# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 202276Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # 202276 SUPPL # HFD #

Trade Name STENDRA

Generic Name avanafil

Applicant Name VIVUS, Inc.

Approval Date, If Known April 27, 2012

**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)

c) 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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years (based on the criteria that this is an NME)

e) 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:

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 ☐

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 ☐

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"):

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 # | YES ☐ | ! NO ☐ |
| | | ! Explain: |

| | | |
|---|---|---|
| Investigation #2 | | ! |
| | | ! |
| IND # | 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:
Eufrecina DeGuia
Title: Senior Regulatory Health Project Manager
Date: April 27, 2012

Name of Office/Division Director signing form:
Victoria Kusiak, M.D
Title: Deputy Director, Office of Drug Evaluation III

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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
04/25/2012

VICTORIA KUSIAK
04/27/2012

## Deguia, Eufrecina P

**From:** Greeley, George
**Sent:** Tuesday, March 27, 2012 12:07 PM
**:** Deguia, Eufrecina P
**:** Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Beitz, Julie G
**Subject:** NDA 202-276 (b) (4)

**Importance:** High

**Attachments:** 1_Pediatric_Record.pdf

Hi Freshnie,

This email serves as confirmation of the review for (b) (4) (Avanafil) conducted by the PeRC PREA Subcommittee on February 29, 2012.

The Division presented a full waiver in pediatric patients because the disease/condition does not exist in the pediatric population and is indicated for the treatment of erectile dysfunction.

The PeRC agreed with the Division to grant a full waiver for this indication.

(b) (4)

The pediatric record is attached for (b) (4)

1_Pediatric_Record .pdf (58 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

NDA 202276

Debarment Certification

Certification has been verified. Statement is acceptable.

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA # 202276<br>BLA # | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type: |
| Proprietary Name: STENDRA<br>Established/Proper Name: avanafil<br>Dosage Form: tablet | | Applicant: VIVUS, Inc.<br>Agent for Applicant (if applicable): |
| RPM: E. DeGuia | | Division: Division of Reproductive and Urologic Products |

**NDAs and NDA Efficacy Supplements:**

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

**505(b)(2) Original NDAs and 505(b)(2) NDA supplements:**

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

**For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.**

**On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

☐ No changes ☐ Updated Date of check:

**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.**

| ❖ Actions | |
|---|---|
| • Proposed action<br>• User Fee Goal Date is April 29, 2012 | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☒ None |

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (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., nrew listed drug, patent certification revised).

| | |
|---|---|
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | ☐ Received |
| ❖ Application Characteristics [3] | |

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

| | |
|---|---|
| ❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) | ☐ Yes, dates |
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☐ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☒ Yes ☐ No |
| • Press Office notified of action (by OEP) | ☒ Yes ☐ No |
| • Indicate what types (if any) of information dissemination are anticipated | ☐ None<br>☒ HHS Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☐ Other |

[3] 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.

| | |
|---|---|
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity? | ☒ No ☐ Yes |
| • NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.* | ☒ No ☐ Yes<br>If, yes, NDA/BLA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)* | ☐ No ☐ Yes<br>If yes, NDA # and date exclusivity expires: |
| • NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)* | ☒ No ☐ Yes<br>If yes, NDA # and date 10-year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |
| • Patent Certification [505(b)(2) applications]:<br>Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(*i*)(A)<br>☐ Verified<br><br>21 CFR 314.50(i)(1)<br>☐ (ii) ☐ (iii) |
| • [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | ☐ No paragraph III certification<br>Date patent will expire |
| • [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).* | ☐ N/A (no paragraph IV certification)<br>☐ Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

| | |
|---|---|
| (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?<br><br>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).<br><br>*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*<br><br>*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.* | ☐ Yes ☐ No |

## CONTENTS OF ACTION PACKAGE

| | |
|---|---|
| ❖ Copy of this Action Package Checklist[4] | Yes |
| **Officer/Employee List** | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |
| **Action Letters** | |
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s) Approval - April 27, 2012 |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | April 26, 2012 |
| • Original applicant-proposed labeling | June 29, 2011 |
| • Example of class labeling, if applicable | None |

[4] Fill in blanks with dates of reviews, letters, etc.

| | |
|---|---|
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* | ☐ Medication Guide<br>☐ Patient Package Insert<br>☐ Instructions for Use<br>☐ Device Labeling<br>☒ None |
| • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | |
| • Original applicant-proposed labeling | |
| • Example of class labeling, if applicable | |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | |
| • Most-recent draft labeling | April 26, 2012 |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s)*<br>• *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.* | April 24, 2012<br>Reviews: July 22, 2011, January 23, 2012, March 5, 2012, April 24, 2012 |
| ❖ Labeling reviews *(indicate dates of reviews and meetings)* | ☒ RPM August 24, 2011<br>☒ DMEPA see dates above<br>☒ DMPP/PLT (DRISK) 4-17-12<br>☒ ODPD (DDMAC) 4-18-12<br>☒ SEALD 4-25-12<br>☐ CSS N/A<br>☐ Other reviews |
| **Administrative / Regulatory Documents** | |
| ❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* | August 26, 2011 |
| ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte | ☒ Not a (b)(2) |
| ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)* | ☒ Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary *(signed by Division Director)* | ☒ Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| • Applicant is on the AIP | ☐ Yes ☒ No |
| • This application is on the AIP<br>o If yes, Center Director's Exception for Review memo *(indicate date)*<br>o If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☒ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC February 29, 2012<br>If PeRC review not necessary, explain: _____<br>• Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)* | ☒ Included |

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| | |
|---|---|
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)* | ☒ Verified, statement is acceptable |
| ❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)* | Included |
| ❖ Internal memoranda, telecons, etc. | Internal Filing Memos included |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing *(indicate date of mtg)* | ☒ No mtg |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☒ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | ☐ No mtg October 20, 2010 |
| • EOP2 meeting *(indicate date of mtg)* | ☐ No mtg November 2, 2005 |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)* | |
| ❖ Advisory Committee Meeting(s) | ☒ No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available *(do not include transcript)* | |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | ☐ None 4-27-12 |
| Division Director Summary Review *(indicate date for each review)* | ☐ None 4-26-12 |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | ☐ None 4-25-12 |
| PMR/PMC Development Templates *(indicate total number)* | ☐ None 2 |
| **Clinical Information**[6] | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | see CDTL review (4-25-12) |
| • Clinical review(s) *(indicate date for each review)* | April 17, 2012 |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☒ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | see MO review page 17 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* | ☐ None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☒ Not applicable |
| ❖ Risk Management<br>• REMS Documents and Supporting Statement *(indicate date(s) of submission(s))*<br>• REMS Memo(s) and letter(s) *(indicate date(s))*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | ☒ None |

[6] Filing reviews should be filed with the discipline reviews.

| | |
|---|---|
| ❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)* | ☐ None requested Included |
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ None |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☐ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☒ None |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☒ None |
| Statistical Review(s) *(indicate date for each review)* | ☐ None April 9, 2012 |
| **Clinical Pharmacology** ☐ None | |
| ❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☒ None |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☒ None |
| Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None March 9, 2012 (2) |
| ❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)* | ☒ None |
| **Nonclinical** ☐ None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☐ None March 26, 2012 |
| • Supervisory Review(s) *(indicate date for each review)* | ☐ None March 26, 2012 |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | ☐ None August 17, 2011, March 21 and 22, 2012 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☒ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☒ No carc |
| ❖ ECAC/CAC report/memo of meeting | ☐ None March 10, 2009 Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)* | ☒ None requested |
| **Product Quality** ☐ None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) *(indicate date for each review)* | ☒ None |
| • Branch Chief/Team Leader Review(s) *(indicate date for each review)* | ☐ None April 17, 2012 |
| • Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)* | ☐ None March 1, 2012, April 17, 2012 |
| ❖ Microbiology Reviews<br>☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*<br>☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)* | ☒ Not needed |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)* | ☒ None |

| | |
|---|---|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | See CMC review dated 3/1/2012, page 78. |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Facilities Review/Inspection | |
| ☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])* | Date completed:<br>☒ Acceptable<br>☐ Withhold recommendation<br>☐ Not applicable |
| ☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)* | Date completed:<br>☐ Acceptable<br>☐ Withhold recommendation |
| ❖ NDAs: Methods Validation *(check box only, do not include documents)* | ☒ Completed<br>☐ Requested<br>☐ Not yet requested<br>☐ Not needed (per review) |

[7] 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.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

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JENNIFER L MERCIER
04/27/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202276

**PROPRIETARY NAME REQUEST WITHDRAWN**

VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040

Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated June 29, 2011, received June 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avanafil Tablets, 50 mg, 100 mg, and 200 mg.

We acknowledge receipt of your April 6, 2012, correspondence, on April 6, 2012, notifying us that you are withdrawing your March 23, 2012, request for reconsideration of the proposed proprietary name, (b) (4). This proposed proprietary name request for reconsideration is considered withdrawn as of April 6, 2012.

We note that you requested the continuation of the review for the proposed proprietary name, Stendra, submitted on March 14, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Freshnie DeGuia , at (301) 796-0881.

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
04/25/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202276

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040

ATTENTION: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated and received June 29, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Avanafil Tablets, 50 mg, 100 mg, and 200 mg.

We also refer to your correspondence dated and received March 14, 2012, requesting review of your proposed proprietary name, Stendra.

We have completed our review of the proposed proprietary name Stendra, and have concluded that it is acceptable. If **any** of the proposed product characteristics as stated in your March 14, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

The proposed proprietary name, Stendra 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 you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Eufrecina DeGuia at (301) 796-0881.

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
04/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202276

**LABELING PMR/PMC DISCUSSION COMMENTS**

VIVUS, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated and received June 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for avanafil.

We also refer to our September 1, 2011, Filing Communications Letter, in which we notified you of our target date of March 11, 2012, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

We are providing in the attached labeling our preliminary revisions/comments to the Pharmacology/Toxicology and Chemistry, Manufacturing and Controls CMC) sections that are available at this time. Please note that significant labeling revisions are forthcoming as we complete our reviews.

We also reiterate, as outlined in the Filing Communications Letter, that a longer term human sperm study that includes more than single dose administration of your product will be needed. The Division believes that this study would need to be conducted as a post-marketing requirement (PMR). Details on this study, including milestones, are still under discussion at this time. We plan to have further discussion with you regarding this PMR in the near future.

If you have any questions, call me, at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

Eufrecina P. DeGuia
Senior Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

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EUFRECINA P DEGUIA
03/08/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202276

**PROPRIETARY NAME REQUEST**
**UNACCEPTABLE**

VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040

ATTENTION: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated June 29, 2011, received June 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avanafil Tablets, 50 mg, 100 mg, and 200 mg.

We also refer to your December 8, 2011, correspondence, received December 8, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reason:

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated December 8, 2011. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Eufrecina Deguia at (301) 796-0881.

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
03/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202276

**GENERAL ADVICE**

VIVUS, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated and received June 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for avanafil.

We also refer to your September 14, 2011, submission, containing your proposed container and carton labeling as well as your proposed Physician sample blister card and carton.

We have reviewed the referenced materials and, in consultation with the Division of Medication Error Prevention Analysis (DMEPA), we have the following comments and recommendations. Please be advised that revised labeling incorporating these comments be submitted for further review.

A. Container Label (50 mg, 100 mg, and 200 mg)

1. Revise the presentation of the proprietary name from all upper case letters (TRADENAME) to title case (Tradename) to improve readability.

2. We note that the established name is half the size of the proprietary name. However, it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast and other printing factors in accordance with 21 CFR 201.10(g) (2).

