow data entry up to 72 hours, rather than limiting to 24-hours as done in the current studies)
- Minimize the impact of recall, setting and timing in patients' assessment using the FSFI SD domain
- Confirm the content validity (i.e., recall period, response options) and psychometric performance of the (modified) FSFI SD, in the targeted population. This will be of particular concern if the FSFI SD is modified (e.g., by changing the recall period).

**Additional Discussion at the Meeting:**

The Sponsor asked whether additional documentation of the psychometric performance of the FSFI in Study 511.147 will constitute adequate evidence of the validity of the FSFI. SEALD noted that documentation of the measurement properties of the instrument using blinded data from phase 3 studies such as Study 511.147 is acceptable. The analyses pertaining to documentation of the psychometric performance of the instrument should be prespecified in the analysis plan; however, they could be positioned as exploratory analyses. The Sponsor is reminded that evaluation of the measurement properties of the FSFI, including the FSFI-SD, should be done on the final instrument, including any modifications made to the recall period.

The Division clarified that bullet 1 above refers to following all subjects for efficacy. The Division has been concerned that, due to high levels of early trial discontinuation mandated by the protocol, as much as 30% of efficacy data in the current NDA was based on LOCF imputation. There was also a disparity in discontinuation rates between flibanserin and placebo arms. The high rate of discontinuations from the study and the disparity between treatment groups makes the interpretation of study results difficult, especially when the treatment effect is modest. The Sponsor suggested that it would not force study discontinuation upon subjects in order to minimize missing data. Women who choose to terminate study treatment early will be encouraged to return for study visits despite discontinuing medication.

Regarding bullet 4, the Sponsor noted that the ongoing Study 511.147 and two studies in postmenopausal women with HSDD do not include daily diary evaluation of sexual desire. However, some of the Division's questions and issues noted above could be evaluated through analysis of existing trial data in which both the eDiary and the FSFI were used. The Sponsor will not be able to evaluate longer lock-out periods for eDiary recording of desire, as the Division had suggested in response to Question 2, but this is not mandatory.

The Sponsor proposed to address bullet 5 (regarding minimizing the impact of timing and setting on FSFI assessment) by randomizing subjects to complete the FSFI at either the start or end of the study visits. SEALD recommended that the FSFI be completed first in the study visit, before the physical exam, discussion with the investigator, or completion of any other questionnaires. Each participating clinical site should be trained accordingly to ensure consistency. The Sponsor will address this with a protocol amendment. Only about 100 subjects have completed Study 511.147, so this amendment can be implemented for most of the study population, and a comparative analysis can be done of responses obtained early in the visit vs. those obtained later.

### **Question 3**

*Following the June 18, 2010 Advisory Committee meeting, what is the Division's current thinking on key safety data/issues that need to be addressed before flibanserin could be approved for the treatment of HSDD?*

### **Division Response:**

The Division believes that the following safety issues need to be addressed pre-approval:

- **Safety in patients with co-morbid conditions or taking concomitant medications:**  
The Division recommends that a placebo-controlled clinical trial of flibanserin be conducted in a broad population of women with HSDD. Exclusion criteria, which were extensive in the clinical trials conducted thus far for the indication, should be limited. For example, women with mild psychiatric conditions, such as depression, should be included, assuming the HSDD is not a function of the underlying psychiatric diagnosis. Subjects taking concomitant medications, including centrally acting drugs such as triptans, should also be enrolled. Data from such a study may facilitate understanding of the safety of flibanserin in the general population of women who suffer from HSDD.

### **Additional Discussion at the Meeting:**

The Sponsor stated that they believe that ongoing Study 511.147, which has less restrictive entry criteria with respect to comorbid conditions and prohibited medications, addresses these concerns. Use of SSRI and SNRI medications is still exclusionary in Study 511.147, but a dedicated study will be performed to address concomitant use of these drugs with flibanserin. Contraception for reproductive aged women is also required, due to the lack of information about fetal safety. Subjects with hepatic impairment continue to be excluded; use of flibanserin in subjects with hepatic impairment would be a contraindication in the label.

