

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202276Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: 04/26/2012

Team Leader Zachary Oleszczuk, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name(s) Stendra (Avanafil) Tablets
and Strength(s): 50 mg, 100 mg, and 200 mg

Application Type/Number: NDA 202276

Submission Number: Supporting Document 29

Applicant/sponsor: Vivus, Inc.

OSE RCM #: 2011-3056-1

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the revised container labels, Physician Sample labels, Physician Sample, Carton labeling, and packaging for Stendra (Avanafil) NDA 202276, submitted by the Applicant on April 26, 2012 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

DMEPA reviewed the initial proposed labels and labeling for this product in OSE Review #2011-3056, on January 26, 2012. DMEPA recommended multiple revisions and the Applicant submitted new labels and labeling on April 26, 2012, to address our recommendations.

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels, Physician Sample Label, Physician Sample Carton Labeling and packaging submitted April 26, 20120 (Appendix A)

Additionally, DMEPA had previously reviewed the labels and labeling and we looked at the reviews to ensure all our recommendation were implemented.

3 CONCLUSIONS

Review of the container labels and Physician sample labels and packaging find that the revised labels submitted on April 26, 2012, are acceptable to DMEPA. Specifically related to our recommendations in OSE Review #2011-3056, dated January 26, 2012, we requested that Applicant revise their Physician Sample to be child resistant. However, the Applicant provided more information regarding their Physician Sample via email on April 24, 2012. The email stated that their Physician Sample packaging has cardboard covering the foil backing for each tablet. This packaging configuration is similar to other drugs within the same class (Levitra). Additionally, the Applicant included the state “This package is not child resistant” on the principal display panel of their Physician sample and it is prominently located directly under the proprietary and established name of the product. Therefore, DMEPA finds the revised labels, labeling and packaging for this product acceptable and we have no further comments.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

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

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

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/s/

ZACHARY A OLESZCZUK
04/26/2012

PMR/PMC Development Template

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

NDA/BLA # 202276
Product Name: STENDRA (avanafil)

PMR/PMC Description: A randomized, placebo-controlled, double-blind, single-dose, vision trial to assess the effects of avanafil on multiple parameters of vision, including, but not limited to visual acuity, intraocular pressure, pupillometry, and color vision discrimination, in healthy male subjects.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>August 2012</u>
	Study/Trial Completion:	<u>February 2013</u>
	Final Report Submission:	<u>August 2013</u>

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

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

Effects of avanafil on color discrimination were evaluated in two phase 1 studies (studies HP-01 and TA-016) which provided limited vision safety data. Only one subject in the Phase 3 trials reported a change in color vision. A dedicated vision safety trial, to include multiple parameters of vision such as visual acuity, intraocular pressure, pupillometry and color vision discrimination, is needed for a robust assessment of the effect of avanafil on vision.

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

Additional evidence from a dedicated vision trial is needed for a robust assessment of the effects of avanafil in vision. See also our comment above.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

A randomized, placebo-controlled, double-blind, randomized, placebo-controlled single dose trial to evaluate the effect of avanafil on multiple parameters of vision.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Two completed Phase 1 studies provide limited information concerning the effect of avanafil on vision. An additional study is needed to provide a robust assessment.

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

 - Other
-

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

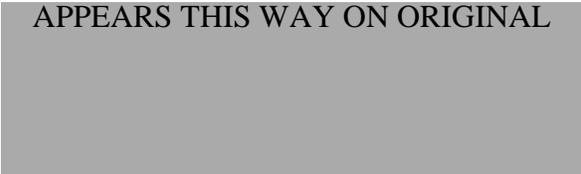
- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine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

PMR/PMC Development Coordinator:

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

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/s/

MEREDITH ALPERT
04/25/2012

AUDREY L GASSMAN
04/26/2012

See our response to Question #1. A preclinical signal in rats was identified for adverse effects on sperm. The effect is reversible with discontinuation of treatment. A single dose study in humans showed no adverse effects on sperm. A multiple-dose sperm study is being requested to assure reproductive safety in men who use avanafil at the maximum recommended frequency of once per day.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

This PMR is for a multiple-dose human sperm trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
This PMR is for a special safety study to assess the effect of multiple doses of avanafil on human sperm.
-

Agreed upon:

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

-
- Other
-

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

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

PMR/PMC Development Coordinator:

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

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/s/

MEREDITH ALPERT
04/25/2012

AUDREY L GASSMAN
04/26/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	STENDRA (avanafil) tablets, for oral use
Applicant	VIVUS, Inc.
Application/Supplement Number	NDA 202276
Type of Application	Original Submission
Indication(s)	Treatment of erectile dysfunction
Established Pharmacologic Class ¹	Phosphodiesterase 5 (PDE5) inhibitor
Office/Division	ODE III/DRUP
Division Project Manager	Eufrecina Deguia
Receipt Date	June 29, 2011
PDUFA Goal Date	April 29, 2012
SEALD Review Date	April 25, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A (not applicable)**: This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information (SRPI) Revised

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Selected Requirements of Prescribing Information (SRPI)

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Reference For Last Bulleted Item Under Dosage And Administration Heading Is Missing. Insert Reference (2.3). Also, The Two Bulleted Items Under Use In Specific Populations Heading Incorrectly Reference (2.3). Delete.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information (SRPI) Revised

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: 4-digit year is missing. Insert.

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information (SRPI) Revised

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI) Revised

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *There Is Fda-Approved Patient Labeling For This Application And The Statement Must Read "See 17 For Patient Counseling Information And Fda-Approved Patient Labeling" And Not "See 17 For Patient Counseling Information."*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment: The Horizontal Line Is Missing. Insert.

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *There Are 3 Subsection Headings (5.11, 5.12 And 5.13) In The TOC Which Are Not In The FPI And Need Deleted From The TOC.*

Selected Requirements of Prescribing Information (SRPI) Revised

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- NO** 37. All section and subsection headings and numbers must be **bolded**.
Comment: *In The FPI, Subsection 12.3 Pharmacokinetics Is Not Bolded.*
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information (SRPI) Revised

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Many Of The Cross References In The FPI Cross Reference To Incorrect Subsections Or Information For Subsections That Do Not Exist. DRUP To Correct All Cross References In FPI Prior To Approval.*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI) Revised

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), 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.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JEANNE M DELASKO
04/25/2012

LAURIE B BURKE
04/25/2012

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

PATIENT LABELING REVIEW

Date: **April 17, 2012**

To: Scott Monroe, MD, Director
Division of Reproductive and Urologic Products (DRUP)

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

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): STENDRA (avanafil)

Dosage Form and Route: Tablet, for Oral Use

Application Type/Number: NDA 202-276

Applicant: **Vivus Inc.**

1 INTRODUCTION

On June 29, 2011, Vivus Inc. submitted for the Agency's review a New Drug Application (NDA 202-276) for STENDRA (avanafil) Tablets, indicated for the treatment of erectile dysfunction (ED).

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI), for STENDRA (avanafil) Tablets.

2 MATERIAL REVIEWED

- Draft STENDRA (avanafil) Patient Package Insert (PPI) received on June 29, 2011 and received by DMPP on April 13, 2012.
- Draft STENDRA (avanafil) Prescribing Information (PI) received June 29, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on April 13, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
04/17/2012

MELISSA I HULETT
04/17/2012

LASHAWN M GRIFFITHS
04/17/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 15, 2012

TO: Eufrecinia DeGuia, Regulatory Project Manager
Guodong Fang, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

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

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

THROUGH: Tejashri Purohit-Sheth, M.D.
Division Director (Acting)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202276

APPLICANT: VIVUS, Inc.

DRUG: (b) (4)® (avanafil)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of erectile dysfunction (ED) (b) (4)

CONSULTATION REQUEST DATE: September 1, 2011

DIVISION ACTION GOAL DATE: March 30, 2012

PDUFA DATE: April 29, 2012

I. BACKGROUND:

The Applicant submitted this NDA for the use of (b) (4)® to support an indication for the treatment of ED (b) (4)®. Two studies, Protocol #TA-301, entitled "A Randomized, Double-Blind, Placebo-Controlled Evaluation Of The Safety And Efficacy Of Avanafil (TA-1790) In Subjects With Generalized Erectile Dysfunction", and Protocol #TA-302 entitled "A Randomized, Double-Blind, Placebo-Controlled Evaluation Of The Safety And Efficacy Of Avanafil (TA-1790) In The Treatment Of Erectile Dysfunction In Diabetic Men", were submitted in support of the indication.

The conduct of clinical studies for Protocol #TA-301 and #TA-302 was inspected. Protocol #TA-301 was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel design, four-arm Phase 3 trial to assess the safety and efficacy of avanafil in the treatment of mild-to-severe ED in adult heterosexual males. Inclusion criteria required, but were not limited to, being 18 years of age or older, having a history of mild to severe ED of at least six months duration, being compliant with protocol requirements, and not using any confounding treatments for ED.

Protocol #TA-302 was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel design, three-arm Phase 3 trial to assess the safety and efficacy of avanafil in the treatment of mild-to-severe ED in adult heterosexual males with Type 1 or Type 2 diabetes. Inclusion criteria required, but were not limited to, being 18 years of age or older, having a history of mild to severe ED of at least six months duration, having a documented diagnosis of Type 1 or Type 2 diabetes, being compliant with protocol requirements, and not using any confounding treatments for ED.

The three co-primary endpoints for this study were the following:

- The change in percent of sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse between the run-in period and the 12-week treatment period;
- The change in percent of sexual attempts in which subjects were able to insert the penis into the partner's vagina between the run-in period and the 12-week treatment period;
- The change in score on the erectile function (EF) domain of the International Index of Erectile Function (IIEF) questionnaire from baseline (visit 2) to end of treatment.