3. Increase the prominence of the statement "Protect from light".

4. Revise the storage statement from (b) (4)

5. Relocate the net quantity away from the statement of strength.

6. Ensure that the barcode is included on the container label in accordance with 21 CFR 201.25.

7. The 50 mg, 100 mg, and 200 mg strengths are not well differentiated from each other. All three strengths use shades of gray for strength differentiation which makes the labels look identical. To avoid selection errors, revise the labels to provide more visual differences between the three strengths by using unique colors for each strength.

8. Increase the prominence of the three middle numbers in the NDC number as this information is how the pharmacist identifies the correct strength for drug products. For example, NDC 62541-301-01 becomes 62541-301-01 for the 50 mg strength.

B. Physician Sample Blister Card

1. See Comment A.1 through A.5.

2. Professional samples are dispensed to patients for use at home. Consider using containers compliant with the Poison Prevention Protection Act (PPPA) designed with Child Resistant Closures (CRC). This may help mitigate exposure of children to this medication when used in the home setting.

3. Include the statement "Each tablet contains 100 mg" on the front panel.

4. On the inside center panel, next to each tablet, ,include statement "100 mg" so that it is clear that each tablet contains 100 mg and that 100 mg is not a combination of the three tablets together.

C. Physician Sample Display Carton

See Comment A.1 through A.5.

D. Insert Labeling

General Comment:
You have used throughout the HIGHLIGHTS OF PRESCRIBING INFORMATION, and FULL PRESCRIBING INFORMATION error prone abbreviations. The symbols <, ≤, >, ≥ were utilized in the insert labeling to represent "less than," "less than or equal to," "greater than," or "greater than or equal to," respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. In particular, a "< 10" can be misread as "40." As part of a national campaign to decrease the use of dangerous symbols, the FDA agreed not to use such error-prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, we recommend that < be replaced with "less than," ≤ be replaced with "less than or equal to," > be replaced with "greater than," and ≥ be replaced with "greater than or equal to."

If you have any questions, please call me at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

Eufrecina DeGuia
Senior Regulatory Health Project Manager
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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EUFRECINA P DEGUIA
02/21/2012

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202276

**PROPRIETARY NAME REQUEST**
**UNACCEPTABLE**

VIVUS, Inc.
1172 Castro Street
Mountain View, CA 94040

ATTENTION: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated June 29, 2011, received June 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avanafil Tablets, 50 mg, 100 mg, and 200 mg.

We also refer to your August 9, 2011, correspondence, received August 10, 2011, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)


We note that you have proposed an alternate proprietary name in your submission dated August 9, 2011. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Eufrecina Deguia at (301) 796-0881.

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
11/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202276

**FILING COMMUNICATION**

VIVUS, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your New Drug Application (NDA) dated and received June 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for avanafil.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 11, 2012.

We have identified the following as current review issues:

Clinical

1. While there may be a need for the 200 mg dose in the diabetic population, the clinical benefit of treatment with 200 mg over 100 mg is not clear in the general ED population. Provide additional justification for the need for the 200 mg dose in the general ED population.
2. (b) (4)

3. The extent of the pharmacodynamic interactions between avanafil and other drugs (e.g., nitrates, alpha-blockers, amlodipine, enalapril) and between avanafil and alcohol will be review issues.

4. Sperm studies using more than single dose administration may be needed. In this regard, post-marketing requirement studies are being considered.

Pharmacology and Toxicology

We remind you that the reversibility study for fertility and sperm parameters in rats should be submitted no later than the mid-cycle of the NDA review.

Chemistry, Manufacturing and Controls (CMC)

1. Submit a copy of the drug substance specification to the NDA so that they can be documented within the NDA review.

2. According to the **Guidance for Industry: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products**, bracketing should be performed on the extremes of certain design factors, which includes container size and/or fill, and that only one attribute should be varied. The Guidance also states that if size and fill both vary, it should not be assumed that the smallest and largest sized bottles represent the extremes, but the extremes should be characterized by comparing characteristics that may affect product stability, such as surface area to volume ratio, headspace to volume ratio, etc. (See pages 2 and 3 of the Guidance). With this in mind, provide justification for not including the 60 cc and 90 cc bottles and 100-tablet fills on stability. Provide a comparison of the characteristics of the container closure system that may affect the product stability as outlined in the Guidance.

3. Include a bar code on the container labels and indicate its placement.

Clinical Pharmacology

1. The Phase 3 studies were conducted using multiple units of either 50 or 100 mg tablets. A dose strength of 200 mg is also being requested. The lack of dose proportionality of the to-be-marketed formulation is a review issue. Provide justification as to how the data from studies using 50 and 100 mg tablets can be extrapolated to support the safety and efficacy of the higher dose strength (200 mg tablets).

2. [redacted] (b) (4)

3. The extent of data to support safety and recommended starting dose in the elderly population (≥ 65 years of age) will be a review issue.

4. The impact of severe renal impairment and end stage renal disease (ESRD) on avanafil PK was

not specifically studied.

5. Submit the results from the renal impairment study using the new classification scheme of renal impairment as described in FDA's **Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010)**.

6. The impact of severe hepatic impairment on avanafil PK was not specifically studied.

7. The effect of a mild CYP3A4 inhibitor on avanafil PK was not specifically studied. Use of avanafil in patients taking a mild, moderate or potent CYP3A4 inhibitor will be a review issue.

8. Drug interaction studies, such as Study TA-018 with rosiglitazone and desipramine, were conducted with a single dose of avanafil, but avanafil is recommended for up to once daily use. Provide justification as to how drug interaction studies conducted with a single dose can be extrapolated to multiple dose use.

Biostatistics

In order to assess the sensitivity of missing data, you should analyze the efficacy data from Studies TA-301 and TA-302 for the Erectile Function (EF) domain of the IIEF questionnaire using the ANCOVA model specified in the study protocol, but without LOCF imputation.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. HL must be in a two-column format with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

2. HL is limited in length to one-half page. If it longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

3. All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

4. A horizontal line must separate the TOC and FPI.

5. The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

6. The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

7. Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events" should be avoided.

8. For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

   "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

We request that you resubmit labeling that addresses these issues in two to three weeks. The resubmitted labeling will be used for further labeling discussions.

Please respond to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Eufrecina DeGuia, Senior Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.
Deputy Director
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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GEORGE S BENSON
09/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202276

**NDA ACKNOWLEDGMENT**

VIVUS, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

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: (b) (4) (avanafil) Tablets

Date of Application: June 29, 2011

Date of Receipt: June 29, 2011

Our Reference Number: NDA 202276

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 August 28, 2011, in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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.

If you have any questions, please call me at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

Eufrecina DeGuia
Senior Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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EUFRECINA P DEGUIA
07/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration**
**Silver Spring MD 20993**

IND 051235

**MEETING MINUTES**

VIVUS, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Corporate Compliance
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TA-1790 (avanafil).

We also refer to the October 20, 2010, face-to-face meeting between representatives from your firm and the FDA to discuss and seek agreement on the overall format, structure and content of your upcoming New Drug Application (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, please call Eufrecina DeGuia, Senior Regulatory Health Project Manager at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | October 20, 2010 @ 11AM – 12:30PM |
| **Meeting Location:** | CDER WO Building 51, Room 1211 |
| **Application Number:** | IND 051235 |
| **Product Name:** | TA-1790 (avanafil) |
| **Indication:** | treatment of erectile dysfunction |
| **Sponsor/Applicant Name:** | VIVUS, Inc. |
| **Meeting Chair:** | Mark Hirsch, M.D. |
| **Meeting Recorder:** | Eufrecina DeGuia |

**FDA ATTENDEES**

George Benson, M.D. – Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D. – Medical Team Leader, DRUP
Guodong Fang, M.D. – Medical Officer, DRUP
Yangmee Shin, Ph.D. – Pharmacology and Toxicology Reviewer, DRUP
LaiMing Lee, Ph.D. – Acting Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCP3)
Chongwoo Yu, Ph.D. – Clinical Pharmacology Reviewer, OCP, DCP3
Donna Christner, Ph.D. – CMC Lead, Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment (ONDQA)
Eufrecina DeGuia – Senior Regulatory Health Project Manager, DRUP
Mahboob Sobhan, Ph.D. – Team Leader, Division of Biometrics II, Office of Biometrics
Jia Guo, Ph.D. – Statistical Reviewer, DB II, OB
Maria Walsh – Associate Director of Regulatory Affairs, Office of Drug Evaluation III
Roy Blay, Ph.D. – Associate Director, Division of Good Clinical Practices, Division of Scientific Investigations (DSI), Office of Compliance
Elizabeth Piault-Loius, Pharm.D., MA – Endpoint Qualification Fellow, Study Endpoint and Development (SEALD), Office of New Drugs (OND)
Patrick Marroum, Ph.D. –Special Assistant to the Office Director/ Biopharmaceutics Supervisor, ONDQA
Anne Marie Trentacosti, M.D. – Medical Team Leader, SEALD, OND (via phone)
Jun Yan, Pharm.D. – Labeling Reviewer, SEALD, OND

**VIVUS, Inc. Attendees**

Karen Benson, M.B.A., M.P.H. - Senior Associate, Regulatory Affairs
Ted Broman - V.P., CMC
Charles H. Bowden, M.D. Senior Director, Clinical Development
Wesley W. Day, Ph.D. - V.P., Clinical Development

Karen DiDonato, R.N., M.S.N. - Associate Director, Clinical Development
Malcolm McKay, Ph.D. - VP, Regulatory Affairs and Corporate Compliance
Joseph Parks, M.S. – Senior Director, Clinical Development
(b) (4)
(b) (4)

## 1.0 BACKGROUND

TA-1790 (avanafil), a phosphodiesterase 5 (PDE5) inhibitor, is being developed for treatment of erectile dysfunction. It is a solid oral tablet and intended to be **used as an "on-demand" therapy.**

The clinical program includes 17 phase 1 studies, three phase 2 studies and four phase 3 studies which randomized a total of 2319 adult male subjects, including 2076 subjects who received one or more doses of active drug. Three of the 4 phase 3 studies have been completed; TA-301 in the general ED population, TA-302 in diabetic men, and TA-314 (long-term safety and tolerability). These 3 studies randomized a total of 1036 subjects. An additional phase 3 study, TA-303, in subjects with ED following radical prostatectomy, is still ongoing.

Sponsor will seek approval of 50, 100, and 200 mg doses in their upcoming NDA submission.

## 2. DISCUSSION

Preliminary draft responses were provided to the sponsor on October 19, 2010, in response to questions posed in the September 18, 2010, Briefing Package. The sponsor's questions from the meeting package are presented below (bolded text), followed by the Division's responses presented in normal text as provided to the sponsor on October 19, 2010. Additional discussion and comments made at the meeting are presented below in *italics.*

**Regulatory:**

**Question 1: Is the overall content and organizational structure of each Module given in the Table of Contents acceptable for an NDA filing?**

Response: Yes. We have the following request related to Chemistry, Manufacturing and Controls (CMC):

In the NDA submission, provide a comprehensive table/list of all facilities involved in production of the drug substance and drug product with full street addresses of the actual manufacturing and/or testing site (not the corporate office), contact information of an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA. This comprehensive table should be attached to the FDA Form 356h. Full information should still be provided in the appropriate sections of Modules 2 and 3. Inspections cannot be requested unless all the above information is provided. If this information is not provided when the NDA is submitted, it will delay inspection requests and may adversely affect the outcome of a first cycle review decision.

*The sponsor will provide the requested information in the NDA.*

**Question 2: Would the reviewers like VIVUS to provide a demonstration of the overall eCTD structure for this NDA at a later date?**

Response: No.

**Question 3: Does the agency concur with the likelihood that avanafil will not be used in any pediatric patients and should the request be submitted to the IND or included in the NDA?**

Response: (b) (4)
You should submit a request for pediatric waiver in the NDA submission, and it will be conveyed to the Pediatric Review Committee (PeRC).