The Sponsor proposed to submit a document highlighting the changes in entry criteria and prohibited medications in Study 511.147 as compared to the trials already conducted for the current NDA. The Division stated that such a document would be helpful in

clarifying whether Study 511.147 will help to address the concerns regarding safety of flibanserin in patients with co-morbid conditions and on concomitant medications.

- **Safety with concomitant CYP3A4 inhibitors**

The proposed risk management plan, which includes a drug-drug interaction (DDI) study to evaluate the interaction between flibanserin and moderate CYP3A4 inhibitors, does begin to address the Division's concern regarding drug interactions between flibanserin and CYP3A4 inhibitors.

The Division requests that the Sponsor submit its meta-analysis of women who received flibanserin and oral contraceptives in phase 1 studies. A determination of the need for a drug-drug interaction study between flibanserin and weak CYP3A4 inhibitors will be made following the review of the requested meta-analysis.

**Additional Discussion at the Meeting:**

The Division acknowledged the Sponsor's plan to address CYP3A4 inhibitors, and recommended that a moderate inhibitor to be utilized in the DDI study be selected from the list of examples of moderate CYP3A4 inhibitors in the 2006 draft *Guidance to Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*. The need for a drug interaction study with a weak CYP3A4 inhibitor will be determined based upon review of the meta-analysis report of women using oral contraceptives (a presumed weak CYP3A4 inhibitor) with flibanserin and the review of a drug interaction study with a moderate CYP3A4 inhibitor.

- **Safety with selective serotonin/norepinephrine reuptake inhibitors (SS/NRIs)**

The ongoing phase 3b safety study of flibanserin in women taking an SSRI or SNRI is likely to provide needed clarification on this issue.

- **Risk of depression and accidental injury**

Ongoing and future clinical trials in the HSDD population (both pre- and post-menopausal) should include monitoring for and analysis of the frequency of these adverse events. Special attention should be paid to exacerbation of depression in subjects with a prior history of major depressive disorder (MDD). Data from the SSRI/SNRI safety study is likely to be helpful in clarifying the risk of depression in vulnerable patients.

- **Safety with concomitant alcohol use**

In a clinical trial setting, the effect of simultaneous administration of flibanserin 100 mg with alcohol should be assessed.

**Additional Discussion at the Meeting:**

The Division clarified that the evaluation of concomitant alcohol use could be done as a DDI study, providing pharmacokinetic and adverse event data.

- **Evaluation of risk of syncope**

In order to understand the true risk of syncope in the setting of supra-therapeutic flibanserin exposure, a phase 1 study should be performed in healthy subjects using supra-therapeutic

doses of flibanserin to assess the effect of supra-therapeutic exposure on orthostatic vital signs.

Finally, if this new molecular entity drug is approved in the future, a large post-approval safety study to monitor for less common adverse events will be required.

**Additional Discussion at the Meeting:**

The Sponsor asked for clarification regarding the type of information sought in a post-approval safety study. The Division stated that the goal of a post-marketing study would be to further evaluate the risk of adverse events for which signals were observed in flibanserin trials to date (e.g., suicidality, accidental injury and depression). In addition, a large study will be helpful in determining the risk of less common adverse events that may not have become apparent in the clinical trials completed thus far. Nonclinical data on flibanserin have raised concern about a potential for increased risk of breast cancer (i.e., mammary tumors observed in mice): (b) (4)



**Question 4**

*Does the draft risk management plan begin to address the potential safety concerns highlighted by the Division? What measures in addition to those submitted would help address the concerns?*

**Division Response:**

Please see response to Question 3.

The Division agrees that it will be important to monitor pregnancy and fetal outcomes, and will provide additional comments upon receipt of a more detailed proposal for pregnancy outcome assessment from the Sponsor.

**Additional Discussion at the Meeting:**

The Sponsor is considering a claims database-type pregnancy outcome evaluation and asked if such a method was acceptable. The Division stated that such a proposal seemed reasonable, but a final decision regarding the design of a pregnancy outcome study will be made in consultation with the Office of Surveillance and Epidemiology (OSE). The Sponsor should submit a protocol for such a study, and DRUP will seek advice from OSE.