The sites listed below were selected for inspection because of their relatively large enrollment and significant primary efficacy results pertinent to decision-making. Some of the sites had a high rate of drop-outs.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Ronald Surowitz 411 W. Indiantown Road Jupiter, FL 33458	TA-301/ Site #140/ 38 subjects and TA-302/ Site #221/ 33 subjects	23-27 Jan 2012	NAI
David Cook 1901 S. Hawthorne Rd., #306 Winston-Salem, NC 27103	TA-301/ Site #116/ 28 subjects and TA-302/ Site #233/ 19 subjects	28 Nov – 12 Dec 2011	NAI
Jeffrey Rosen 275 Alhambra Cir., Ground Floor Coral Gables, FL 33134	TA-301/ Site #127/ 36 subjects and TA-302/ Site #222/ 20 subjects	30 Jan – 2 Feb 2012	VAI
VIVUS, Inc. (sponsor) 1172 Castro Street Mountain View, CA 94040	TA-301 and TA-302	28-30 Nov 2011	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. Ronald Surowitz
411 W. Indiantown Road
Jupiter, FL 33458

- a. **What was inspected:** At this site for Protocol #301, 91 subjects were screened, 38 subjects were enrolled, and 30 subjects completed the study. For Protocol #302, 105 subjects were screened, 33 subjects were enrolled, and 31 subjects completed the study. The records were reviewed for 25 subjects in Protocol #301 and for 21 subjects in Protocol #302. Records reviewed for both studies included, but were not limited to, source documents and corresponding electronic case report forms (eCRFs), all informed consent forms, inclusion/exclusion forms, IVRS documentation, subject diaries, IRB and sponsor correspondence, adverse event reporting, laboratory records, ECGs, study visit forms, physical examination forms, and drug accountability records.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data appear acceptable in support of the respective indication.

2. David Cook
1901 S. Hawthorne Rd., #306
Winston-Salem, NC 27103

- a. **What was inspected:** At this site for Protocol #301, 62 subjects were screened and 28 subjects were enrolled and completed the study. For Protocol #302, 95 subjects were screened and 19 subjects were enrolled and completed the study. The records were reviewed for 14 subjects in Protocol #301 and for ten subjects in Protocol #302. Records reviewed included, but were not limited to, all informed consent forms, IRB correspondence, case reports forms (CRFs), delegation of duties, medical histories, laboratory reports, concomitant medications, adverse events, drug accountability, and primary efficacy endpoints.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data appear acceptable in support of the respective indication.

3. Jeffrey Rosen
275 Alhambra Cir., Ground Floor
Coral Gables, FL 33134

- a. **What was inspected:** At this site for Protocol #TA-301, 58 subjects were screened, 36 subjects were enrolled, and 35 completed the study. For Protocol #TA-302, 50 subjects were screened, 20 subjects were enrolled, and 20 completed the study. The records were reviewed for 19 subjects in Protocol #TA-301 and for 20 subjects in Protocol #TA-302. Records reviewed included, but were not limited to, all informed consent forms, subject diaries and questionnaires, sponsor, monitor, and IRB correspondence, source documents, CRFs, drug accountability records, laboratory certifications, specimen handling and shipment logs, and test article storage conditions.

General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection which noted that some required elements of physical examinations (i.e., genital or neurological examination) were not conducted for multiple subjects in each of the two studies. The omission of these examinations was discussed with the medical officer, Dr. G. Fang, and the medical team leader, Dr. M. Hirsch. Dr. Hirsch said that the lack of these examinations does not pose a safety concern since genital or neurological abnormalities are rarely seen in studies of phosphodiesterase type 5 (PDE5) inhibitors. In addition, other safety assessments including laboratory chemistries, urinalyses, and adverse event reporting would serve to alert the investigator of a problem.

- c. **Assessment of data integrity:** The studies (other than the conduct of complete physical examinations as noted above) appear to have been conducted adequately, and the data appear acceptable in support of the respective indication.

4. VIVUS, Inc. (sponsor)
1172 Castro Street
Mountain View, CA 94040

- a. **What was inspected:** Records reviewed included, but were not limited to documentation detailing transfer of responsibilities from sponsor to contract research organizations (CROs), flowcharts of communication lines between sponsor and CROs, Form FDA 1572s, financial disclosure forms, monitoring reports, adverse event reporting, CRF handling and storage, and test article reconciliation.

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

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

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Surowitz, Cook, and Rosen, and the sponsor, Vivus, Inc., were inspected in support of this NDA. No significant regulatory violations were noted at the clinical sites of Drs. Surowitz and Rosen and neither site was issued a Form FDA 483. Dr. Rosen's site was issued a Form FDA 483 because not all of the protocol-required elements of physical examinations (i.e., genital and neurological examinations) were conducted for multiple subjects in each of the two studies. Omission of these components of the physical examinations would not appear to affect the safety evaluations of these studies for the reasons described above.

Overall, the studies at these three clinical sites appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

{See appended electronic signature page}

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/s/

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03/16/2012

TEJASHRI S PUROHIT-SHETH
03/16/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date	January 23, 2012
Reviewer	Samantha Cotter, PharmD, BCPS, FISMP Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strength	(b) (4) (Avanafil) Tablets, 50 mg, 100 mg, and 200 mg
Application Type/Number	NDA 202276
Applicant	Vivus, Inc.
OSE RCM	2011-3056

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, professional sample blister cards, professional sample carton labeling, and insert labeling for (b) (4) (Avanfil) Tablets, 50 mg, 100 mg, and 200 mg (NDA 202276), for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

(b) (4) (Avanafil) 50 mg, 100 mg, and 200 mg tablets are a New Molecular Entity (NME). The labels and labeling were submitted by the Applicant on August 15, 2011. The name is being reviewed in a separate proprietary name review (OSE 2011-3054).

1.2 PRODUCT INFORMATION

(b) (4) is a phosphodiesterase type 5 (PDE 5) inhibitor with the established name, Avanafil.

- **Indications for use:** Indicated for the treatment of erectile dysfunction
- **Route:** Oral
- **Dosage Form:** Tablet
- **Strength:** 50 mg, 100 mg, 200 mg
- **Dose:** 100 mg approximately 30 minutes before sexual activity on an as needed basis. Dose may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability. (b) (4) maybe taken no more than once a day.
- **How supplied:** For each dosage strength, (b) (4) will be supplied in bottles of 30 tablets and bottles of 100 tablets. Physician samples will also be available.
- **Storage:** Store at (b) (4) excursions permitted to (b) (4)
- **Container Closure System:** Avanafil tablets are supplied in two package types: foil-sealed, (b) (4) high density polyethylene (HDPE) bottles with child-resistant screw caps containing 30 or 100 tablets, and a blister card containing three 100 mg tablets (for physician samples only).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels for 50 mg (30 count and 100 count), 100 mg (30 count and 100 count bottle), and 200 mg (30 count and 100 count bottle) submitted September 13, 2011 (See Appendix A for image)
- Physician Sample Blister Card (100 mg, 3 count) submitted September 13, 2011 (See Appendix B for image)
- Physician Sample Display Carton (100 mg) submitted September 13, 2011 (See Appendix C for image)
- Insert Labeling submitted August 9, 2011 (no image)

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

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors. The established name, strength, net quantity, NDC number, and the statement “Protect from Light” are not prominent. The strengths are not well differentiated from each other and may lead to selection errors. In addition, it is not clear of the strength of each tablet in the Physician samples. We also note some error prone abbreviations, symbols and acronyms are used throughout the labeling. We advise that the following recommendations be implemented prior to approval:

- A. Container Label (50 mg, 100 mg, and 200 mg)
1. Revise the presentation of the proprietary name from all upper case letters (b) (4) to title case (b) (4) 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 of (b) (4)
- B. Physician Sample Blister Card
1. See Comment A.1. through A.5.
 2. Professional samples are dispensed to patients for use at home. DMEPA recommends 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 the 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

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

D. Insert Labeling

1. General Comments:

The applicant has used throughout the HIGHLIGHTS OF PRESCRIBING INFORMATION, and FULL PRESCRIBING INFORMATION error prone abbreviations. The symbols $<$, \leq , $>$, \geq 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 symbols², 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, DMEPA recommends that $<$ be replaced with “less than,” \leq be replaced with “less than or equal to,” $>$ be replaced with “greater than,” and \geq be replaced with “greater than or equal to.”

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

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² Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

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/s/

LUBNA A MERCHANT
01/26/2012

CAROL A HOLQUIST
01/26/2012

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	202276
Brand Name	(b) (4)
Generic Name	Avanafil
Sponsor	Vivus, Inc.
Indication	Treatment for Erectile Dysfunction
Dosage Form	Oral
Drug Class	PDE5 inhibitor
Therapeutic Dosing Regimen	Avanafil 100 mg no more than once a day; may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability.
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	800 mg single dose (Highest dose studied)
Submission Number and Date	SDN 001, June 29, 2011
Review Division	DRUP / HFD 580

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The largest upper bound of the 2-sided 90% CI for the mean difference between therapeutic avanafil (100 mg) and placebo was below 10 ms. However, the largest upper bound of the 2-sided 90% CI for the mean difference between suprathreshold avanafil (800 mg) and placebo was 11.6 ms. Suprathreshold avanafil failed to exclude a 10-ms increase in QT which is the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CIs for the $\Delta\Delta QTcF$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

This was a randomized, double-blind, 4-arm crossover study. Fifty-seven subjects were enrolled to receive therapeutic avanafil, suprathreshold avanafil, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Therapeutic and Supratherapeutic Avanafil and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Therapeutic Avanafil	0.5 min	3.6	(1.5, 5.7)
Supratherapeutic Avanafil	3	9.4	(7.2, 11.6)
Moxifloxacin 400 mg*	3	10.5	(8.3, 12.8)

*Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 7.4 ms.