*The Sponsor agreed to submit a request for pediatric waiver at the time of NDA submission.*

**CMC/Quality**

**Question 1: Given that FDA and VIVUS agree that, per ICH Q7 the data support designating (b) (4) as starting materials for the manufacture of avanafil API, VIVUS proposes that FDA will be notified of any changes made to the listed starting materials manufacturers or manufacturing processes via a Changes Being Effected in 30 Days supplement, rather than via a Prior Approval supplement. Does the Agency concur with this proposal?**

Response: We recommend that a Prior Approval supplement be submitted. However, the final designation of the supplement type is made upon submission of the supplement.

*The Sponsor questioned why the supplement would need to be a Prior Approval. The CMC team stated that the supplement may be submitted as a CBE but the type of supplement will be determined after further evaluation of the submission.*

**Question 2: Does the Agency agree with the acceptance criteria for the starting materials (b) (4)**

Response: The acceptance criteria appear reasonable at this time. However, final concurrence will be made at the time of NDA review once all the data are available for review.

*The Sponsor had no further questions. They agreed with the above response.*

**Question 3. Does the Agency agree that the proposed commercial specifications for avanafil API are acceptable?**

Response: While the specification appears reasonable at this time, we have the following comments:

- The (b) (4) for Total Impurities appears to be generous based on your submitted batch analysis. This limit may need to be tightened based on the NDA review. Impurity limits will also take into account your stability data.
- The limit for the (b) (4) may be tightened during the NDA review.
- Residual Solvents should be reported in ppm.

We remind you that the acceptability of the final specification is an NDA review issue and will be made at that time.

*The Sponsor had no further questions. They agreed with the above response.*

**Question 4: Does the Agency agree that the proposed commercial specifications for avanafil tablets are acceptable?**

Response: The acceptance criteria appear reasonable at this time. However, final concurrence will be made at the time of NDA review once all the data are available for review.

*The Sponsor had no further questions. They agreed with the above response.*

**Question 5: Is the post-approval completion of concurrent validation plan for avanafil tablets acceptable to the Agency?**

Response: We concur.

**Additional CMC Comment:** Please be aware that if a decision is made to package drug product in blisters for commercial distribution, the blister packs would need to comply with 16 CFR 1700.14(a)(10) for child resistance. Refer to the US Consumer Product Safety Commission website (http://www.cpsc.gov/businfo/dreg.html) for more information.

*The Sponsor had no further questions. They acknowledged the above comment.*

**Clinical**

**Question 1: Does the Agency agree with VIVUS' plan for data pooling for the ISS?**

Response: No.

- In addition to pooling phase 3 studies TA-301 and TA 302 with the phase 2 study TA-05, we request a separate dataset and separate analysis in the ISS just for the controlled phase 3 studies TA-301 and TA-302.
- In addition to safety data presented by individual phase 1 study, we request an overall summary of safety from the seventeen phase 1 studies.

*Sponsor asked whether the Division needed 2 separate datasets for: 1) Study TA-301, TA-302, and TA-05 and 2) Study TA-301 and TA-302. The Division stated that the planned single dataset was sufficient.*

*For Bullet #2, Sponsor proposed to provide a narrative summary for the overall safety from phase 1 studies. Division agreed with the proposal and will also review each study separately.*

**Question 2: Does the Agency agree with VIVUS' plan for the outline of primary and additional analyses for the ISS?**

Response: No. You should also pre-define the analyses that will be conducted for the open-label, safety extension study TA-314 and include this information in the ISS, but keep it separate from the controlled studies.

*Sponsor agreed with the above response.*

**Question 3: Does the Agency agree with VIVUS' plan for data pooling for the ISE?**

Response: All pooling of efficacy data in the ISE will be considered exploratory.

*The Sponsor agreed with the above response.*

**Question 4: Does the Agency agree with VIVUS' plan for the outline of primary and secondary analyses for the ISE?**

Response: Yes, we agree. See also our response to Clinical Question 3.

*The Sponsor agreed with the above response.*

**Question 5: Does the Agency agree with VIVUS' plan regarding the format of the clinical data and documentation components for the individual studies in the avanafil NDA?**

Response: Yes.

*The Sponsor acknowledged the above response.*

**Question 6: Does the Agency agree that the pooled databases for the ISS and ISE will consist of ADaM data only, and will not include pooled tabulations data?**

Response: No. Also include the SDTM files for the ISS and ISE.

*The Sponsor stated that SDTM and ADaM datasets will be available for each of the TA-05, TA-301, TA-302 and TA-314 studies and clarified that their plan is to use the ADaM datasets for the individual studies to create the pooled ADaM databases to support the integrated analyses. The Division agreed.*

**Question 7: Does the Agency agree with VIVUS' plan for identification and assessment of TMEs and related submission of patient profiles?**

Response: No. In addition to the patient profiles, we request that you provide individual narratives for the TMEs.

*The sponsor agreed to the Division's request. In addition to patient profiles, individual patient narratives will be provided for all identified subjects with TMEs.*

**Question 8: Does the Agency agree with VIVUS' plans to submit case report forms (CRFs) for all patients who died, experienced a serious adverse event (SAE), or discontinued study drug due to an AE for all studies?**

Response: Yes. In addition to the CRFs, we request that you provide individual narratives for patients who died, had a serious adverse event, or discontinued due to an adverse event.

*The Sponsor agreed to the above response.*

**Question 9: Does the Division agree that the avanafil program's patient exposure is sufficient to support approval?**

Response: Yes.

**Question 10: Does the Agency agree that the clinical pharmacology program as presented in Appendix 2 is adequate to support the NDA submission for avanafil?**

Response: We have the following comments regarding the clinical pharmacology program:

1. Regarding **Renal Impairment** studies: Reference is made to the *Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling.* Renal impairment can adversely affect some pathways of hepatic/gut drug metabolism and has also been associated with changes in absorption, plasma protein binding, transport, and tissue distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug. Thus, for most drugs that are likely to be administered to patients with renal impairment, including drugs that are not primarily excreted by the kidney, pharmacokinetics (PK) should be assessed in patients with renal impairment to provide appropriate dosing recommendations. The impact of severe renal impairment including End State Renal Disease (ESRD) on avanafil PK has not been assessed. This will be a review issue and might become a post-marketing requirement (PMR) given that avanafil is an NME. We request that you address this in your NDA submission.

2. Regading **Hepatic Impairment** studies: The impact of severe hepatic impairment on avanafil PK has not been assessed. This will be a review issue. We request that you address this in your NDA submission.

*The Sponsor stated that there was no requirement stipulated at the end of Phase 2 meeting to study severely impaired renal or hepatic patients. The Clinical Pharmacology team stated that*

*the Agency's current thinking and guidance regarding PK in patients with impaired renal or hepatic function has evolved, especially for new molecular entities (NME). The product label needs to provide clear recommendations based on scientific evidence for use of the drug in patients with impaired renal or hepatic function. This will be a review issue and might become a Postmarketing Requirement (PMR). The Sponsor acknowledged the Division's request to address this issue in the NDA submission.*

3. Regarding **Drug-Drug Interaction** (DDI) studies:
   - The following studies were conducted by giving a single-dose of 200 mg avanafil that does not represent the worst case scenario of administering 200 mg avanafil (b) (4):

     Study TA-016: Warfarin DDI
     Study TA-018: CYP 2C and CYP 2D6 DDI
     Study TA-015: Alcohol DDI
     Study TA-017: α-blockers DDI
     Study TA-019: enalapril, amlodipine DDI

   Address how data obtained from these studies can be extrapolated into the worst case scenario of (b) (4) of avanafil.
   - Address the effect of CYP 3A4 inducer (e.g., rifampin) co-administration on avanafil PK.
   - Address the effect of avanafil on P-glycoprotein (e.g., digoxin).
   - Elaborate on the effect of mild, moderate and strong CYP3A4 inhibitor coadministration on avanafil PK.

*The Division reiterated that Sponsor should address how data from the above studies can be extrapolated into the worst case scenario of (b) (4) Sponsor stated that they will consider this issue and may decide not to reques(b) (4) in the NDA submission.*

*The Sponsor stated there is a low potential for in vivo drug interaction with digoxin based on results of an in-vitro study.*

*The Division stated that the effects of CYP 3A4 inducers and inhibitors on avanafil PK, as well as the effect of avanafil on P-glycoprotein, are important information that needs to be addressed in the NDA submission and reflected in the product labeling. The Sponsor acknowledged the Division's comments.*

4. Also address the following **additional clinical pharmacology issues** in your NDA submission:
   - The effect of age on avanafil exposure.
   - What the starting dose of avanafil is and how it is determined.
   - The safety of the worst case scenario (i.e., (b) (4) of avanafil).

*The Sponsor acknowledged the above response.*

5. In regard to the sperm study, the single-dose design is insufficient. A multiple-dose study, with assessment of WHO sperm parameters, including sperm concentration, is needed. Additional discussion is needed regarding the timing of this study.

*The Division reiterated the need for a multiple dose sperm study, but was willing to consider this as a PMR. The sponsor was receptive to this suggestion and will address it in the NDA submission.*

6. The potential interaction of avanafil with alcohol and with alpha-blockers will be a review issue. Substantial evidence will be needed to support claims (b) (4)

*Sponsor acknowledged the above comment.*

7. The meeting package states that avanafil can be taken without regard to food. However, food appears to delay the time to maximum plasma concentration. Food effect will be a review issue.

*The Sponsor will address food effect in the NDA submission. Because $T_{max}$ is delayed, pharmacodynamic (PD) effects should also be considered in addressing the food effect.*

**Question 11: Given that the 3 dosage strengths (50, 100 and 200 mg) are a (b) (4) (b) (4), does the Agency agree that a dosage form equivalence study is not needed to support the marketing of the 3 dosage strengths?**

Response: This question is still being considered internally and will be discussed at the meeting on October 20, 2010.

*Dr. Marroum, Biopharmaceutics Supervisor in ONDQA, stated that ONDQA was in agreement since the Sponsor has plasma levels for the three strengths. Dr. Marroum stated that a request for biowaiver was actually not even needed.*

*The Clinical Pharmacology review team stated that the following will be review issues:*

- *Dose proportionality of the to-be-marketed (TBM) formulation has not been established.*
- *The Phase 3 studies were conducted using multiple units of either 50 mg or 100 mg tablets. In the NDA submission, Sponsor should address how data from these studies can be extrapolated to support the approval of a higher dose strength (i.e., 200 mg tablet)*

**Clinical Pharmacology Post-Meeting Comment**

*Since the Sponsor is using a (b) (4) and the product is an immediate release (IR) product, and the dissolution is acceptable across the three dosage forms, a biowaiver could be granted. However, this waiver request can only be granted after the information is submitted and reviewed. It is Clinical Pharmacology's position, therefore, that a biowaiver would appear to be appropriate but the final determination is a review issue.*

*OCP's concern is that in the Sponsor's assessment the 1 x 50 mg and 2 x 100 mg study did not show dose proportionality. The results of this study will be a review issue. It is also OCP's understanding that the PK of the proposed 200 mg tablet was characterized but in a separate study from where 50 mg and 100 mg PK was characterized. This is also of concern and will be a review issue. Considering these two review issues, the NDA submission needs to address how the data obtained with the 50 and 100 mg tablets (given that there were no PK assessments in any of the 3 Phase 3 studies) can be extrapolated to support the safety and efficacy of the 200 mg dosage form.*

**Additional Clinical Comments:**

1. In Study TA-301, avanafil 200 mg provided no statistically or clinically significant benefit over avanafil 100 mg. However, avanafil 200 mg was associated with an increased incidence of headache compared to lower doses. Therefore, the NDA should contain justification for approval of the 200 mg dose in the non-diabetic ED population.