Action Item/Description	Owner	Due Date
Meeting minutes	FDA	August 21, 2010

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22526

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GI-1

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BOEHRINGER  
INGELHEIM  
PHARMACEUTICA  
LS INC

-----  
FLIBANSERIN

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/s/  
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LISA M SOULE  
08/10/2010

From: Meredith Alpert  
To: 'alex.rochefort@boehringer-ingelheim.com'  
Subject: Information Request

Dear Alex:

Below is an Information Request from the Division:

On May 14, 2010, you submitted "Response to April 29, 2010 Statistical Information Request" (Sequence 0022). The response to Request 6, which asked for an exploratory analysis of the relationship between the outcomes on 'eDiary desire" and on SSEs, includes tables that present the mean SSE for each level of eDiary sexual desire. In these tables, all the mean SSEs are less than one, which are much less than the mean SSEs reported elsewhere in the NDA. For example, the clinical study reports indicate the baseline SSE was close to 3 in Studies 71 and 75. However, the baseline SSEs in the response to Request 6 are less than .5 .

Please explain these inconsistencies in the reported SSEs.

Thank you,

Meredith Alpert, M.S.  
Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of New Drugs  
Division of Reproductive and Urologic Products  
Phone: 301-796-1218, Fax: 301-796-9897  
Email: meredith.alpert@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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MEREDITH H ALPERT  
06/07/2010

**To: 'alex.rochefort@boehringer-ingelheim.com'**

Hi Alex:

Please see attachment for the information we are requesting from your company. We would like to receive the responses by early next week.



6-4-10 Info  
Request for cross ...

Thank you,

Meredith Alpert, M.S.  
Regulatory Health Project Manager  
Center for Drug Evaluation and Research  
Office of New Drugs  
Division of Reproductive and Urologic Products  
Phone: 301-796-1218, Fax: 301-796-9897  
Email: meredith.alpert@fda.hhs.gov

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**Request for analyses:**

In order to compare the 4-week recall period assessment of sexual desire frequency (FSFI desire item 1) and intensity (FSFI desire item 2) to the daily assessment (eDiary Desire item), please provide the following three cross tab tables using actual reported data at week 4. Please repeat this analysis for week 16 and week 24, using both actual reported data and imputation for missing data. This should be done separately for studies 511.71 and 511.75. So this will entail a total of 36 tables.

**eDiary desire item**

Indicate your most intense level of sexual desire...

["in the last 24 hours" for first assessment or if last entry > 24 hours ago] OR

["since your last entry DAY DATE TIME" if last entry < 24 hours ago]

- No desire (0)
- Low desire (1)
- Moderate desire (2)
- Strong desire (3)

**FSFI 4 weeks recall period**

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

**Table I. Frequency cross tab (Women who report desire on the eDiary)\***

Item 1 of the eDiary \ FSFI		FSFI (4-week recall) desire item 1				
		Almost never/never	A few times	Sometimes	Most time	Almost always/ Always
# of Women who report desire (i.e., low desire, moderate desire or strong desire) on the e-Diary item 1	0 to 6 days					
	7 to 12 days					
	13 to 18 days					
	19 to 24 days					
	25 to 28 days					

\* Woman who reports desire (i.e., low desire, moderate desire or strong desire) on the e-Diary item 1 on any day among 28 days of completion

**Table II. Frequency cross tab (Women who report no desire on the eDiary)\***

Item 1 of the eDiary \ FSFI		FSFI (4-week recall) desire item 1				
		Almost never/never	A few times	Sometimes	Most time	Almost always/ Always
# of Women who report <b>no desire</b> on the eDiary item 1	0 to 6 days					
	7 to 12 days					
	13 to 18 days					
	19 to 24 days					
	25 to 28 days					

\* Woman who report no desire on the e-Diary item 1 on any day among 28 days of completion