The supratherapeutic dose (800 mg) produces C_{\max} values 6.8-fold greater than the mean C_{\max} for the therapeutic dose (100 mg). Only single dose treatment with avanafil was evaluated in this study; however, there is minimal accumulation of the drug (accumulation ratio: 1.09) after 14 days of dosing. Co-administration with a potent CYP3A4 inhibitor (ketoconazole) resulted in a 3- and 14-fold increase in avanafil C_{\max} and AUC, respectively. To address this drug-drug interaction, the sponsor recommends avanafil dose reduction to 50 mg every other day. All together, the supratherapeutic dose of 800 mg is sufficient to describe the steady state high exposure scenario anticipated in patients administered avanafil 50 mg every other day with a potent concomitant CYP3A4 inhibitor (i.e., ketoconazole).

The effect of the renal and hepatic impairment on the PK of avanafil was explored with no observed increases in avanafil exposure for patients with mild or moderate renal impairment or mild or moderate hepatic impairment.

1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS TO THE REVIEW DIVISION

The upper bound of 90%CI for $\Delta\Delta\text{QTcF}$ exceeds 10 ms at one time point for the supratherapeutic dose (800 mg). However, after accounting for the effect of known intrinsic and extrinsic factors, neither the therapeutic doses of avanafil (100 or 200 mg), nor the proposed adjusted avanafil dose when coadministered with a potent CYP3A4 inhibitor is expected to cause > 10 ms increase in QT, the threshold for regulatory concern.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert.

“12.2 Pharmacodynamics

Effects on Cardiac Electrophysiology

[REDACTED] (b) (4)

2.2 QT-IRT PROPOSED LABEL

QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

12.2 Pharmacodynamics

Effects on Cardiac Electrophysiology

The effect of avanafil 100 and 800 mg following a single oral dose on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 57 healthy subjects. In a study with demonstrated ability to detect small effects, no significant changes in placebo adjusted, baseline-corrected QTc were observed. The dose of 800 mg is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Avanafil is a potent and highly specific type 5 phosphodiesterase (PDE5) inhibitor for the treatment of erectile dysfunction (ED).

3.2 MARKET APPROVAL STATUS

Avanafil is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.4.3

“A battery of in vitro assays evaluated the potential of TA-1790 to produce electrocardiographic changes. In the hERG assay, a test used to predict the potential for lengthening of the QT interval, TA-1790 had an IC₅₀ of 15.8 μM (Study 020507.WJW), which represents a concentration approximately 416-fold above the unbound C_{max} (~0.038 μM) reached in human subjects after a single oral dose of 200 mg (2030 ng/mL; Study TA-011), the maximum recommended dose.

“In studies examining the function of L-type calcium channels and sodium channels, TA-1790 had weak effects and IC₅₀s could not be calculated (Studies 021021.WJW and 021022.WJW). Further tests of isolated heart tissue served to evaluate the risk of cardiac conduction abnormalities: in canine Purkinje fibers (Study 020508.WJW), TA-1790 at concentrations up to 100 μM produced only a slight decrease in the duration of the action potential (APDs) and TA-1790 at concentrations up to 10 μM produced no effects in guinea pig cardiac papillary muscle (Study 10-AVANAFIL-PHARM-26).

“When 30 mg/kg of TA-1790 was orally administered to unanesthetized, restrained dogs, the plasma concentration of unchanged TA-1790 increased to approximately 3 μg/mL or higher in some animals and heart rate, blood pressure and electrocardiographic variables, including QTc, were not consistently affected (Study 10-AVANAFIL-PHARM-17). Considering that the plasma concentration of TA-1790 at 200% of the pharmacological effective dose was 24.7 ng/mL in dogs and that the changes observed in dogs occurred at 14-fold higher than the free plasma concentration associated with the MRHD (200 mg), it

was concluded that the clinical dose of TA-1790 has a low risk of producing cardiovascular or electrocardiographic abnormalities in humans.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

“The avanafil clinical development program included 17 Phase 1 studies, three Phase 2 studies, and four Phase 3 studies. These studies evaluated the pharmacokinetics, efficacy, and safety of avanafil at doses ranging from 12.5 mg to 800 mg.

“Three Phase 3 clinical studies of avanafil have been completed: TA-301 (erectile dysfunction in the general male population), TA-302 (erectile dysfunction in diabetic men), and TA-314 (long-term safety and tolerability). Collectively, these studies randomized a total of 1036 subjects. An additional Phase 3 clinical study (TA-303) in subjects with erectile dysfunction following a bilateral, nerve-sparing, radical prostatectomy is ongoing. Three Phase 2 clinical studies of avanafil (TA-01, TA-03, and TA-05) have been completed. These studies are considered supportive of the indication for avanafil for the treatment of erectile dysfunction. The safety data from the 17 Phase 1 studies are included in this NDA.

“The incidence of SAEs in the Phase 3 double-blind cohort was low (TA-301 and TA-302): 3 (1.0%) subjects in the placebo group, 1 (0.6%) subject in the avanafil 50 mg group, 6 (2.1%) subjects in the avanafil 100 mg group, and 7 (2.4%) subjects in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group.

“

Table 2 summarizes targeted medical events by class and preferred term for the Phase 3 double-blind cohort

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Table 2: Summary of Targeted Medical Events by Class and Preferred Term – Phase 3 Double-Blind Cohort

TME Class Preferred Term	Placebo (N=291) n (%)	Avanafil 50 mg (N=160) n (%)	Avanafil 100 mg (N=288) n (%)	Avanafil 200 mg (N=293) n (%)	Avanafil Total (N=741) n (%)	Total (N=1032) n (%)
Upper respiratory events	18 (6.2)	13 (8.1)	32 (11.1)	32 (10.9)	77 (10.4)	95 (9.2)
Nasopharyngitis	8 (2.7)	1 (0.6)	6 (2.1)	10 (3.4)	17 (2.3)	25 (2.4)
Nasal congestion	2 (0.7)	1 (0.6)	7 (2.4)	4 (1.4)	12 (1.6)	14 (1.4)
Sinusitis	3 (1.0)	0 (0.0)	5 (1.7)	3 (1.0)	8 (1.1)	11 (1.1)
Bronchitis	1 (0.3)	3 (1.9)	1 (0.3)	4 (1.4)	8 (1.1)	9 (0.9)
Sinus congestion	1 (0.3)	1 (0.6)	2 (0.7)	5 (1.7)	8 (1.1)	9 (0.9)
Influenza	0 (0.0)	1 (0.6)	5 (1.7)	1 (0.3)	7 (0.9)	7 (0.7)
Upper respiratory tract infection	1 (0.3)	3 (1.9)	2 (0.7)	1 (0.3)	6 (0.8)	7 (0.7)
Cough	1 (0.3)	0 (0.0)	2 (0.7)	1 (0.3)	3 (0.4)	4 (0.4)
Pneumonia	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.7)	3 (0.4)	3 (0.3)
Acute sinusitis	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	2 (0.3)	2 (0.2)
Lower respiratory tract infection	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	2 (0.3)	2 (0.2)
Sinus headache	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.2)
Pharyngitis streptococcal	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Respiratory tract infection viral	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Rhinorrhea	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Viral pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	1 (0.1)
Postnasal drip	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hemodynamic changes	0 (0.0)	1 (0.6)	3 (1.0)	0 (0.0)	4 (0.5)	4 (0.4)
Dizziness	0 (0.0)	1 (0.6)	2 (0.7)	0 (0.0)	3 (0.4)	3 (0.3)
Syncope	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Major cardiac events	1 (0.3)	1 (0.6)	0 (0.0)	1 (0.3)	2 (0.3)	3 (0.3)
Transient ischemic attack	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	2 (0.2)
Acute myocardial infarction	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)

Data from studies TA-301 and TA-302 are included.
TME = targeted medical event.
Source: ISS Post-text Table 6.5.1

TME Class Preferred Term	Placebo (N=291) n (%)	AVANAFIL 50 mg (N=160) n (%)	AVANAFIL 100 mg (N=288) n (%)	AVANAFIL 200 mg (N=293) n (%)	AVANAFIL Total (N=741) n (%)	Total (N=1032) n (%)
Upper respiratory events	18 (6.2)	13 (8.1)	32 (11.1)	32 (10.9)	77 (10.4)	95 (9.2)
Nasopharyngitis	8 (2.7)	1 (0.6)	6 (2.1)	10 (3.4)	17 (2.3)	25 (2.4)
Nasal congestion	2 (0.7)	1 (0.6)	7 (2.4)	4 (1.4)	12 (1.6)	14 (1.4)
Sinusitis	3 (1.0)	0 (0.0)	5 (1.7)	3 (1.0)	8 (1.1)	11 (1.1)
Bronchitis	1 (0.3)	3 (1.9)	1 (0.3)	4 (1.4)	8 (1.1)	9 (0.9)
Sinus congestion	1 (0.3)	1 (0.6)	2 (0.7)	5 (1.7)	8 (1.1)	9 (0.9)
Influenza	0 (0.0)	1 (0.6)	5 (1.7)	1 (0.3)	7 (0.9)	7 (0.7)
Upper respiratory tract infection	1 (0.3)	3 (1.9)	2 (0.7)	1 (0.3)	6 (0.8)	7 (0.7)
Cough	1 (0.3)	0 (0.0)	2 (0.7)	1 (0.3)	3 (0.4)	4 (0.4)

Source: eCTD 2.7.4, Table 24

“Eleven subjects had an SAE during study TA-314. No subject had an SAE that was considered by the investigators to be related to study drug. The SAE resulted in discontinuation of study drug for 6 subjects: 1 subject with acute psychosis, 1 subject with femoral artery occlusion, 1 subject with coronary artery disease, 1 subject with aortic valve stenosis, 1 subject with cervical vertebral fracture, and 1 subject with congestive cardiac failure.