*The Sponsor believes that there is justification for the 200 mg dose in some individuals.*

2. (b) (4)

*The Sponsor acknowledged the comment and stated that they might not request approval of* (b) (4) *dosing in the NDA submission.*

3. The NDA should contain information on the direct effect of avanafil on blood pressure.

4. Claims related to the (b) (4) need to be supported by substantial evidence. Analyses of data supporting the (b) (4) The NDA should contain information supporting both these claims, and these will be review issues.

5. The NDA should contain information as to when nitroglycerin may be taken after dosing with avanafil, in the event nitroglycerin is deemed absolutely necessary after taking avanafil.

6. The Division of Scientific Investigation (DSI) has several requests for your NDA (see attachments).

*The Sponsor acknowledged the above comments.*

**Nonclinical**

**Question 1: In addition to the translated and edited version of nonclinical reports, VIVUS plans to also submit the original reports (in English or Japanese). Does the Agency consider this to be necessary, and if so, would the Agency prefer copies of the original Japanese or translated documents included as an Appendix to the NDA?**

Response: All reports should be submitted in English. The submission of the original reports in Japanese is not necessary. However, any corrections or additions to the original reports need to be clearly identified, and the reasons for the amendment should be described by the person responsible.

*No further issues. Division will accept Sponsor's translation.*

**Question 2: Does the Agency agree that based on the combined nonclinical and clinical data which do not indicate an immunotoxic risk with TA-1790 that a nonclinical immunotoxicity study is not required?**

Response: Yes.

**Question 3: Does the Agency agree that the database of nonclinical information on TA-1790 is sufficient to support approval of avanafil?**

Response: Overall, the nonclinical development program for avanafil appears sufficient to support filing of the NDA. (b) (4)
(b) (4)

*The Division requested clarification of avanafil plasma half-lives ranging from 1-13 hours in clinical studies. The Sponsor stated that while the half-life of avanafil did appear to increase with dose in humans, different analytical methods were used in different clinical studies.*

*The Sponsor contended that a comparison of AUC exposure between nonclinical and clinical species, rather than number of dose administrations, is more appropriate for toxicity assessment. The Division noted that toxicity profile may also depend on other PK parameters such as bioavailability, $C_{max}$ and half-life, in addition to AUC exposure multiples. The Division encouraged the Sponsor to provide justification in the NDA submission* (b) (4)
(b) (4)

*The Sponsor explained that they might not ultimately request approval for* (b) (4)

The Division recommends that the following be addressed in the NDA application.

- A return to fertility study in rats based on the effects on fertility and sperm abnormalities.

*The Sponsor requested clarification for the comment above. The Division stated that a return to fertility study was being requested based upon evidence of histopathologic findings in reproductive tissues in male rats following chronic administration. The Sponsor stated their opinion that a return to fertility study might not be necessary. The Sponsor also stated that such a study was lengthy and would interfere with the timing their NDA submission. The Division was willing to accept the results of the return to fertility study no later than the mid-cycle meeting if the sponsor was planning to submit the NDA soon.*

Additional Comment from Study Endpoint and Labeling Development (SEALD):

The sponsor was reminded to comply with regulatory requirement for the content and format of the PI in the NDA submission. Below is the website for New Content and Format Requirements for Prescription Information (PI):

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

## 3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that were identified requiring further discussion.

## 4.0 ACTION ITEMS

VIVUS plans to submit their NDA by first Quarter 2011.

## 5.0 ATTACHMENTS AND HANDOUTS

Copy of presented slides is attached.

FROM: Roy Blay, Ph.D.
Associate Director
Good Clinical Practices Branch II
Division of Scientific Investigations
Office of Compliance

DSI has 2 types of requests for data to be submitted to the NDA; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

## I. Request for general study related information and specific Clinical Investigator information

A. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

## II. Request for Site Level Data

1. For each site in the pivotal clinical trials: Name of primary investigator, accurate address and phone number, e-mail contact
2. For each pivotal trial: Sample blank CRF and case report data tabulations for the site with coding key
3. For each pivotal trial: Site-specific individual subject data ("line") listings from the datasets:

a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements
b. Line listings by site and subject, of treatment assignment (randomization)
c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
e. Line listings by site and subject, of AEs, SAEs, deaths and dates
f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
i. Line listings by site and by subject, of laboratory tests performed for safety monitoring

**III. Request for Individual Patient Data Listings format:**

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application.

# Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

## I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

## II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

### Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in theDefine file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR".

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

## III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

**Exhibit 1: Summary Level Clinical Site Data Elements**

| Variable Name | Variable Label | Type | Controlled Terms or Format | Notes or Description | Sample Value |
|---|---|---|---|---|---|
| IND | IND Number | Num/Char | 6 digit identifier | FDA identification number for investigational new drug | 010010 |
| TRIAL | Trial Number | Char | String | Study or Trial identification number | ABC-123 |
| SITEID | Site ID | Num/Char | String | Investigator site identification number | 50 |
| ARM | Treatment Arm | Num/Char | String | Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters) | Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo |
| ENROLL | Number of Subjects Enrolled | Num | Integer | Total number of subjects enrolled at a given site | 20 |
| SCREEN | Number of Subjects Screened | Num | Integer | Total number of subjects screened at a given site | 100 |
| DISCONT | Number of Subject Discontinuations | Num | Integer | Number of subjects discontinuing from the study after being enrolled at a site | 5 |
| ENDPOINT | Endpoint | Char | String | Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters) | Average increase in blood pressure |
| ENDPTYPE | Endpoint Type | Char | String | Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other) | Continuous |
| TRTEFFR | Treatment Efficacy Result | Num | Floating Point | The efficacy result for each primary endpoint, by treatment arm | 0, 0.25, 1, 100 |
| TRTEFFV | Treatment Efficacy Result Variance | Num | Floating Point | The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm | 0, 0.25, 1, 100 |
| SITEEFFE | Site-Specific Efficacy Effect Size | Num | Floating Point | The effect size should be the same representation as reported for the primary efficacy analysis | 0, 0.25, 1, 100 |
| SITEEFFV | Site-Specific Efficacy Effect Size Variance | Num | Floating Point | The variance of the site-specific efficacy effect size (SITEEFFE) | 0.065 |
| CENSOR | Censored Observations | Num | Integer | The number of censored observations for the given site and treatment | 5 |
| NSAE | Number of Non-Serious Adverse Events | Num | Integer | Total number of non-serious adverse events at a given site. This value should include multiple events per subject. | 10 |
| SAE | Number of Serious Adverse Events | Num | Integer | Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject. | 5 |
| DEATH | Number of Deaths | Num | Integer | Total number of deaths at a given site | 1 |

| Variable Name | Variable Label | Type | Controlled Terms or Format | Notes or Description | Sample Value |
|---|---|---|---|---|---|
| PROTVIOL | Number of Protocol Violations | Num | Integer | Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject. | 20 |
| FINLDISC | Financial Disclosure Amount | Num | Integer | Total financial disclosure amount ($USD) by the site investigator | 50000.00 |
| LASTNAME | Investigator Last Name | Char | String | Last name of the investigator as it appears on the FDA 1572 | Doe |
| FRSTNAME | Investigator First Name | Char | String | First name of the investigator as it appears on the FDA 1572 | John |
| PHONE | Investigator Phone Number | Char | String | Phone number of the primary investigator | 555-555-5555, 44-555-555-5555 |
| FAX | Investigator Fax Number | Char | String | Fax number of the primary investigator | 555-555-5555, 44-555-555-5555 |
| EMAIL | Investigator Email Address | Char | String | Email address of the primary investigator | john.doe@mail.com |
| COUNTRY | Country | Char | ISO 3166-1-alpha-2 | Country in which the site is located | US |
| STATE | State | Char | String | Unabbreviated state or province in which the site is located | Maryland |
| CITY | City | Char | String | Unabbreviated city, county, or village in which the site is located | Silver Spring |
| POSTAL | Postal Code | Char | String | Postal code for the site | 20850 |
| STREET | Street Address | Char | String | Street address and office number at which the site is located | 1 Main St, Suite 100 |

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: General Structure of Data Submission Template**

| IND | TRIAL | SITEID | ARM | ENROLL | SCREEN | DISCONT | ENDPOINT | ENDTYPE | TRTEFFR |
|---|---|---|---|---|---|---|---|---|---|
| 000001 | Study 1 | 001 | Active | 26 | 61 | 3 | Percent Responders | Binary | 0.48 |
| 000001 | Study 1 | 001 | Placebo | 25 | 61 | 4 | Percent Responders | Binary | 0.14 |
| 000001 | Study 1 | 002 | Active | 23 | 54 | 2 | Percent Responders | Binary | 0.48 |
| 000001 | Study 1 | 002 | Placebo | 25 | 54 | 4 | Percent Responders | Binary | 0.14 |
| 000001 | Study 1 | 003 | Active | 27 | 62 | 3 | Percent Responders | Binary | 0.54 |
| 000001 | Study 1 | 003 | Placebo | 26 | 62 | 5 | Percent Responders | Binary | 0.19 |
| 000001 | Study 1 | 004 | Active | 26 | 29 | 2 | Percent Responders | Binary | 0.46 |
| 000001 | Study 1 | 004 | Placebo | 27 | 29 | 1 | Percent Responders | Binary | 0.12 |

| TRTEFFV | SITEEFFE | SITEEFFV | CENSOR | NSAE | SAE | DEATH | PROTVIOL | FINLDISC | LASTNAME | FRSTNAME | PHONE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.0096 | 0.34 | 0.0198 | NA | 0 | 2 | 0 | 1 | 0.00 | Doe | John | 555-123-4567 |
| 0.0049 | NA | NA | NA | 2 | 2 | 0 | 1 | 0.00 | Doe | John | 555-123-4567 |
| 0.0108 | 0.33 | 0.0204 | NA | 3 | 2 | 1 | 0 | 45000.00 | Washington | George | 020-3456-7891 |
| 0.0049 | NA | NA | NA | 0 | 2 | 0 | 3 | 45000.00 | Washington | George | 020-3456-7891 |
| 0.0092 | 0.35 | 0.0210 | NA | 2 | 2 | 0 | 1 | 0.00 | Jefferson | Thomas | 01-89-12-34-56 |
| 0.0059 | NA | NA | NA | 3 | 6 | 0 | 0 | 0.00 | Jefferson | Thomas | 01-89-12-34-56 |
| 0.0095 | 0.34 | 0.0161 | NA | 4 | 1 | 0 | 0 | 0.00 | Lincoln | Abraham | 555-987-6543 |
| 0.0038 | NA | NA | NA | 1 | 2 | 0 | 1 | 0.00 | Lincoln | Abraham | 555-987-6543 |

| FAX | EMAIL | COUNTRY | STATE | CITY | POSTAL | STREET |
|---|---|---|---|---|---|---|
| 555-123-4560 | John@mail.com | RU | Moscow | Moscow | 103009 | Kremlin Road 1 |
| 555-123-4560 | John@mail.com | RU | Moscow | Moscow | 103009 | Kremlin Road 1 |
| 020-3456-7890 | george@mail.com | GB | Westminster | London | SW1A 2 | 10 Downing St |
| 020-3456-7890 | george@mail.com | GB | Westminster | London | SW1A 2 | 10 Downing St |
| 01-89-12-34-51 | tom@mail.com | FR | N/A | Paris | 75002 | 1, Rue Road |
| 01-89-12-34-51 | tom@mail.com | FR | N/A | Paris | 75002 | 1, Rue Road |
| 555-987-6540 | abe@mail.com | US | Maryland | Rockville | 20852 | 1 Rockville Pk. |
| 555-987-6540 | abe@mail.com | US | Maryland | Rockville | 20852 | 1 Rockville Pk. |

IND 51,235

# Avanafil for the Treatment of Erectile Dysfunction

Pre-NDA Meeting (NDA # 202,276)