**Table III. Intensity Cross tab**

		<b>FSFI (4-week recall) desire item 2</b>			
		<b>Very low or none at all</b>	<b>Low</b>	<b>Moderate</b>	<b>High or Very High</b>
<b>e-Diary item 1 (score range 0-84)</b>	<b>0-14</b>				
	<b>15-28</b>				
	<b>29-56</b>				
	<b>57-84</b>				

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLIBANSERIN

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MEREDITH H ALPERT  
06/04/2010

**From:** alex.rochefort@boehringer-ingenelheim.com  
**Sent:** Wednesday, January 20, 2010 2:01 PM  
**To:** Williamson, Charlene  
**Subject:** RE: Flibanserin Tox Study  
Charlene,

For the 13-week oral toxicity study in mice study (study no. 98R002) with corresponding toxicity report U99-3212, the respective toxicokinetic data are given in detail in the associated toxicokinetic report U99-3125. In study no. 98R002 (report U99-3212), only one dose level of 1000 mg/kg/day was investigated (as dietary admixture). Blood samples were taken for exposure profiling (AUC) in week 2 and monitoring (C(t)) in week 13 between approximately 8:00 and 10:00 a.m.

We confirm the flibanserin plasma AUC(0-24h)<sub>ss</sub> values at the dose level of 1000 mg/kg/day of 18.232 µg-h/mL for male and 12.246 µg-h/mL for female mice in week 2 (please refer to the amendment to the toxicity report U99-3212-AM2, page no 7, last two lines and to the toxicokinetic report U99-3125, page no 8, last paragraph, 2nd line).

Regards,

Alex

-----Original Message-----

**From:** Williamson, Charlene [mailto:Charlene.Williamson@fda.hhs.gov]  
**Sent:** Wednesday, January 20, 2010 8:48 AM  
**To:** Rochefort,Alex DRA BIP-US-R  
**Subject:** Flibanserin Tox Study

Alex,

I have a request from the Tox Team, they would like for you to verify the AUC values for the 13 week oral tox in mice, study no. 98R002; document no. U99-3212, in the toxicokinetics section.

I will also be contacting you in a separate email regarding your voice mail.

Thanks

Charlene

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ZETA-MAE C WILLIAMSON  
04/23/2010

**Information Request for the Applicant (4-20-10)**

1. Has Study 511.147 to evaluate the FSFI desire domain as a primary or key secondary endpoint been started yet? If so, how many subjects are receiving treatment and how many have completed the 24-week trial?
2. For Studies 71 and 75, fill in the following table:

	511.71	511.75
# Enrolled (screened)	N= 1,429	N= 2,486
SIDI score > 1	N=	N=
SIDI score = 1	N=	N=
SIDI score = 0	N=	N=

SIDI score 0 meant that subject was dissatisfied with the sexual aspect of the relationship with their partner. SIDI score 1 meant that subject was somewhat dissatisfied with the sexual aspect of the relationship with their partner.

3. We need data of the efficacy findings for women < 35 years old and ≥ 35 in Study 511.71 and 511.75. This topic was mentioned at the pre-NDA meeting held on 10-10-07.
4. What is the status on enrollment (screened and treated), discontinuations, and completers in the Following studies: #147 (premenopausal women), and 130 and 156 (postmenopausal women)?

	511.147	511.130	511.156
# Enrolled (screened)			
# Treated			
# Discontinuations			
# Completers			

5. eDiary compliance values (% of women with compliance) for the sexual desire question for treated subjects: fill in the following table.

	511.71	511.75	511.74
Baseline 26 of 28 days			
Baseline ≥ 21 of 28 days			
Last 4 wks of treatment- 26 of 28 last days			
Last 4 wks of treatment- ≥ 21 of 28 last days			

6. Fill in the N (sample size) for the four trials listed in the following table:

**PGI-I Anchoring of Key Endpoints**

Trial →  Pivotal Endpoint ↓	Clinically Meaningful Value (FAS, LOCF) “Difference between Minimally Improved and No Change”				
	Pivotal Trial		Pooled 71/75	Supportive Trials	
	511.71 N=	511.75 N=		511.77 N=	511.70 N=
SSE (0-10+)	1.22	1.25	1.24	1.55	1.55
eDiary sexual desire score (0-84)	7.80	7.91	7.87	7.25	8.15
FSDS-R total score (0-52)	-5.63	-5.07	-5.27	-5.86	-4.89