“One subject in the integrated cohorts died. TA-301 Subject 108-020 in the avanafil 100 mg group died from a self-inflicted gunshot wound; the event was not considered by the investigator to be related to study drug.

“From the individual studies, no important differences among the treatment groups in changes in ECG parameters were noted. See TA-301 CSR Post-text Tables 14.3.5.1 and 14.3.5.2, TA-302 CSR Post-text Tables 14.3.5.1 and 14.3.5.2, and TA-314 CSR Post-text Tables 14.3.5.1 and 14.3.5.2.”

Reviewer's Comments: No syncope, seizures, sudden cardiac death or ventricular arrhythmias were reported. No clinically relevant ECG changes were reported in avanafil's development program.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of avanafil's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 51,235. The sponsor submitted the study report TA-140 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Blinded, Randomized Crossover Trial to Define the ECG Effects of TA-1790 (Avanafil) Using a Single Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin in Healthy Men: A Through ECG Trial.

4.2.2 Protocol Number

TA-140

4.2.3 Study Dates

First subject enrolled: October, 6, 2008
Last subject completed: January 6, 2009

4.2.4 Objectives

The objective of this study was to assess whether treatment with a therapeutic (100 mg) or supratherapeutic (800 mg) dose of avanafil has the potential to cause QT/QTc prolongation in healthy volunteers.

4.2.5 Study Description

4.2.5.1 Design

This study was performed in a double-blind, randomized, single-site, four-arm crossover design in healthy male subjects. Fifty-seven healthy male subjects were randomized to receive four treatments in one of four sequences. Each treatment consisted of a single dose of study drug and was followed by at least a 3-day washout period between treatments.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Avanafil and placebo administration were blinded. The investigator and subjects were not blinded to positive (moxifloxacin) control

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

- Placebo: Eight placebo tablets.
- Positive Control: One 400 mg moxifloxacin tablet.
- Therapeutic Dose: One 100 mg avanafil tablet and seven placebo tablets.
- Supratherapeutic Dose: Eight 100 mg avanafil tablets (800 mg dose).

4.2.6.2 Sponsor's Justification for Doses

The clinical dose of avanafil is 100 mg (though some subjects may respond to a lower dose and some may require a higher dose). The supratherapeutic dose was designed to test the maximum studied dose, 800 mg (four times the maximum clinical dose), which should have been sufficient to cover ECG effect modifiers in the target population.

Reviewer's Comments: The supratherapeutic dose used in this study was sufficient to address the anticipated high exposure scenario of co-administration with a potent CYP3A4 inhibitors at steady state. AUC and C_{max} of avanafil (50 mg q.d.) was increased by 13- to 14-fold and 2- to 3-fold, respectively, following co-administration with ketoconazole (400 mg q.d.) or ritonavir (600 mg b.i.d.). Likewise, multi-dose studies with avanafil 100 and 200 mg q.d. indicate an accumulation ratio for avanafil of 1.09 over 14 days. Finally, the maximum recommend dose of avanafil is 50 mg, not to exceed once every 48 hr in the presence of a potent CYP3A4 inhibitor. Accounting for all of these conditions, an AUC and C_{max} similar to 770 mg and 165 mg, respectively, is anticipated. As such, the proposed 800 mg supratherapeutic dose is sufficient to cover both the anticipated increase in AUC and C_{max} for this scenario.

4.2.6.3 Instructions with Regard to Meals

Each treatment will be taken orally with approximately 240 mL of water following a 10-hr overnight fast. Dose administration will be followed by a 4-h fast from food. Water is restricted for 1 h prior to dose administration and for 2 h post-dose.

Reviewer's Comments: The sponsor's administration of avanafil under fasted conditions is appropriate. Administration of avanafil with a high-fat meal resulted in a 39% reduction in avanafil C_{max} and no effect on AUC, which would not properly address the high exposure scenario for avanafil.

4.2.6.4 ECG and PK Assessments

Blood for PK analysis was obtained in all subjects on Day 1 of each treatment arm of this trial, though only samples during avanafil treatment were analyzed. The ECG time points (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 18, and 23 h post-dose) were also used for PK sampling. All ECG measurements were obtained prior to PK sampling.

Reviewer's Comment: The proposed PK and ECG sampling times are appropriate to describe the peak avanafil concentration (T_{max} 0.5-2 h) and time-course.

4.2.6.5 Baseline

The sponsor used pre-dose measurements as their QTc baseline values.

4.2.7 ECG Collection

Twelve-lead ECGs obtained digitally using a Mortara Instrument (Milwaukee, Wisconsin) H-12+ ECG continuous 12-lead digital recorder, which obtained ECGs on Days 1 and 2 of each treatment arm of this crossover trial. The ECGs were stored continuously on a flash card. Electrocardiograms for analysis were selected by predetermined time points and were read centrally using a high-resolution manual on-screen caliper semiautomatic method with annotations. The H-12+ recording was started 1 h prior to the dosing to obtain baseline ECGs.

Electrocardiograms were sent to a central laboratory (b) (4) for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to subject identifiers, study treatment, and visit. All ECGs for a given subject were analyzed by the same reader. Quality Assurance reports for inter- and intra-observer variability were produced by eRT and provided to the Sponsor.

Digital 12-lead Holter ECGs were recorded continuously (using the Mortara Instrument Digital H-12+ ECG continuous recorder which continuously recorded all 12 leads simultaneously) for approximately 24 h (Days 1 through 2). The ECG signal for each 24 h session in each subject was recorded on 40-MB compact flash memory cards provided to the site. The subject's unique identification number and demographic information were recorded for each card. Without knowledge of subject treatment assignment, eRT generated a 10-second, 12-Lead digital ECG at each time point specified in the protocol. If targeted ECG time points were artifactual and of poor quality, eRT captured analyzable 10-second ECGs as close as possible to the targeted time points.

Digital ECGs were transmitted to the central ECG laboratory's validated data management system, EXPeRT. Interval duration measurements were first collected using computer assisted caliper placements on three consecutive beats. Trained analysts then reviewed all ECGs for correct lead and beat placement and adjudicated the pre-placed algorithm calipers as necessary using the proprietary validated electronic caliper system applied on a computer screen (manual adjudication methodology). A cardiologist then verified the interval durations and performed the morphology analysis, noting any T-U wave complex that suggested an abnormal form compatible with an effect on cardiac repolarization.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 57 subjects were planned and enrolled. Fifty-two subjects completed all four periods per protocol. Subjects No. 20 and 22 voluntarily withdrew from the study during Period 1 and following Period 3, respectively. Subjects No. 15 and 41 were discontinued

from the study due to failure to comply with protocol requirements or study-related procedures at the start of Periods 2 and 1, respectively. One subject, Subject No. 31 withdrew due to an ongoing AE after Period 3.

A summary of demographic and baseline characteristics for the randomized safety population is presented in Table 3.

Table 3: Demographics and Baseline Characteristics (Population: Randomized Safety Population)

Characteristic	Total n = 57
Gender, n (%)	
Male	57 (100%)
Ethnicity, n (%)	
Hispanic	6 (10.5%)
Non-Hispanic	51 (89.5%)
Race, n (%)	
White	47 (82.5%)
Black or African American	7 (12.3%)
Asian	1 (1.8%)
Other	2 (3.5%)
Age, years (SD)	28 (6.7)
Height, cm (SD)	176.0 (8.6)
Weight, kg (SD)	76.8 (9.81)
Body Mass Index, kg/m ² (SD)	24.7 (1.92)

Reference: [Table 14.1-2](#).