20 October 2010

# Avanafil Proposed Indication

- Avanafil is indicated for the treatment of erectile dysfunction (ED)
- Avanafil will be made in three oral (tablet) dosage strengths:
  - 50 mg
  - 100 mg
  - 200 mg

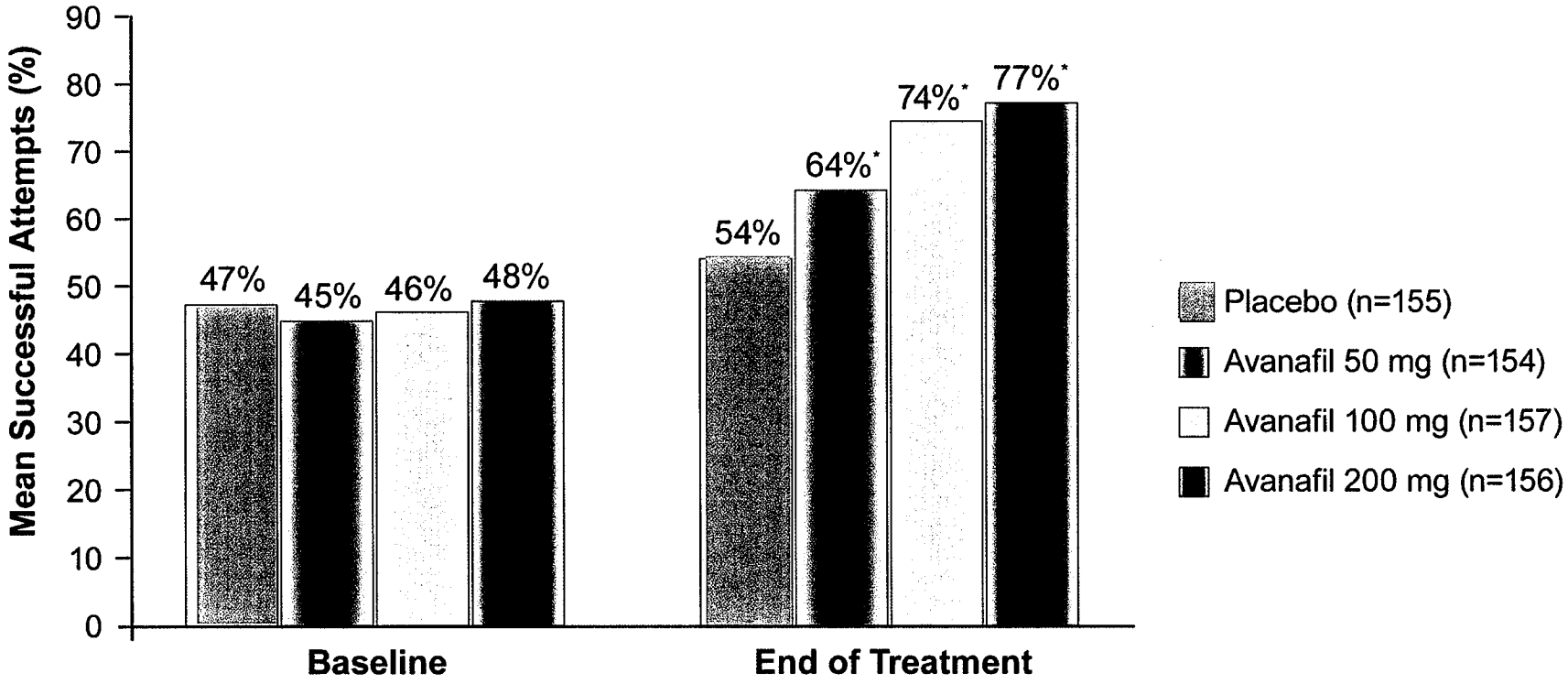
# Background

- Avanafil (TA-1790): A potent and selective phosphodiesterase (PDE) 5 inhibitor


- A complete package of nonclinical pharmacology, PK toxicology and clinical pharmacology has been completed by VIVUS and (b) (4)
- The Phase 3 program comprised studies TA-301, TA-302, TA-303 and TA-314. TA-301 and TA-303 were conducted under SPAs

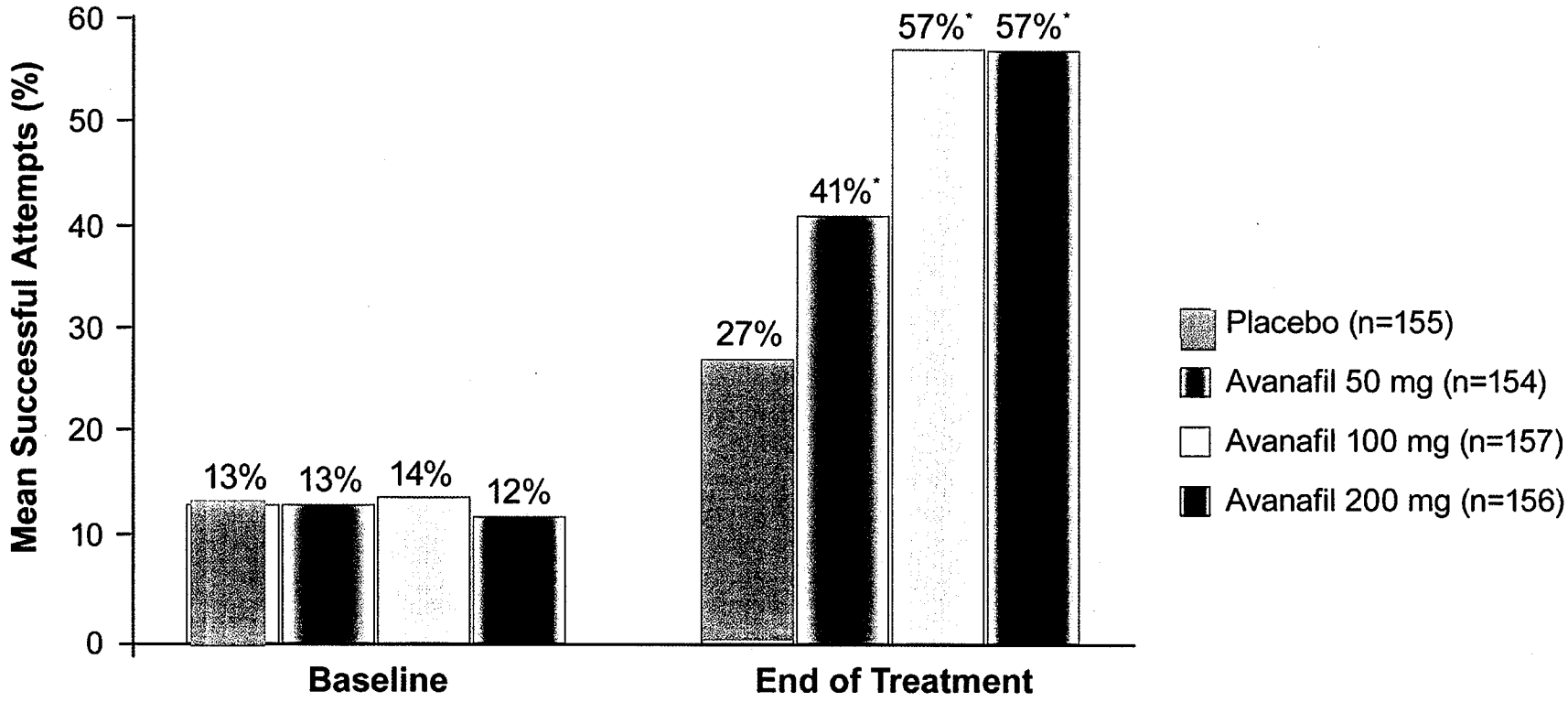
# TA-301: ED in the Generalized Population

# TA-301: Co-Primary Endpoint
## *SEP 2 (Vaginal Penetration) ITT*



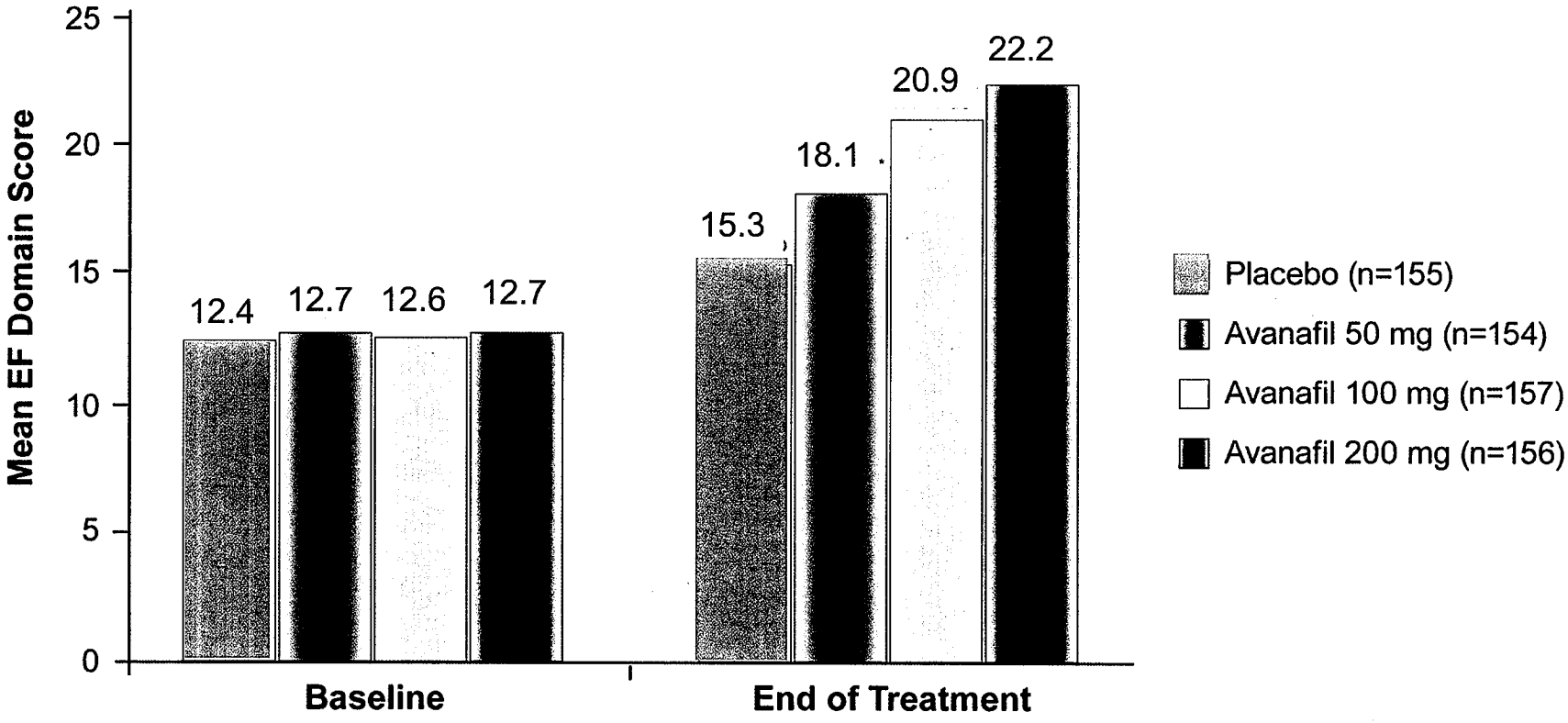

***p<0.001 vs placebo**

# TA-301: Co-Primary Endpoint
## *SEP 3 (Successful Intercourse) ITT*




***p<0.001 vs placebo**

# TA-301: Co-Primary Endpoint
## *Mean IIEF-EF Domain Score (ITT)*




***p≤0.001 vs placebo**

# TA-301: Treatment-Emergent Adverse Events

| N (%) | Placebo (n=161) | Avanafil 50 mg (n=160) | Avanafil 100 mg (n=161) | Avanafil 200 mg (n=162) |
|---|---|---|---|---|
| **TEAE** | **42 (26.1)** | **52 (32.5)** | **68 (42.2)** | **63 (38.9)** |
| **TEAE related to study drug** | **4 (2.5)** | **14 (8.8)** | **25 (15.5)** | **27 (16.7)** |
| **Discontinuations due to AE** | **5 (3.1)** | **3 (1.9)** | **6 (3.7)** | **4 (2.5)** |
| **Serious AE** | **2 (1.2)** | **1 (0.6)** | **3 (1.9)** | **3 (1.9)** |
| **Death** | **0** | **0** | **1 (0.6)** | **0** |