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ZETA-MAE C WILLIAMSON  
04/23/2010

**From:** Williamson, Charlene  
**Sent:** Wednesday, April 21, 2010 12:08 PM  
**To:** 'alex.rochefort@boehringer-ingenelheim.com'  
**Cc:** Williamson, Charlene  
**Subject:** Flibanserin IV

**Attachments:** 4-12-10 Qns for the Applicant.doc  
[Alex,](#)

[Another Information Request.](#)

[Please provide responses by April 27th.](#)

[Please acknowledge receipt of this email.](#)

[Thanks](#)

[Charlene](#)



4-12-10 Qns for the  
Applicant....

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ZETA-MAE C WILLIAMSON  
04/21/2010

**From:** Williamson, Charlene  
**Sent:** Tuesday, April 20, 2010 11:44 AM  
**To:** 'alex.rochefort@boehringer-ingenelheim.com'  
**Cc:** Williamson, Charlene  
**Subject:** Flibanersin Request III

**Attachments:** 4-12-10 Qns for the Applicant.doc  
Alex,

Attached is another request for flibanserin.

Please provide your response by COB April 27, 2010.

Please acknowledge receipt of this email

Thanks

Charlene



4-12-10 Qns for the  
Applicant....

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ZETA-MAE C WILLIAMSON  
04/21/2010

**From:** Williamson, Charlene  
**Sent:** Monday, April 19, 2010 12:17 PM  
**To:** 'alex.rochefort@boehringer-ingenelheim.com'  
**Cc:** Williamson, Charlene  
**Subject:** : Dataset issues

**Attachments:** summary of desire imputed values.pdf; summary of sse imputed values.pdf; MERGESSEDES.sas; sseimpute by desimpute.pdf

Alex,

Dr. Kammerman had 2 additional request for your statistician. I do not think that these request were addressed in the previous telcoms.

Please acknowledge receipt of this email.

Thanks

Charlene

#### 1. Sample sizes for FAS dataset

Please explain why the sample size of the FAS dataset that I created using the FAS flag differs from what is reported in Table 11.1:1 of the CTR.

Here's what I have for Study 511.71.

For the FAS population, Table 11.1:1 shows

N=290, Placebo

N=293, 50 mg

N=280, 100 mg

My dataset shows:

N=286, Placebo

N=292, 50 mg

N=275, 100 mg

To create my dataset, I used the code that was emailed to me on Friday, 4/16/10.

I find similar discrepancies for 511.75.

#### 2. LOCF imputation for SSE and SEXDES

Please explain the use of the EPTF variable in the datasets. According to my understanding of define.xml, EPTF flags whether a value for an endpoint was imputed. using LOCF. So, for the ANATYP=LOCF dataset, a value of EPTF=1 indicates LOCF was implemented; a value of 0 indicates the value was not imputed.

My reading of the clinical trial report for 551.71 and suggests the SEXDES endpoint was imputed more frequently than the SSE endpoint. However, when I run summary statistics for these two endpoints, the rates of imputation are identical; see the two attached files, 'Summary of desire imputed values.pdf' and 'Summary of SSE imputed values.pdf'. I've also included a cross tabulation of the imputed values; see 'sseimpute by desimpute.pdf'.

I've included the code I used to merge INDER\_SSEFAS1 and INDER\_SSEDEFAS1.

I'm also having the same problem for 551.75

## 2. Sample sizes by visit number

Sample sizes change by visit number. Also, they do not match the numbers for the FAS reported in Table 11.1:1 of the trial report. Please explain.

Here's what I have for 511.75:

Visit number	100 mg	25 mg	50 mg	Placebo	Total
2	377	381	376	388	1522
4	373	376	371	381	1501
5	373	378	372	382	1505
6 through 9	373	379	372	382	1506

I have the same issue with 511.71.



summary of desire  
imputed valu...



summary of sse  
imputed values...