Source: CSR, Table 4

4.2.8.2 Statistical Analyses

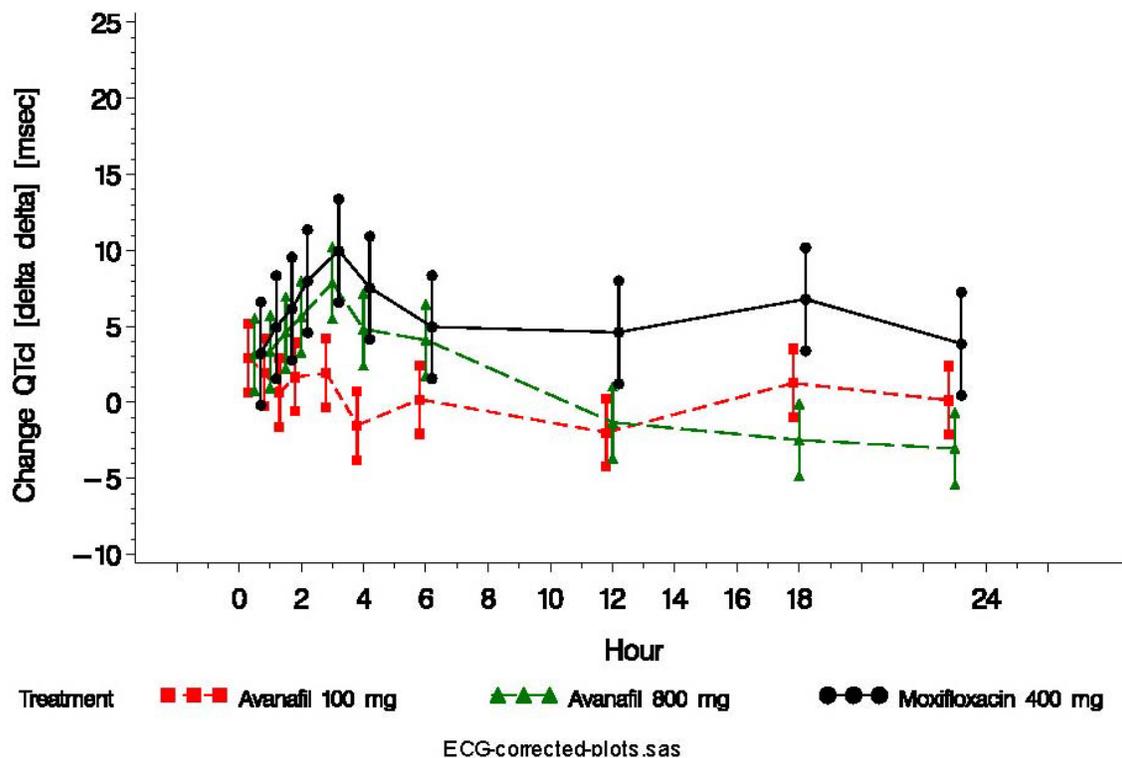
4.2.8.2.1 Primary Analysis

The primary endpoint was the change from the baseline-adjusted mean differences between avanadil (therapeutic and suprathapeutic doses) and placebo in QTcI. The sponsor used a liner mixed model and the result is presented in Table 4 and Figure 1. This model included treatment, time, period, sequence and treatment by time interaction. Baseline values as a covariate. The upper limits for the therapeutic avanadil of the 2-sided 90% CI were below 10 ms and the largest upper limits for the suprathapeutic avanadil of the 2-sided 90% CI was 10.2 ms.

Table 4: Sponsor's results for $\Delta\Delta Q_{TcI}$ for Avanafil 100 mg, Avanafil 800 mg and Moxifloxacin 400 mg

Time (hr)	Avanafil 100 mg (n=54)			Avanafil 800 mg (n=56)			Moxifloxacin 400 mg (n=53)		
	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
0.5 hr	2.9	0.7	5.2	3.2	0.8	5.5	3.2	-0.2	6.6
1 hr	2.0	-0.3	4.2	3.3	1.0	5.7	5.0	1.6	8.3
1.5 hr	0.6	-1.6	2.9	4.6	2.2	7.0	6.2	2.8	9.6
2 hr	1.7	-0.6	3.9	5.6	3.3	8.0	8.0	4.6	11.4
3 hr	1.9	-0.3	4.2	7.9	5.5	10.2	10.0	6.6	13.4
4 hr	-1.5	-3.8	0.7	4.8	2.4	7.2	7.5	4.2	10.9
6 hr	0.2	-2.1	2.4	4.1	1.7	6.5	5.0	1.6	8.4
12 hr	-2.0	-4.2	0.3	-1.3	-3.7	1.1	4.6	1.2	8.0
18 hr	1.3	-1.0	3.5	-2.5	-4.9	-0.1	6.8	3.4	10.2
23 hr	0.1	-2.1	2.4	-3.0	-5.4	-0.7	3.9	0.5	7.3
Time Ave.	0.7	-0.8	2.2	2.7	1.2	4.2	6.0	4.5	7.5

Figure 1: The Sponsor's 90% CI $\Delta\Delta$ QTcI Time Course for Avanafil Treatment Groups and Moxifloxacin 400 mg



Source: Sponsor's TA-140 Study report, Table and Figure on pages 60-61//82

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze Δ QTcI effect for moxifloxacin. The analysis results were presented in Table 4. The lower bounds of each 97.5% CI exceed 5 ms based on the least squares estimates.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 500 ms and Δ QTc $>$ 60 ms.

4.2.8.3 Safety Analysis

One subject, Subject No. 31 withdrew after Period 3 due to a tender erythema vein in left arm.

The majority of AEs were judged treatment-related by the Investigator (217 of the 296 AEs). The most common treatment-related AEs were headache (38 subjects [66.7%]), nausea (23 subjects [40.4%]), vomiting (15 subjects [26.3%]), and dizziness (11 subjects [19.3%]).

Overall, the greatest number of treatment-related AEs (196 AEs) were reported by the greatest number of subjects (42 subjects) following administration of the suprathreshold dose of avanafil (800 mg).

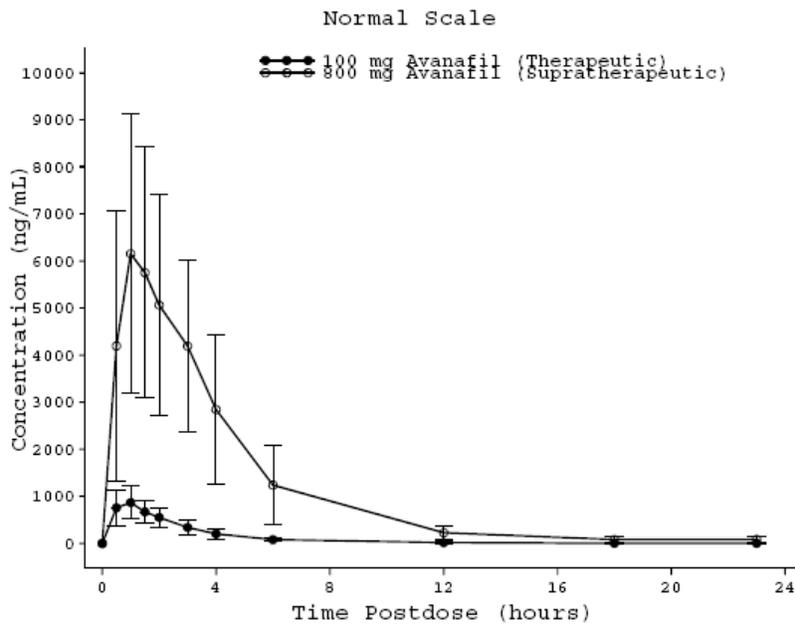
There were no deaths or SAEs during this study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean concentration time profiles for avanafil are shown in Figure 2 (similar time courses for M4 and M16 metabolites). The PK results for avanafil, metabolite M4, and metabolite M16 are presented in Table 5-Table 7. C_{max} and AUC values in the thorough QT study were 6.9-fold higher following administration of 800 mg avanafil compared with 100 mg avanafil, the intended clinical dose (~ 6-fold higher for M4 and M16).

Figure 2: Mean (SD) Concentration-Time Profiles for Avanafil



Source: Sponsor's TA-40 Study Report, pg 170

Table 5: Summary of Mean (SD) Plasma PK Parameter Data for Avanafil

Parameter	Units	Avanafil Tablet			
		N	Therapeutic Dose: 100 mg	N	Supratherapeutic Dose: 800 mg
C _{max}	(ng/mL)	54	980 (343)	55	6802 (2873)
T _{max} ^a	(hr)	54	1.00 (0.500, 3.00)	55	1.00 (0.500, 4.00)
AUC _{0-t}	(ng*hr/mL)	54	2523 (974)	55	27303 (11450)
AUC _{0-∞}	(ng*hr/mL)	52	2657 (1014)	55	27879 (11555)
t _{1/2}	(hr)	52	2.44 (1.65)	55	4.34 (1.44)

Source: Sponsor's TA-40 Study Report, pg 56

Table 6: Summary of Mean (SD) Plasma PK Parameter Data for M4

Parameter	Units	Avanafil Tablet			
		N	Therapeutic Dose: 100 mg	N	Supratherapeutic Dose: 800 mg
C _{max}	(ng/mL)	54	248 (77.0)	55	1521 (506)
T _{max} ^a	(hr)	54	1.00 (0.500, 3.02)	55	2.00 (0.500, 4.03)
AUC _{0-t}	(ng*hr/mL)	54	1040 (288)	55	9398 (3194)
AUC _{0-∞}	(ng*hr/mL)	54	1081 (290)	55	9740 (3271)
t _{1/2}	(hr)	54	3.49 (0.992)	55	4.98 (1.46)

Source: Sponsor's TA-40 Study Report, pg 57

Table 7: Summary of Mean (SD) Plasma PK Parameter Data for M16

Parameter	Units	Avanafil Tablet			
		N	Therapeutic Dose: 100 mg	N	Supratherapeutic Dose: 800 mg
C _{max}	(ng/mL)	54	359 (120)	55	2098 (883)
T _{max} ^a	(hr)	54	1.00 (0.500, 3.00)	55	1.00 (0.500, 3.00)
AUC _{0-t}	(ng*hr/mL)	54	838 (220)	55	8198 (2868)
AUC _{0-∞}	(ng*hr/mL)	54	873 (223)	54	8495 (2905)
t _{1/2}	(hr)	54	3.41 (1.83)	54	5.79 (2.37)

Source: Sponsor's TA-40 Tables-Figures, pg 58

4.2.8.4.2 Exposure-Response Analysis

The concentration-QT model results showing the slopes of the avanafil concentration- $\Delta\Delta$ QTcI, $\Delta\Delta$ QTcF, and $\Delta\Delta$ QTcB relationships are shown in Table 8. Similar significant concentration- $\Delta\Delta$ QTc relationships were observed for the M4 and M16 metabolites.