- SAEs included non-cardiac chest pain, depression suicidal, acute myocardial infarction, prostate cancer stage 1, gun shot wound, bladder transitional cell carcinoma, hypoesthesia, coronary artery disease, infected bite
- No drug-related serious AEs in the study

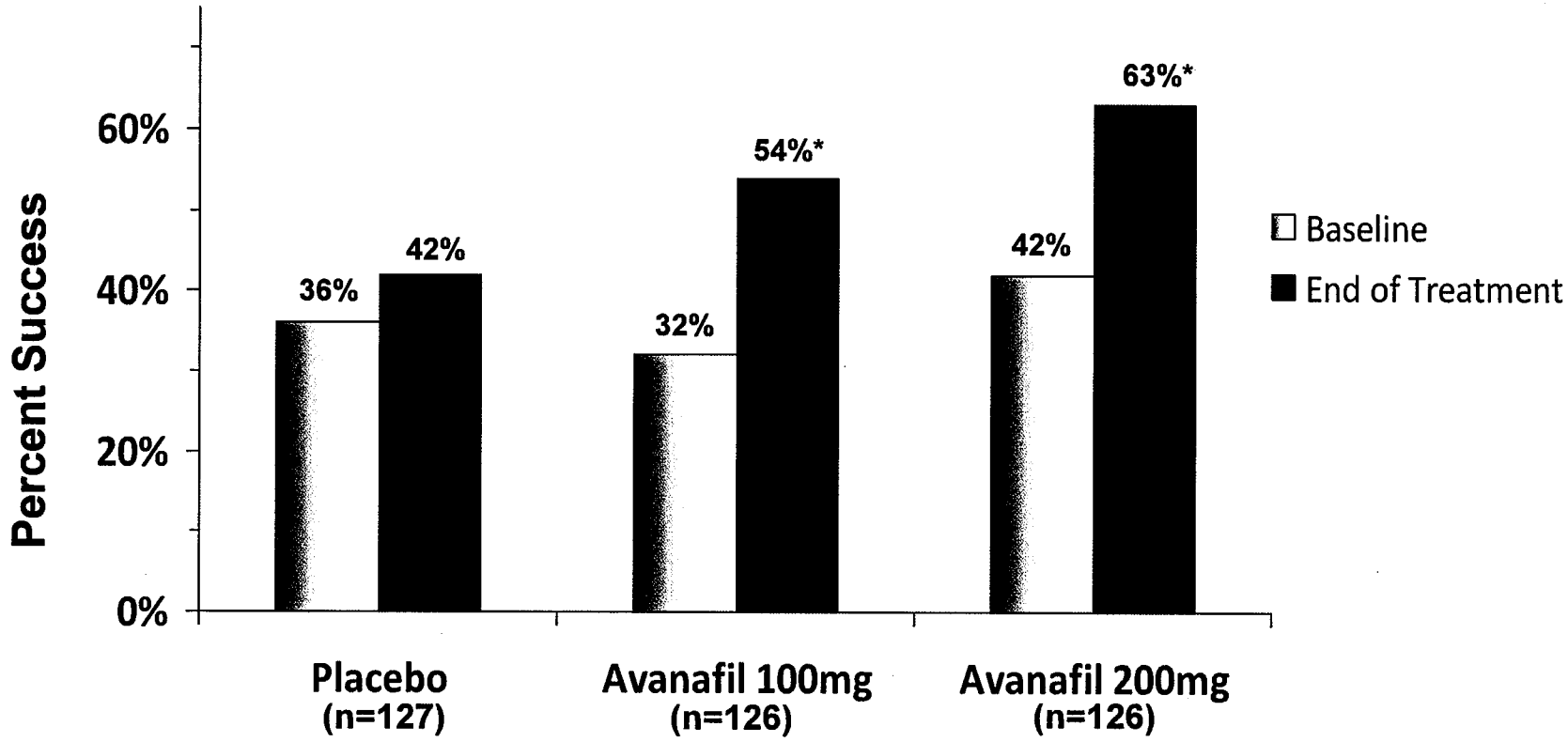
# TA-301: Treatment Emergent Adverse Events
## Reported >2% of Subjects

| | Placebo (n=161) | Avanafil 50 mg (n=160) | Avanafil 100 mg (n=161) | Avanafil 200 mg (n=162) |
|---|---|---|---|---|
| Headache | 1.2% | 4.4% | 7.5% | 9.3% |
| Flushing | 0% | 3.8% | 6.2% | 3.7% |
| Nasal Congestion | 1.2% | 0.6% | 4.3% | 1.9% |
| Back Pain | 0.6% | 2.5% | 2.5% | 1.9% |
| Bronchitis | 0.6% | 1.9% | 0.6% | 2.5% |
| Nasopharyngitis | 1.2% | 0.6% | 1.2% | 3.7% |