MERGESEDES.sas  
(5 KB)



sseimpute by  
desimpute.pdf (5 ...)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ZETA-MAE C WILLIAMSON  
04/21/2010

**From:** Williamson, Charlene  
**Sent:** Wednesday, April 14, 2010 3:20 PM  
**To:** Williamson, Charlene  
**Subject:** FW: Flibanserin request II

---

**From:** Williamson, Charlene  
**Sent:** Monday, April 12, 2010 12:06 PM  
**To:** 'alex.rochefort@boehringer-ingenelheim.com'  
**Subject:** FW: Flibanserin request II

Alex,

To answer your question...I am not sure which Phase II studies we are referring to...the statement quoted from the Clinical Summary only states, "because Phase II results, using higher doses of flibanserin, showed an increased incidence of bleeding AEs with flibanserin." Are these Phase II HSDD data? or MDD data?

In any case, we recognize that the Phase II HSDD study reports are included in the NDA. Please provide us with the data that prompted the statement above. (i.e.frequency of AE category "Hemorrhage" according to dose received and concomitant use of NSAIDs). These data can not be gleaned from the study report since the xpt dataset files are not categorized by dose received.

Let me know if you need a further explanation.

Thank you.

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**From:** Williamson, Charlene  
**Sent:** Monday, April 12, 2010 11:54 AM  
**To:** Easley, Olivia  
**Subject:** FW: Flibanserin request II  
**Importance:** High

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**From:** alex.rochefort@boehringer-ingenelheim.com [mailto:alex.rochefort@boehringer-ingenelheim.com]  
**Sent:** Monday, April 12, 2010 11:09 AM  
**To:** Williamson, Charlene  
**Subject:** RE: Flibanserin request II  
**Importance:** High

Charlene,

Are you requesting flibanserin Phase II HSDD studies (511.68 & 511.69) clinical datasets in which higher doses of Flibanserin were administered, as both these flibanserin phase II clinical trial reports are included in module 5.3.5.1 of the flibanserin NDA 22-626 sequence # 0000?

Thanks,

Alex

PS. When do you expect to be able to send the Division's preliminary response to the 9 meeting questions for our Flibanserin IND (b) (4) Monday July 26, 2010 Type C (pre-AC) meeting?

Thanks.

-----Original Message-----

**From:** Williamson, Charlene [mailto:Charlene.Williamson@fda.hhs.gov]

**Sent:** Friday, April 09, 2010 6:15 PM

**To:** Rochefort,Alex DRA BIP-US-R

**Subject:** Flibanserin request II

Alex,

I have another request. On page 53 of the Clinical Overview, the you state that "because Phase II results, using higher doses of flibanserin, showed an increased incidence of bleeding AEs with flibanserin, particularly in patients using aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) along with flibanserin, compared to placebo..."

Can you submit these Phase II data using higher doses of flibanserin?

Thank you.

Charlene

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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ZETA-MAE C WILLIAMSON  
04/21/2010

## Drug Substance

1. Please provide the following information for starting materials (b) (4) from the drug substance:
  - a. Detailed information regarding structure elucidation/characterization and impurity profiles
  - b. Manufacturers, description of manufacturing process and process controls
  - c. Revised synthesis flow diagram (b) (4)
  - d. Method validation using HPLC for assay and impurities. Of particular, validation for the genotoxic impurity (b) (4)
  - e. Batch analysis results.
2. Please include testing and acceptance limit (b) (4) the drug substance specification (with appropriate analytical method and validation) to ensure that the daily dose of (b) (4) is less than (b) (4)

## Drug Product

3. Regarding the alternative method for content uniformity using (b) (4) spectroscopy, please provide the following information:
  - a. Description of the proposed (b) (4)
  - b. Tests and acceptance criteria for system suitability and model performance verification.
  - c. Description of (b) (4) and its function.
4. Please provide real value for each individual impurity detected in the stability studies instead of using (b) (4) %

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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ZETA-MAE C WILLIAMSON  
03/24/2010



NDA 022526

**INFORMATION REQUEST**

Boehringer Ingelheim Pharmaceuticals, Inc.  
Attention: Alex Rochefort  
Director, Drug Regulatory Affairs  
900 Ridgebury Road, P.O. Box 368  
Ridgefield, CT 06877

Dear Mr. Rochefort:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for flibanserin tablets 100 mg for the treatment of women with Hypoactive Sexual Desire Disorder (HSDD).