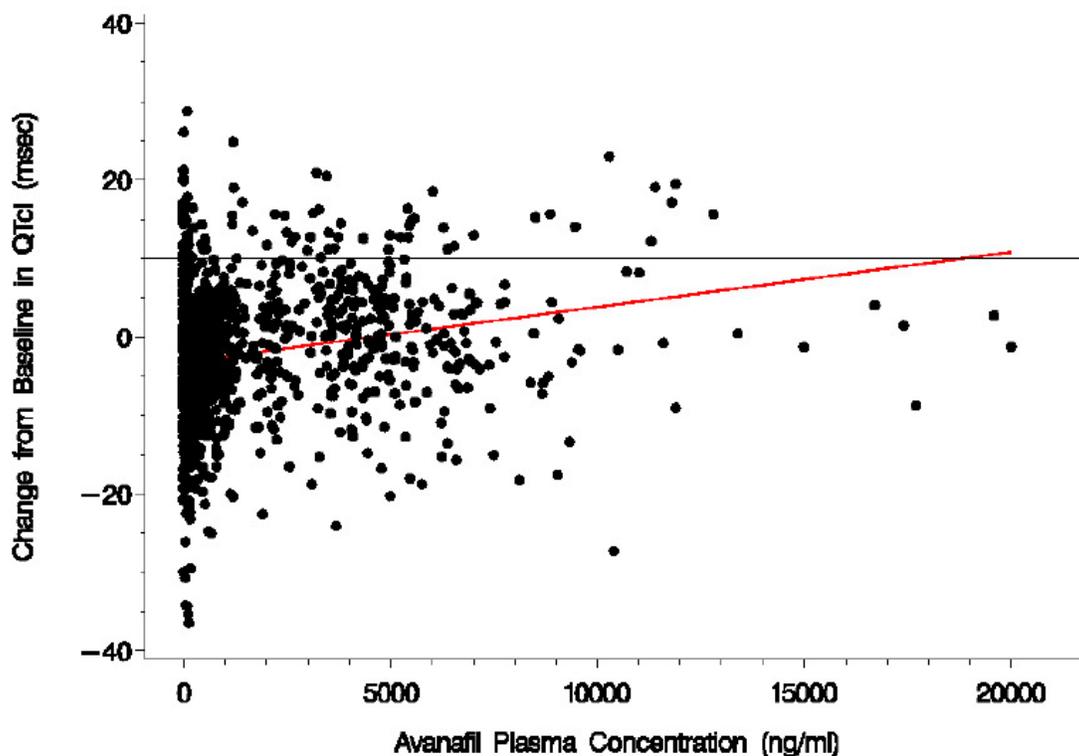
Table 8: Placebo-Corrected QTc Versus Avanafil Concentrations-Estimates from a Linear Mixed Effect Model (QTcI, QTcF, and QTcB)

QT Parameter	Slope of Plasma Concentration	Standard Error of Plasma Concentration	p-value	Predicted QTc at Average C _{max} 998.185 ng/ml	One-sided Upper 95% Confidence Bound of Predicted QTc	Supra-Therapeutics Predicted QTc at Average C _{max} 7185.893 ng/ml	One-sided Upper 95% Confidence Bound of Predicted QTc	Overall Model Fit
QTcI	0.0007	0.0001	0.0000	-2.5280	-1.5471	1.6138	2.8886	<.0001
QTcF	0.0009	0.0001	0.0000	-0.9664	0.0828	4.4386	5.7163	<.0001
QTcB	0.0016	0.0001	0.0000	5.1127	6.4772	14.8552	16.5661	<.0001

Source: Sponsor's TA-40 Tables-Figures, pg 64

Figure 3 shows the relationship between $\Delta\Delta\text{QTcI}$ and plasma concentration from paired samples taken in both dose groups for avanafil. The results of the PK-PD model for parent and metabolites show that the suprathreshold dose C_{max} predicted $\Delta\Delta\text{QTcI}$ and upper CIs were well less than 5 ms. These data do not support any effect of avanafil on cardiac repolarization.

Figure 3: QTcI Change from Baseline Versus Avanafil Concentration



Source : Sponsor's TA-40 Tables-Figures, pg 66

Reviewer's Comments: The sponsor's use of $\Delta\Delta QTcI$ is not appropriate as each patient does not have sufficient baseline measurements across a wide enough RR interval to encompass the RR interval observed on treatment. Instead, analysis focusing on $\Delta\Delta QTcF$ should have been utilized, which is further explored in the reviewer's analysis.

The sponsor's concentration- $\Delta\Delta QTcF$ model has a lower slope (0.0009 versus 0.0013 mL/ng ms) and a lower intercept (-1.8 versus 0.6 ms) than values identified during the reviewer's analysis. The values identified from the reviewer's analysis demonstrate that exposures at the suprathreshold dose have a $\Delta\Delta QTcF$ of 8.9 ms with an upper 90% CI of 10.6 ms.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor chose to use QTcI as their primary correction method. We disagree with using QTcI as the primary endpoint because (1) QTcI was derived based on 3 pre-dose baseline values across 4 periods, which does not have a wide range of RR intervals to derive a reliable individual correction factor; and (2) we do not recommend including placebo data to derive QTcI and then use the same placebo data to validate QTcI, which was what the sponsor did. For these reasons, we choose to use QTcF as the primary correction method.

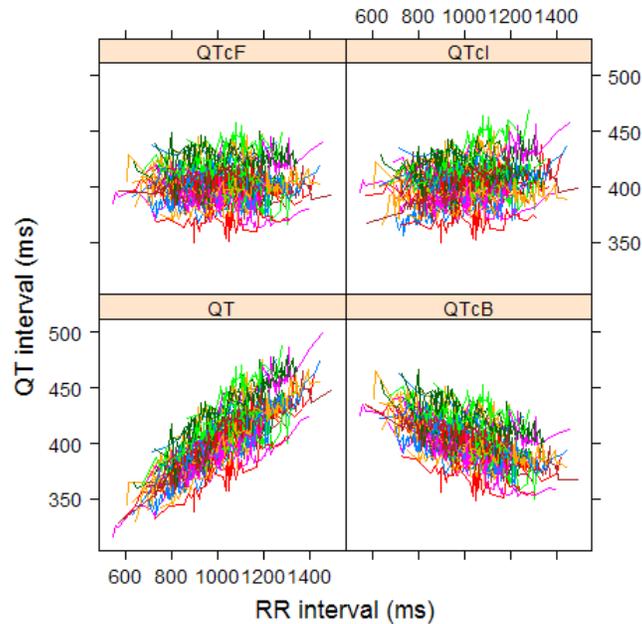
We used the criterion of Mean Sum of Squared Slopes (MSSS) from each individual regression of QTc versus RR to compare different correction methods. The smaller this value is, the better the correction. Based on the results listed in Table 9, it appears that QTcF is slightly better than QTcI. QTcB performs the worst. The smaller number for QTcI in the placebo cell is not reliable since the placebo data were also included for deriving the individual correction factor.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Moxifloxacin	62	0.0079	62	0.0023	58	0.0050
Placebo	59	0.0125	59	0.0035	58	0.0031
Suprathreshold Avanafil	58	0.0126	58	0.0025	57	0.0031
Therapeutic Avanafil	61	0.0134	61	0.0029	58	0.0036
All	65	0.0099	65	0.0016	58	0.0021

The QT-RR interval relationship is presented Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and Individual QT correction (QTcI).

Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Avanafil

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic avanafil and placebo, and between suprathreshold avanafil and placebo are 5.7 ms and 11.6 ms, respectively. This reviewer also used the same statistical analysis to analyze the Δ QTcI effect and the results are similar than those for Δ QTcF.

Table 10: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Therapeutic Avanafil, Supratherapeutic Avanafil and Moxifloxacin 400 mg

		Treatment Group													
		Avanafil 100 mg				Avanafil 800 mg				Moxifloxacin 400 mg					
		Δ QTc		$\Delta\Delta$ QTc		Δ QTc		$\Delta\Delta$ QTc		Δ QTc		$\Delta\Delta$ QTc			
Time (h)	Placebo	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-3.5	53	0.1	3.6	(1.5, 5.7)	55	2.6	6.1	(4.0, 8.2)	53	-0.2	3.3	(1.1, 5.4)	(0.4, 6.2)	
1	-3.6	54	-0.8	2.8	(0.8, 4.8)	55	3.1	6.7	(4.7, 8.7)	53	2.0	5.6	(3.6, 7.6)	(2.9, 8.3)	
1.5	-2.8	54	-1.9	0.9	(-1.0, 2.8)	56	4.3	7.1	(5.2, 9.0)	53	4.4	7.2	(5.3, 9.1)	(4.6, 9.8)	
2	-3.9	54	-2.8	1.2	(-0.8, 3.2)	56	2.9	6.9	(4.9, 8.8)	53	4.3	8.3	(6.3, 10.2)	(5.6, 10.9)	
3	-6.5	54	-4.5	2.0	(-0.3, 4.2)	56	2.9	9.4	(7.2, 11.6)	53	4.0	10.5	(8.3, 12.8)	(7.4, 13.6)	
4	-4.1	54	-5.1	-1.1	(-3.4, 1.2)	55	1.8	5.9	(3.6, 8.2)	53	4.0	8.0	(5.7, 10.4)	(4.9, 11.2)	
6	-5.5	54	-4.8	0.7	(-2.1, 3.5)	55	-0.2	5.3	(2.5, 8.1)	53	0.5	6.0	(3.2, 8.8)	(2.1, 9.8)	
12	-4.0	54	-5.6	-1.6	(-4.3, 1.0)	55	-3.5	0.4	(-2.2, 3.1)	53	1.1	5.1	(2.4, 7.7)	(1.5, 8.7)	
18	5.3	54	7.0	1.7	(-1.1, 4.5)	54	4.3	-1.0	(-3.8, 1.8)	53	11.6	6.4	(3.6, 9.2)	(2.6, 10.2)	
23	-1.9	53	-2.3	-0.3	(-2.6, 1.9)	54	-4.2	-2.2	(-4.5, -0.0)	52	1.3	3.3	(1.0, 5.5)	(0.2, 6.3)	

- Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

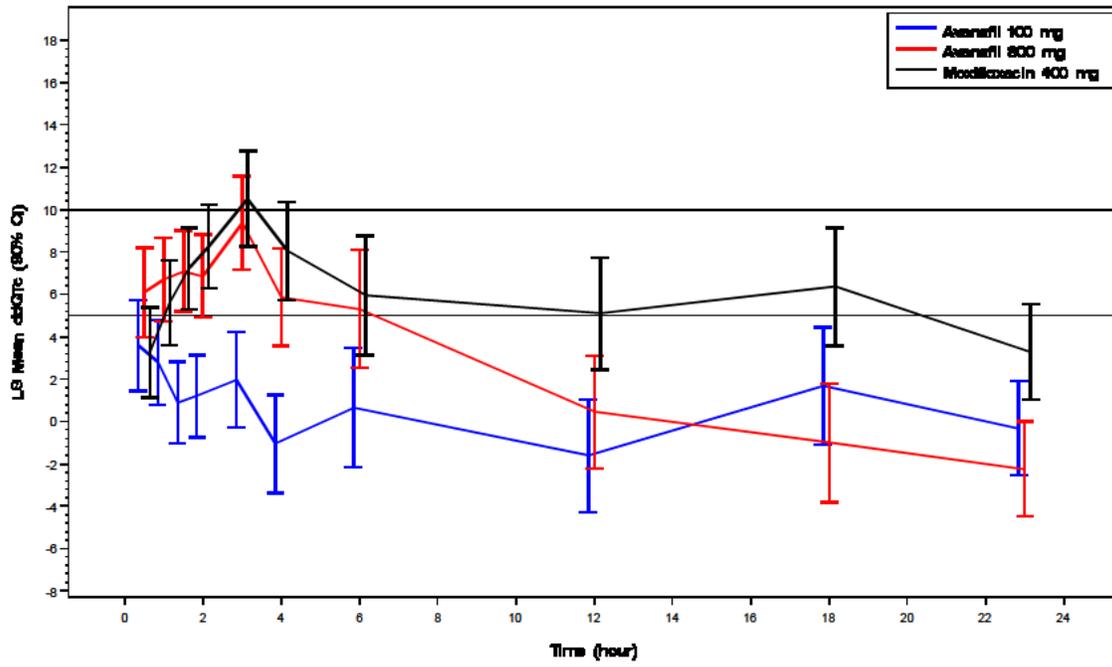
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10. The largest unadjusted 90% lower confidence interval is 8.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.4 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

Figure 5 displays the time profile of $\Delta\Delta$ QTcF for both avanafil treatment groups and moxifloxacin 400-mg group.

Figure 5: Mean and 90% CI $\Delta\Delta Q_TcF$ Time Course for Avanafil Groups and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 11: Categorical Analysis for QTcF

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
Avanafil 100 mg	54	54 (100%)	0 (0.0%)
Avanafil 800 mg	56	56 (100%)	0 (0.0%)
Moxifloxacin 400 mg	53	52 (98.1%)	1 (1.9%)
Placebo	54	54 (100%)	0 (0.0%)

Table 12 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis of Δ QTcF

Treatment Group	Total N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms
Avanafil 100 mg	54	54 (100%)	0 (0.0%)
Avanafil 800 mg	56	56 (100%)	0 (0.0%)
Moxifloxacin 400 mg	53	51 (96.2%)	2 (3.8%)
Placebo	54	54 (100%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% CIs are presented in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic avanafil and placebo, and suprathreshold avanafil are 4.9 bpm and 12.4 bpm, respectively. Table 14 presents the categorical analysis of HR. Three subjects who experienced HR interval greater than 100 bpm were in avanafil treatment groups.

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Therapeutic Avanafil, Supratherapeutic Avanafil, and Moxifloxacin 400 mg

		Treatment Group													
		Avanafil 100 mg				Avanafil 800 mg				Moxifloxacin 400 mg					
		Placebo		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI		
0.5	1.2	53	4.6	3.4	(1.8, 4.9)	55	10.5	9.3	(7.8, 10.9)	53	2.0	0.8	(-0.7, 2.4)		
1	1.6	54	4.8	3.2	(1.7, 4.7)	55	12.4	10.8	(9.3, 12.4)	53	4.0	2.4	(0.9, 4.0)		
1.5	0.6	54	0.8	0.2	(-1.3, 1.6)	56	7.7	7.1	(5.6, 8.5)	53	2.5	1.9	(0.5, 3.4)		
2	1.1	54	0.9	-0.2	(-2.0, 1.6)	56	6.2	5.1	(3.3, 6.9)	53	1.8	0.8	(-1.0, 2.6)		
3	2.2	54	0.7	-1.4	(-3.2, 0.3)	56	5.2	3.1	(1.3, 4.8)	53	2.3	0.1	(-1.6, 1.9)		
4	1.9	54	2.4	0.6	(-1.1, 2.2)	55	6.0	4.2	(2.5, 5.8)	53	3.0	1.1	(-0.6, 2.8)		
6	9.8	54	9.3	-0.5	(-2.5, 1.6)	55	13.3	3.5	(1.5, 5.5)	53	11.1	1.3	(-0.8, 3.3)		
12	9.7	54	10.0	0.3	(-1.9, 2.4)	55	12.9	3.2	(1.0, 5.3)	53	9.8	0.1	(-2.1, 2.2)		
18	-0.4	54	-0.5	-0.1	(-2.1, 2.0)	54	4.2	4.6	(2.6, 6.6)	53	-0.3	0.1	(-1.9, 2.1)		
23	2.6	53	2.7	0.1	(-1.7, 1.9)	54	5.8	3.2	(1.4, 5.1)	52	1.4	-1.2	(-3.1, 0.6)		

Table 14: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR \geq 100 bpm
Avanafil 100 mg	54	54 (100%)	0 (0.0%)
Avanafil 800 mg	56	53 (94.6%)	3 (5.4%)
Moxifloxacin 400 mg	53	53 (100%)	0 (0.0%)
Placebo	54	54 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% CIs are presented in Table 15. The largest uppers bounds of the 2-sided 90% CI for the mean differences between therapeutic avanafil and placebo, and supratherapeutic avanafil are 2.8 ms and 2.5 ms, respectively. Table 16 presents the categorical analysis of PR. Nine subjects who experienced PR interval greater than 200 ms were in avanafil treatment groups.

Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Therapeutic Avanafil, Supratherapeutic Avanafil, and Moxifloxacin 400 mg

		Treatment Group													
		Avanafil 100 mg				Avanafil 800 mg				Moxifloxacin 400 mg					
		Placebo		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI		
0.5	-1.8	53	-1.8	0.0	(-1.9, 1.9)	55	-3.5	-1.8	(-3.6, 0.1)	53	-1.0	0.8	(-1.1, 2.7)		
1	-0.5	54	-1.8	-1.3	(-3.3, 0.8)	55	-3.5	-3.0	(-5.0, -0.9)	53	-1.0	-0.5	(-2.6, 1.6)		
1.5	-1.7	54	-2.5	-0.8	(-3.1, 1.6)	56	-4.0	-2.3	(-4.6, 0.0)	53	-2.0	-0.3	(-2.6, 2.1)		
2	-2.2	54	-2.8	-0.7	(-2.7, 1.4)	56	-4.8	-2.7	(-4.7, -0.6)	53	-2.6	-0.4	(-2.5, 1.7)		
3	-1.2	54	-2.6	-1.3	(-3.4, 0.7)	56	-4.7	-3.4	(-5.5, -1.4)	53	-3.8	-2.6	(-4.6, -0.5)		
4	-2.3	54	-2.8	-0.5	(-2.5, 1.5)	55	-5.2	-2.9	(-4.9, -0.9)	53	-3.6	-1.3	(-3.3, 0.7)		
6	-7.6	54	-7.2	0.3	(-2.2, 2.8)	55	-8.0	-0.4	(-2.9, 2.1)	53	-8.7	-1.2	(-3.7, 1.3)		
12	-6.5	54	-6.7	-0.1	(-2.6, 2.3)	55	-6.5	0.1	(-2.3, 2.5)	53	-7.4	-0.8	(-3.3, 1.6)		
18	-1.2	54	-1.6	-0.3	(-3.1, 2.4)	54	-3.1	-1.8	(-4.5, 0.9)	53	-1.1	0.2	(-2.6, 2.9)		
23	-3.2	53	-3.2	-0.1	(-2.5, 2.4)	54	-4.4	-1.2	(-3.6, 1.3)	52	-4.2	-1.0	(-3.5, 1.5)		

Table 16: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR \geq 200 ms
Avanafil 100 mg	54	49 (90.7%)	5 (9.3%)
Avanafil 800 mg	56	52 (92.9%)	4 (7.1%)
Moxifloxacin 400 mg	53	47 (88.7%)	6 (11.3%)
Placebo	54	48 (88.9%)	6 (11.1%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% CIs are presented in. The largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic avanafil and placebo, and supratherapeutic avanafil are 1.5 ms and 1.7 ms, respectively. No subject who experienced QRS interval greater than 200 ms was in avanafil treatment groups.