# TA-302: ED in Diabetic Men

# TA-302: Co-Primary Endpoint

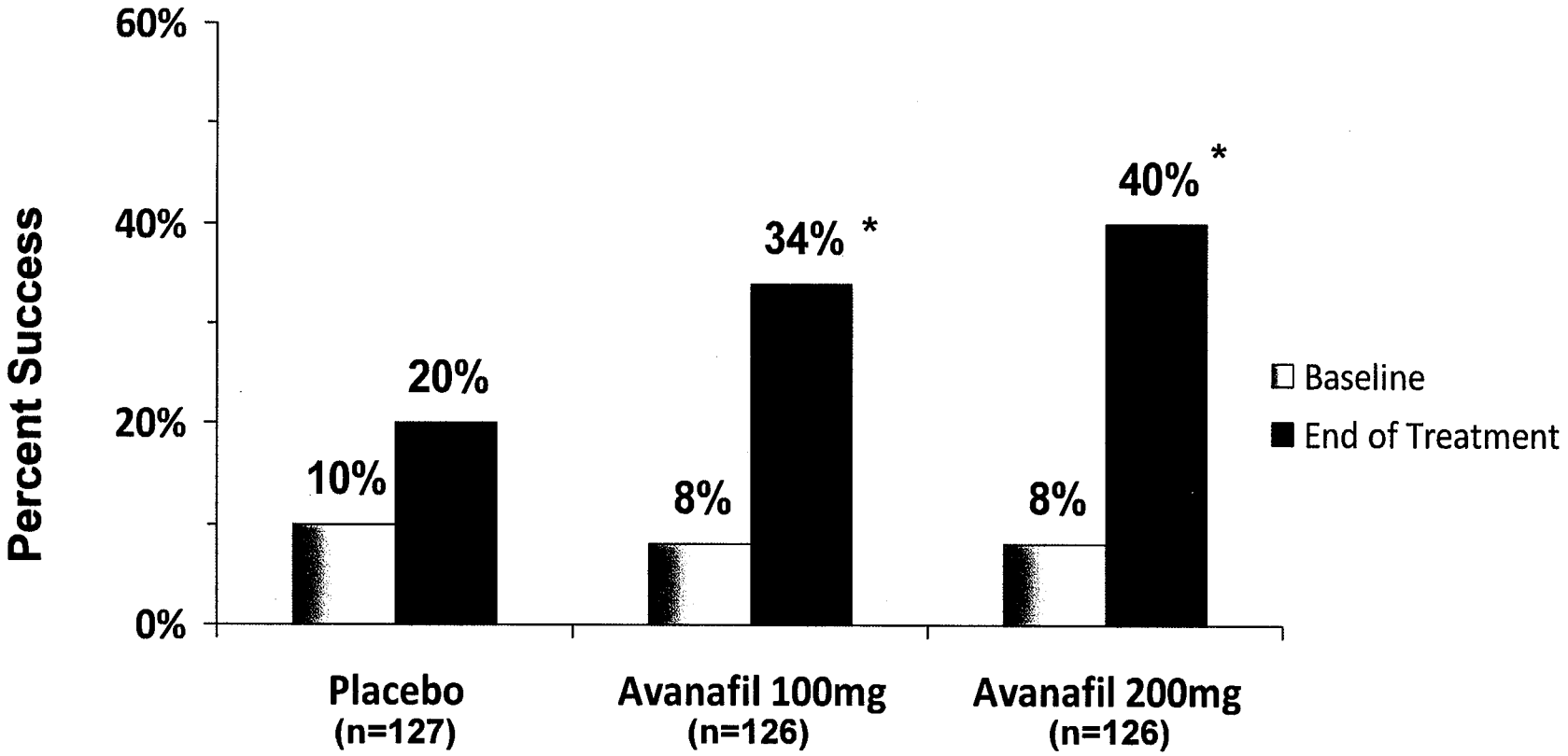
*SEP 2 (Vaginal Penetration) ITT*




***$p$<0.001 vs placebo**

# TA-302: Co-Primary Endpoint

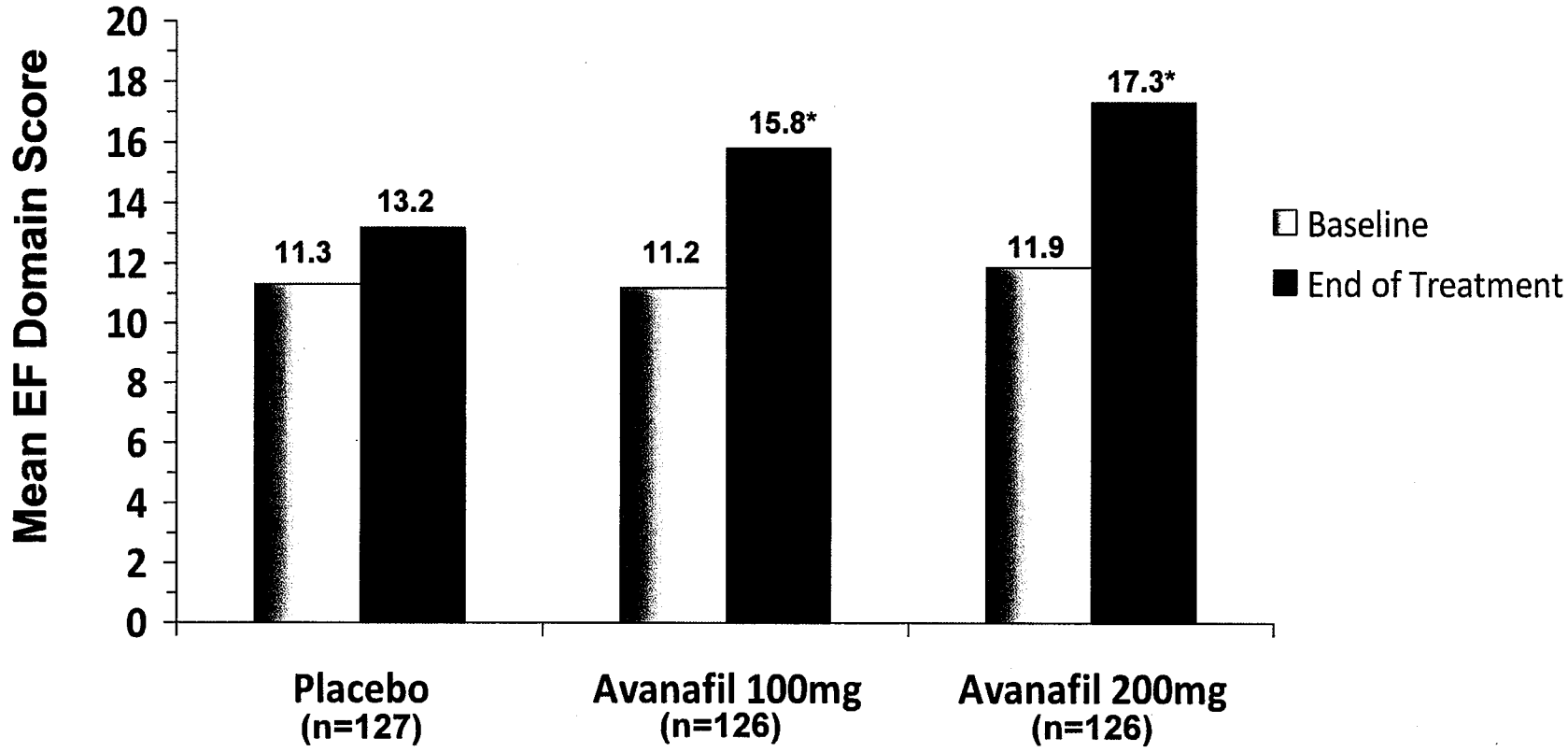
*SEP 3 (Successful Intercourse) ITT*




***$p<0.001$ vs placebo**

# TA-302: Co-Primary Endpoint

*Mean IIEF-EF Domain Score (ITT)*




***$p<0.002$ vs placebo**

# TA-302: Treatment-Emergent Adverse Events

| N (%) | Placebo (n=130) | Avanafil 100 mg (n=127) | Avanafil 200 mg (n=131) |
|---|---|---|---|
| TEAE | 31 (23.8) | 45 (35.4) | 42 (32.1) |
| TEAE related to study drug | 5 (3.8) | 9 (7.1) | 20 (15.3) |
| Discontinuations due to AE | 0 | 3 (2.4) | 2 (1.5) |
| Serious AE | 1 (0.8) | 3 (2.4) | 4 (3.1) |
| Death | 0 | 0 | 0 |

**SAEs included unstable angina, localized infection of the lower leg, pneumonia, urinary tract infection, spine fracture, muscular pain and weakness, bladder cancer and deep vein thrombosis.**

***No drug-related serious AEs in the study**

# TA-302: Treatment-Emergent Adverse Events Reported >2% of Subjects

| | Placebo (n=127) | Avanafil 100 mg (n=126) | Avanafil 200 mg (n=127) |
|---|---|---|---|
| Headache | 1.5% | 3.9% | 11.5% |
| Nasopharyngitis | 4.6% | 3.1% | 3.1% |
| Flushing | 0% | 1.6% | 3.8% |
| Sinus congestion | 0.8% | 0.8% | 3.1% |
| Sinusitis | 0% | 3.1% | 0.8% |
| Dyspepsia | 0% | 0% | 3.1% |
| Influenza | 0% | 2.4% | 0% |
| Back pain | 2.3% | 1.6% | 0.8% |

# TA-314: Open-Label, Long-Term Safety and Tolerability

# TA-314 Study Overview

- Extension of TA-301 and TA-302
- All subjects began at 100 mg avanafil
- Subjects were allowed to increase (200 mg) or decrease (50 mg) their dose
- Same datasets collected for safety and efficacy
- Treatment continued for up to 12 months (total)

# TA-314: Efficacy

| EFFICACY | N = 686 |
|---|---|
| SEP 3 - overall success in TA-314 | 67% |
| SEP 3 – change from baseline | 55% |
| SEP 2 - overall success in TA-314 | 80% |
| SEP 2 – change from baseline | 37% |
| EF-IIEF - end of treatment | 22.6 |
| EF-IIEF – change from baseline | 10.3 |

# TA-314: Discontinuations and SAEs

| Percent of Subjects | N = 712 |
|---|---|
| Discontinuation due to AEs | **2.8%** |
| Serious Adverse Events (SAE) | **1.5%** |
| Severe TEAE | **2.9%** |
| Drug related SAEs | **0%** |
| Deaths | **0%** |

# TA-314: Treatment-Emergent Adverse Events ≥1%

| Percent of Subjects | N = 712 |
|---|---|
| Headache | 5.6 |
| Flushing | 3.5 |
| Nasopharyngitis | 3.4 |
| Nasal Congestion | 2.1 |
| Back Pain | 1.5 |
| Influenza | 1.5 |
| Upper Respiratory Tract Infection | 1.5 |
| Sinusitis | 1.4 |
| Diarrhea | 1.3 |
| Dizziness | 1.3 |
| Hypertension | 1.3 |
| Bronchitis | 1.1 |
| Arthralgia | 1.0 |

# TA-314: Targeted Medical Events

| Number (%) of Subjects | N = 712 |
|---|---|
| Upper respiratory events | 80 (11.2) |
| Hemodynamic changes | 10 (1.4) |
| Special sensory effects (hearing) | 4 (0.6) |
| Special sensory (vision) | 3 (0.4) |
| Other (e.g., priapism) | 3 (0.4) |
| Major cardiac events | 0 |

# Subject Exposure in Avanafil Development Program

| **TOTAL Avanafil Exposure** | **Avanafil** | **Placebo** |
|---|---|---|
| Treated with at least one dose | **1949** | **612** |
| Treatment for at least 3 months | **990** | **290** |
| Treatment for at least 6 months | **493** | NA |
| Treatment for at least 1 year | **153** | |

# Summary – Avanafil Clinical Program

- Avanafil met all three co-primary endpoints at all three doses studied in the general ED population, and at both doses studied in diabetic men with ED
- Avanafil was safe and well-tolerated in subjects treated for as long as 12 months
- No new or unexpected safety issues were identified
- NDA submission planned for Q1 2011
- Study in men following radical prostatectomy is ongoing and will be completed after submission of NDA

# QUESTIONS

## Clinical Questions:

Clinical Question 1: Does the Division agree with VIVUS' plan for data pooling for the ISS?

Clinical Question 6: Does the Division agree that the pooled databases for the ISS and ISE will consist of ADaM data only, and will not include pooled tabulations data?

Clinical Question 10: Does the Division agree that the clinical pharmacology program as presented in Appendix 2 is adequate to support the NDA submission for avanafil?

# QUESTIONS

## Clinical Questions:

Clinical Question 11: Given that the 3 dosage strengths (50, 100 and 200 mg) are a [redacted] (b) (4) does the Division agree that a dosage form equivalence study is not needed to support the marketing of the 3 dosage strengths?

## Nonclinical Questions:

Nonclinical Question 3: Does the Division agree that the database of nonclinical information on TA-1790 is sufficient to support approval of avanafil?

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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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MARK S HIRSCH
11/18/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,235

**SPECIAL PROTOCOL ASSESSMENT –
NO AGREEMENT**

VIVUS, Inc.
Attention: Jacqueline Dombroski, Ph.D.
Senior Director, Regulatory Affairs
1172 Castro Street
Mountain View, CA 94040

Dear Dr. Dombroski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TA-1790 (avanafil).

We also refer to your December 5, 2008 request, received on December 8, 2008, for a special protocol assessment of the proposed [redacted] (b) (4) n for Avanafil Tablets 50 mg, 100 mg and 200 mg that are to be administered in Phase 3 clinical studies.

We have completed our review and, based on the information submitted, we are providing the following responses to your questions:

**Question 1: [redacted] (b) (4) n and number of lots included in the stability study provide adequate data for the FDA to accept and file an NDA for Avanafil Tablets 50 mg, 100 mg and 200 mg, Formulation II?**

FDA Response: *No, since avanafil is a New Molecular Entity, the proposed stability package will not provide enough information for NDA submission.* [redacted] (b) (4) *A bracketing design may be more appropriate for your product.*

*Although the identity of the excipients has not changed between Formulation I and Formulation II, the change in the relative amounts is a major change. Using the scientific reasoning in 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****, this change is determined to be a Level 3 excipient change for which a Bioequivalence study is recommended to provide a link between studies performed with the two different formulations. Please refer to the Guidance for additional information on recommendations for this type of change.*

**Question 2: Will it be acceptable to the CMC reviewers to submit additional data on the lots of Avanafil Tablets from the lots entered into the (b) (4) stability study during the NDA review period?**

FDA response: *In order to adhere to the Good Review Management Practices (GRMP) guidelines, additional stability data will be accepted up to month 5 of the review cycle. After that time, we do not agree that additional data will be reviewed during the review cycle. The expiration dating period will be set based on evaluation of the submitted data.*

**Question 3: Are the proposed tests and specifications for the future lots to be placed in the stability studies acceptable?**

FDA response*: The proposed tests appear to be adequate, with the following comments.*

- *The adequacy of the acceptance criteria is a NDA review issue and will be finalized at that time*
- *Although* ***the Guidance for Industry: ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*** *allows that drug substance process impurities do not need to be reported in the drug product specifications, it is premature to delete these tests and/or not report the results during development. Continue to perform and report results on these tests. Deletion and/or change in reporting can be requested at the time of NDA submission.*
- *Include the microbial limits testing on the specification sheet. The frequency of testing on stability is adequate.*

If you choose to submit a revised protocol, it should address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products*). This meeting would be limited to discussion of this protocol.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

Moo Jhong Rhee, Ph.D.
Branch Chief
Division of Premarketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

| Linked Applications | Sponsor Name | Drug Name / Subject |
|---|---|---|
| IND 51235 | VIVUS INC | TA1790 |

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

/s/

MOO JHONG RHEE
01/16/2009
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,235

Vivus, Inc.
Attention: Peter Tam
Sr. Vice President, Product & Corporate Development
1172 Castro Street
Mountain View, CA 94040

Dear Mr. Tam:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avanafil, 50 mg, 100 mg and 200 mg.

We also refer to your December 20, 2006, request for a special clinical protocol assessment, serial number 044, received on December 22, 2006. The protocol is entitled, "A Double- Blinded, Randomized Phase 3 Evaluation of the Safety and Efficacy of Avanafil in Subjects with Generalized Erectile Dysfunction."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

1. **The attached Phase 3 protocol will enroll men with generalized erectile dysfunction. Does the Division agree that this is an appropriate patient population to be evaluated in this protocol for the indication of erectile dysfunction? As indicated, similar studies will be conducted in men with erectile dysfunction associated with diabetes mellitus and in men with erectile dysfunction associated with a radical prostatectomy.**

   We agree that "men with generalized erectile dysfunction" is an appropriate patient population to be evaluated in this protocol (also see our response to Question #2). As discussed at the End-Of-Phase 2 meeting, we continue to recommend that two Phase 3 trials be conducted in support of the indication. One of these Phase 3 studies may be conducted in the "generalized" ED population. The other should be conducted in men with erectile dysfunction associated with diabetes mellitus.

2. **Does the Division support the use of the inclusion criteria outlined in the draft protocol for the identification and enrollment of the patient population to be studied?**

   No.
   a) Include men aged 18 years and above (not only those aged 35-70).
   b) Do not exclude men who have previously undergone a transurethral resection of the prostate.

3. **The sponsor will be using a daily diary to collect data in assessing two of the co-primary endpoints, as follows:**
   a. **Did your erection last long enough for you to have successful intercourse (Yes/No)?**
   b. **Were you able to insert your penis into your partner's vagina (Yes/No)?**

   **Does the Division agree with the use of these two co-primary endpoints to assess efficacy for men with generalized erectile dysfunction in this patient population and the method of data collection using the diary to assess efficacy?**

   When combined with the third co-primary endpoint of the EF domain of the IIEF, we agree that these two endpoints are acceptable for assessing efficacy. The patient diary should be submitted for our review.