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**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.
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 the established name. Additionally, revise to read: "Usual Dosage: See package insert for dosage information."

(b) (4)



**D. Chemistry, Manufacturing and Control Comments:**

1. Include the excursion range for the storage condition next to 25°C (77°F) on the bottle (b) (4) labels instead of using “see insert.”

If you have any questions, call me at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Charlene Williamson  
Regulatory Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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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ZETA-MAE C WILLIAMSON  
03/08/2010



NDA 022526

**NDA ACKNOWLEDGMENT**

Boehringer Ingelheim Pharmaceuticals, Inc.  
Attention: Alexander Rochefort  
Director Drug Regulatory Affairs  
900 Ridgebury Road, P.O. Box 368  
Ridgefield, CT 06877

Dear Mr. Rochefort:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: flibanserin tablets 100 mg

Date of Application: October 27, 2009

Date of Receipt: October 27, 2009

Our Reference Number: NDA 022526

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 26, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Health Project Manager  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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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ZETA-MAE C WILLIAMSON  
11/20/2009

Executive CAC

Date of Meeting: May 19, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Dan Mellon, Ph.D., OND IO, Alternate Member  
Lynnda Reid, Ph.D., DRUP, Supervisor  
Alex Jordan, Ph.D., DRUP, Presenting Reviewer

Author of Draft: Alex Jordan

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND #: (b) (4)

Drug Name: Flibanserin

Sponsor: Boehringer Ingelheim

Background: Flibanserin is a 5-HT<sub>1A</sub> agonist / 5-HT<sub>2A</sub> antagonist intended for the treatment of premenopausal women with hypoactive sexual desire.

Mouse Carcinogenicity Study Protocol and Dose Selection

This was a two year study of flibanserin given orally in the feed. Doses were 10, 80, 200 and 1000/1200 mg/kg/day. The high dose was initially 1000 mg/kg and increased to 1200 mg/kg on drug week 23 because of lack of toxicity.

Rat Carcinogenicity Study Protocol and Dose Selection

This was a two year study of flibanserin given orally in the feed. Doses were 10, 30 and 100 mg/kg/day.

**Executive CAC Recommendations and Conclusions:**

Rats:

The Committee concurred that the study was adequate, noting prior Exec CAC approval of the protocol on Dec. 23, 1997.

The Committee concurred that there were no clearly drug-related neoplasms in rats

Mice:

The Committee concurred that the study was adequate, noting prior Exec CAC approval of the protocol on July 14, 1998.

The Committee concurred that the increased incidences of hepatocellular carcinomas plus adenomas (combined) in female mice and mammary adenocarcinomas plus adenoacanthomas (combined) were drug related in female mice.

The Committee recommends inclusion of the positive findings of hepatocellular carcinomas and mammary carcinomas in mice in the label. Currently the Sponsor is investigating the possible role of elevated prolactin concentrations as an explanation for the increased incidence of mammary tumors in mice. If the data reveal an increase in the serum concentration of prolactin in mice without a similar increase in women, the Committee feels that the tumors in mice would be of less concern for women and this information should be included in the labeling.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\

/Division File, DRUP  
/Lynnda Reid, PhD., Team leader, DRUP  
/Alex Jordan, PhD., Reviewer, DRUP  
/Project Manager, DRUP  
/ASeifried, OND IO

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

BOEHRINGER  
INGELHEIM  
PHARMACEUTICALS  
INC

BIMT 17 BS (b) (4)

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/s/

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ADELE S SEIFRIED  
05/29/2008

DAVID JACOBSON KRAM  
05/29/2008