4. **The third primary endpoint will be subject scores on the erectile function domain of the International Index of Erectile Function (IIEF). Does the Division agree with the use of this endpoint?**

   Yes. The EF domain of the IIEF is acceptable as a third co-primary endpoint.

5. **Is the proposed statistical method to be used for the primary endpoints acceptable?**

   a. The step-down multiple comparison approach for each endpoint is acceptable.
   b. The details of handling missing values should be specified.

6. **If efficacy and safety is demonstrated in this controlled Phase 3 study (600 subjects) as well as the proposed studies in men with diabetes (300 subjects) and in men after a radical prostatectomy (300 subjects), is the patient population sufficient to support approval of this product for erectile dysfunction? Does the Division agree that these studies will be adequate to support the indication in men for the treatment of generalized erectile dysfunction** (b) (4) (b) (4) (b) (4)

   In conjunction with the usual long-term safety information required for a chronically used new drug, three separate placebo-controlled Phase 3 studies (one in a "generalized" ED population, one in a diabetic ED population, and one in men with ED after a radical prostatectomy) would be sufficient for submission of a new drug application in support of the ED indication.

In addition, we have the following comments:

1. The frequency of use of avanafil should be defined in the protocol. Specifically, how many doses are allowed in each 24 hour period?

2. (b) (4).

3. [redacted] (b) (4)

4. [redacted] (b) (4)

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 796-0881.

Sincerely,

*{See appended electronic signature page}*

Mark Hirsch, M.D.
Acting Deputy Director
Division of Reproductive and Urologic
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Mark S. Hirsch
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,235

VIVUS, INC.
Attention: Carol Zoltowski, V.M.D.
Vice President, Regulatory Affairs
1172 Castro Street
Mountain View, CA 94040

Dear Dr. Zoltowski:

Please refer to your Investigational New Drug Application (IND) submitted on November 30, 2001, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TA-1790.

We also refer to the meeting between representatives of your firm and the FDA on November 2, 2005. The purpose of the meeting was to discuss your plans for the Phase 3 development of avanafil.

The official meeting minutes is enclosed. You are responsible for notifying us of any significant differences in understanding of the meeting outcome.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 796-2130.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

# Meeting Minutes

**Date:** November 2, 2005

**IND 51,235** **Drug Name:** TA-1790 (avanafil)

**Indication:** treatment of erectile dysfunction

**Type of Meeting**: End of Phase 2 Meeting

**Sponsor**: VIVUS, Inc.

**Meeting Chair:** Dr. George Benson **External Participant Lead**: Dr. Carol Zolstowski

**Meeting Recorder:** Ms. Eufrecina DeGuia

**FDA Attendees:**
George Benson, M.D. – Medical Team Leader, Division of Reproductive and Urologic Products (DRUP)
Julie Beitz, M.D. – Deputy Director, Office of Drug Evaluation (ODE) III
Daniel Shames. M.D. – Director, DRUP
Eufrecina DeGuia - Regulatory Health Project Manager, DRUP
Lynnda Reid, Ph.D. – Pharmacology and Toxicology Team Leader, DRUP
Yangmee Shin, Ph.D. – Pharmacology and Toxicology Reviewer, DRUP
Jennifer Mercier – Chief, Project Management Staff, DRUP
Myong Jin Kim, Ph.D. – Clinical Pharmacology Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUP

**VIVUS, Inc. Attendees**
Leland Wilson - President and CEO
John Dietrich, Ph.D. - Vice President, Research and Development
Craig Peterson - Senior Director, Clinical Affairs
Peter Tam - Senior VP, Product and Corporate Development
(b) (4)

**Background:**

TA-1790 (avanafil) is a new orally active phosphodiesterase type 5 (PDE5) inhibitor for the treatment of erectile dysfunction. The sponsor believes that avanafil has a rapid onset of action and a rapid plasma disappearance. To date, VIVUS has conducted a number of preclinical and clinical studies on avanafil that included 648 subjects. Clinical study results showed that $T_{max}$ is between 30 and 45 minutes and $T_{1/2}$ of between 1 and 1.25 hours.

**Discussion and Decision Points:**

**The following responses were revised to reflect the discussions and agreements made in today's meeting. Preliminary responses to questions posed in the September 29, 2005, meeting package were faxed to the sponsor on October 25, 2005.**

*Question 1: Assuming that the drug is efficacious and safe, are these numbers and the duration of double-blind treatment sufficient for approval of avanafil for the treatment of ED?*

**Answer:** The number of patients to be studied in Phase 3 is sufficient and the primary endpoints and the duration of the double-blind treatment are acceptable. Two Phase 3 studies in the "general" ED group should be performed. (Also, see answers to questions #2 and 3). Extension safety trials with at least 100 patients treated for 1 year will be required.

*Question 2: Are the overall designs of the planned Phase 3 trials adequate (**Attachment 9-protocol synopses**)?*

**Answer:** The overall design of the protocol synopses for Studies #1, 2, and 3 appear to be adequate.

*Question 3: If avanafil significantly improves erectile function relative to* (b) (4) *or both timepoints [**Attachment 9, Planned Studies #4 & 5**], will VIVUS be able to make this claim in the label?*

**Answer:** (b) (4)

*Question 4: Are the overall study numbers sufficient, given adequate efficacy and acceptable safety to obtain* (b) (4) *patients?*

**Answer:** The indication would be consistent with other PDE5 inhibitors, i.e., "the treatment of erectile dysfunction." (b) (4) The overall number is sufficient.

*Question 5: VIVUS plans to roll over at least 300 patients who have completed Phase 3 studies into a 6-month, open-label study in order to obtain information on longer term as-needed dosing. Does DRUDP agree with this plan?*

**Answer:** Safety data for at least 300 patients on drug for 6 months and 100 patients for 12 months will be required.

*Question 6: The total clinical development program for avanafil consists of 5 Phase 3 trials described above [see also **Attachment 9**], the completed clinical studies [**Attachment 6**], and the additional studies planned [**Attachment 10**]. These studies form the basis of an adequate clinical development package for avanafil. Does DRUDP agree with this?*

**Answer:** The studies outlined in Attachments 6, 9, and 10 are, in general, acceptable. The drug-drug interaction studies should include two studies to evaluate the effect on blood pressure of co-administration of avanafil and two alpha adrenergic blocking agents.

An absolute bioavailability study and severe hepatic and renal impairment studies are not required but information would be useful. The sponsor should submit the QT study protocol to the Division for review prior to initiating the study. A study to determine the concentration of avanafil in semen should also be conducted.

*Question 7: For the proposed Phase 3 clinical studies, does the Division require that female partners of study patients be consented?*

**Answer:** No.

**Dosing Flexibility**

*Question: Pharmacokinetic studies conducted by VIVUS and* (b) (4) *indicate that avanafil has a plasma half-life of approximately 1.5 hours and that it does not demonstrate any appreciable plasma accumulation when dosed once* (b) (4) *Based on this half-life, VIVUS intends to limit the maximum number of doses* (b) (4)*, to be used on an as-needed basis in its Phase 3 program.*

*If the Phase 3 program demonstrates that the safety profile of such dosing regimen is acceptable, would VIVUS be able to claim in the label that avanafil can be used* (b) (4) (b) (4)

**Answer:** If clinical safety and clinical pharmacology data support the use of avanafil (b) (4) (b) (4) this information could be included in labeling. Pharmacodynamic (PD) studies should also be conducted. PK/PD (including safety) studies should be conducted if the sponsor wishes to include labeling for a (b) (4)

**Nitrate Interaction**

*VIVUS conducted a study [TA-04] in 100 normal, healthy, adult males to evaluate and compare the effects of 200 mg of avanafil, 100 mg of sildenafil, and placebo on the hemodynamic response to sublingual glyceral trinitrate (GTN), 0.4 mg. Results demonstrated that avanafil had less of an effect, compared to sildenafil, with respect to maximum GTN-induced changes in blood pressure and heart rate, and that the effects of avanafil on GTN-induced changes in blood pressure and heart rate disappeared by 12 hours, compared to the hemodynamic effects of sildenafil, which were still present at 12 hours. The study also showed that the number of patients who developed clinically significant orthostatic hypotension on GTN (30 mmHg or greater drop in standing systolic blood pressure) after pretreatment with placebo, avanafil and sildenafil were 11, 14 and 28, respectively.*

*VIVUS intends to use this study to support the nitrate contraindication statement in the label that nitrates should not be used for at least 12 hours after avanafil, as compared to 24 to 48 hours for currently available PDE5 inhibitors. Does the Division concur based on the results of the study?*

**Answer:** If avanafil is approved for the treatment erectile dysfunction, the avanafil – glyceral trinitrate data (for avanafil) would be placed in the Clinical Pharmacology section of the label. The duration of the avanafil-nitrate interaction could be placed in the label based on study data.

*Additionally, on the basis of this study, VIVUS would like to include the results* (b) (4) [redacted] *. Is this acceptable to the Division?*

**Answer:** (b) (4) [redacted] The Division has not yet decided what would appear in the label.

**Drug-Drug Interaction**

*Since avanafil is a vasodilator, interaction studies will be conducted with drugs that decrease blood pressure so as to rule out an additive or synergistic hypotensive effect. In addition, since avanafil is metabolized primarily by CYP3A4 of the hepatic cytochrome P450 enzyme system, interaction studies will be conducted with drugs that are metabolized by the same system to define effects on the PK profile. Pharmacodynamic studies to evaluate the effects on blood pressure will be conducted with avanafil and the following drugs: alcohol, an alpha blocker, amlodipine and enalapril. Pharmacokinetic studies will be conducted using avanafil and the following drugs: ritonavir, ketoconazole and erythromycin. In addition, avanafil will also be combined with aspirin and with warfarin to evaluate if there are any effects on the clotting process.*

*Does the agency agree with VIVUS' plan to evaluate the metabolic effects of avanafil with a representative list of drugs that are affected by the CYP3A4?*

Answer: Yes.

*Does the agency accept this list of drugs as adequate with respect to drug-drug interaction studies?*

a. *Pharmacodynamic- alcohol, an alpha blocker, amlodipine, enalapril*
b. *Pharmacokinetic- ritonavir, ketoconazole, erythromycin*

Answer: Yes. Drug-drug interaction studies should be performed with two alpha-blockers. Patients should be on stable dose of alpha blockers . The Division recommends that ketoconazole 400mg QD be used in the drug interaction study with ketoconazole.

**Nonclinical Studies**

*VIVUS has completed a number of preclinical and nonclinical safety studies, including a 3-month study in mice, a 6-month study in rats and a 9-month study in dogs as well as genotoxicity and in vitro cardiovascular safety studies. Two rodent carcinogenicity studies are ongoing and the in-life portions will be completed in March of 2006. We are planning to conduct reproductive/developmental studies concomitantly with the Phase 3 program. No other safety/nonclinical studies are planned.*

*Is this nonclinical safety program for avanafil adequate for registration?*

**Answer:** No. The following information should be submitted prior to the conduct of the Phase III study:

- Male fertility and the teratogenicity studies are required. The sponsor asked if these studies can be conducted concurrently with Phase 3. This issue was discussed internally and the Division decided that these studies should be conducted prior to initiation of Phase 3 studies unless the sponsor can demonstrate that the drug is not present in semen.
- Comparative metabolic profiles in animals and humans should be provided as requested previously to verify that the major human metabolite(s) are produced in animals and the metabolite profiles are qualitatively similar across species. In vitro metabolic profile is acceptable. However, in vivo is required for Phase 3.
- Address the potential of avanafil and/or metabolites for phototoxicity and immunotoxicity as discussed previously.

**Action Items:**

- VIVUS will submit a request for Special Protocol Assessment.
- The sponsor will request a separate EOP2 CMC meeting.

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/s/

George Benson
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