Table 17: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Avanafil and Moxifloxacin 400 mg

		Treatment Group											
		Avanafil 100 mg				Avanafil 800 mg				Moxifloxacin 400 mg			
	Placebo	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-0.2	53	-0.3	-0.2	(-0.7, 0.4)	55	-0.2	-0.0	(-0.6, 0.6)	53	-0.2	-0.1	(-0.6, 0.5)
1	-0.4	54	-0.6	-0.2	(-0.8, 0.3)	55	-0.0	0.4	(-0.2, 0.9)	53	-0.3	0.1	(-0.4, 0.7)
1.5	-0.4	54	-0.7	-0.4	(-0.9, 0.2)	56	0.1	0.4	(-0.2, 1.0)	53	0.0	0.4	(-0.2, 1.0)
2	-0.5	54	-0.8	-0.3	(-0.9, 0.3)	56	0.3	0.8	(0.2, 1.4)	53	-0.5	0.1	(-0.6, 0.7)
3	-1.0	54	-0.4	0.6	(-0.1, 1.3)	56	0.0	1.0	(0.3, 1.7)	53	-0.5	0.5	(-0.2, 1.2)
4	-0.4	54	-0.4	0.0	(-0.7, 0.7)	55	-0.0	0.4	(-0.3, 1.1)	53	-0.4	-0.0	(-0.7, 0.7)
6	-0.4	54	-0.1	0.3	(-0.6, 1.2)	55	-0.3	0.1	(-0.8, 0.9)	53	-0.9	-0.5	(-1.4, 0.4)
12	-0.4	54	-0.5	-0.1	(-0.9, 0.7)	55	-0.4	-0.0	(-0.8, 0.8)	53	-0.8	-0.4	(-1.2, 0.4)
18	-0.0	54	0.6	0.6	(-0.2, 1.5)	54	-0.0	-0.0	(-0.9, 0.8)	53	0.1	0.1	(-0.7, 0.9)
23	-0.5	53	-0.5	0.0	(-0.7, 0.7)	54	-1.1	-0.6	(-1.3, 0.1)	52	-1.1	-0.5	(-1.2, 0.2)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcF and avanafil concentrations was investigated by linear mixed-effects modeling. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

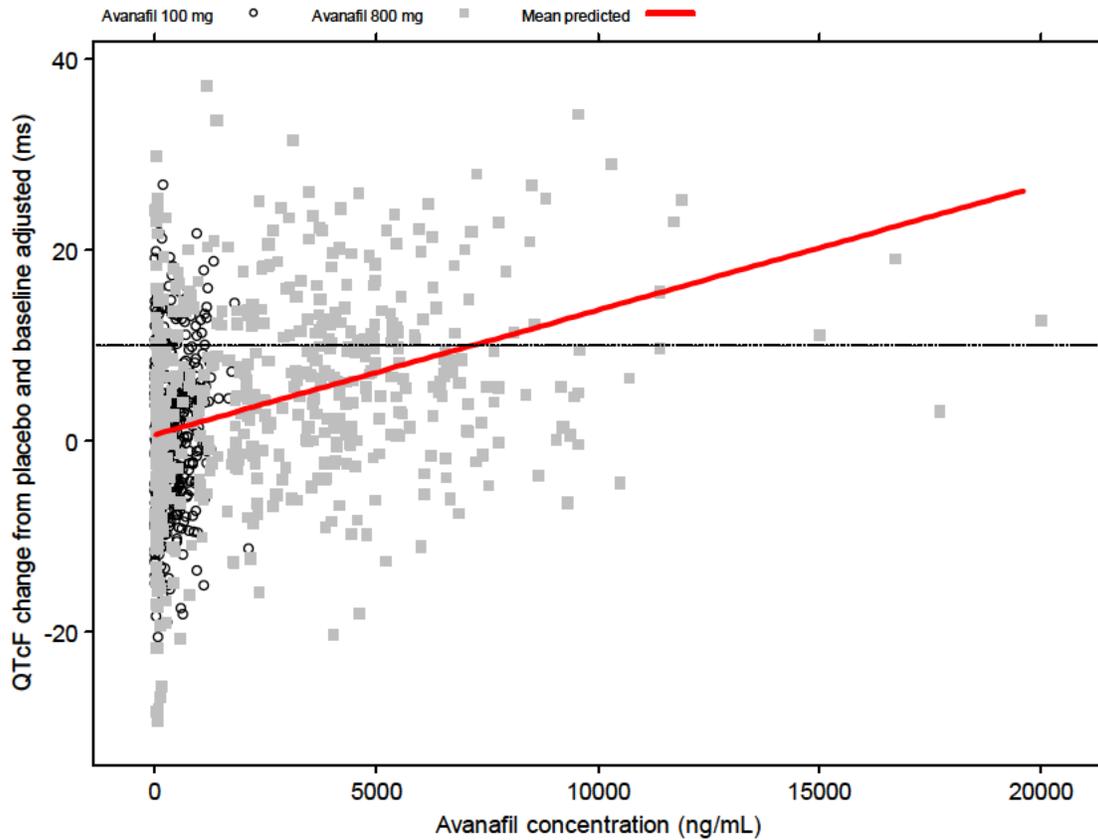
In all three models a significant slope was identified. Model 1 was used for further analysis since the model with intercept was found to fit the data best. Table 18 summarizes the results of the avanafil- $\Delta\Delta$ QTcF analyses.

Table 18: Exposure-Response Analysis of Avanafil Associated with $\Delta\Delta$ QTcF Prolongation

Parameter	Estimate	P-value	Inter-individual Variability (%)
$\Delta\Delta$ QTcF = Intercept + slope * Avanafil Concentration			
Intercept (ms)	0.64 (-0.64; 1.92)	0.41	5.1
Slope (ms per ng/mL)	0.0013 (0.0010; 0.0016)	<.0001	0.8
Residual Variability (ms)	7.7		

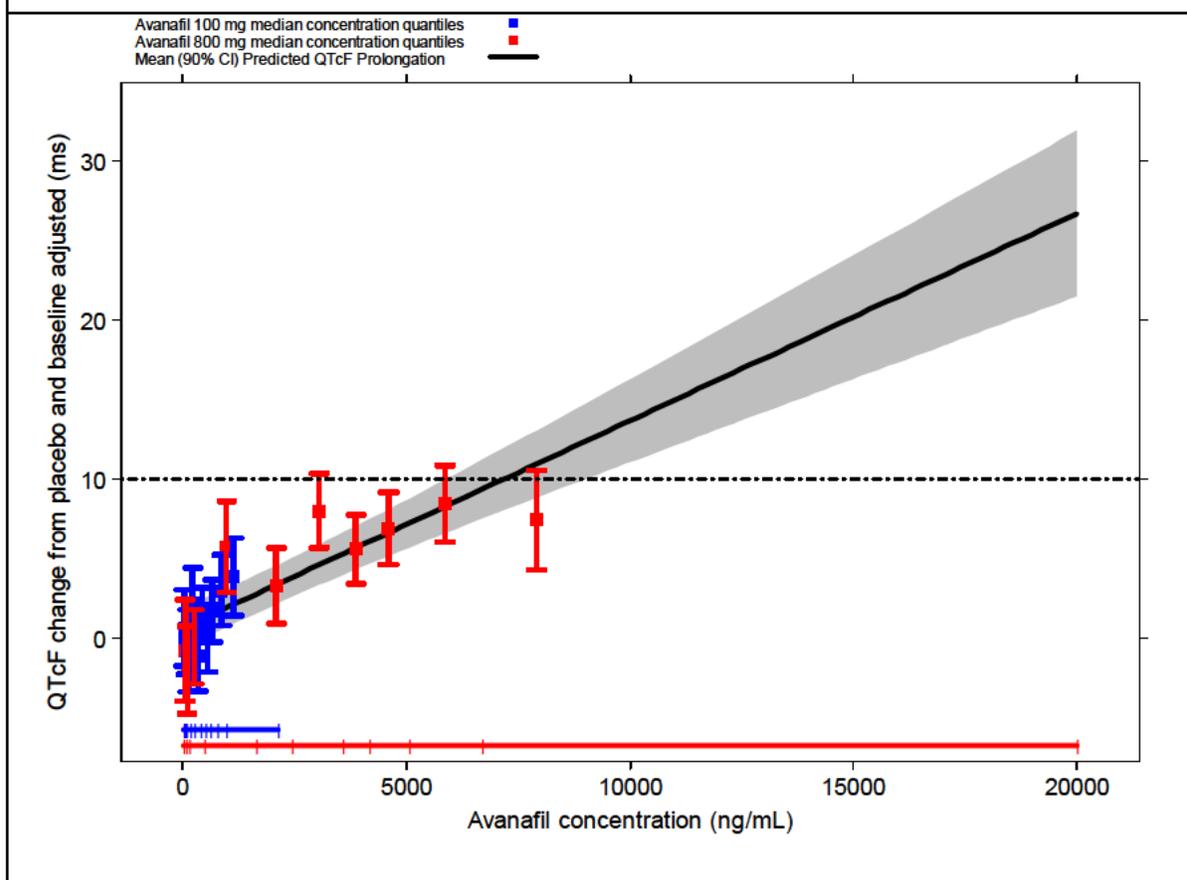
The exposure-response relationship between $\Delta\Delta\text{QTcF}$ and avanafil concentrations is visualized in Figure 6.

Figure 6: Observed $\Delta\Delta\text{QTcF}$ Versus Avanafil Concentrations Together with the Population Predictions (solid red line)



The goodness-of-fit plot in Figure 7 shows the observed median-quantile avanafil concentrations and associated mean (90% CI) $\Delta\Delta\text{QTcF}$ together with the mean (90% CI) predicted $\Delta\Delta\text{QTcF}$.

Figure 7: Observed Median-Quantile Avanafil Concentration and Associated Mean (90% CI) $\Delta\Delta$ QTcF (colored dots) Together with the Mean (90% CI) Predicted $\Delta\Delta$ QTcF (black line with shaded grey area)



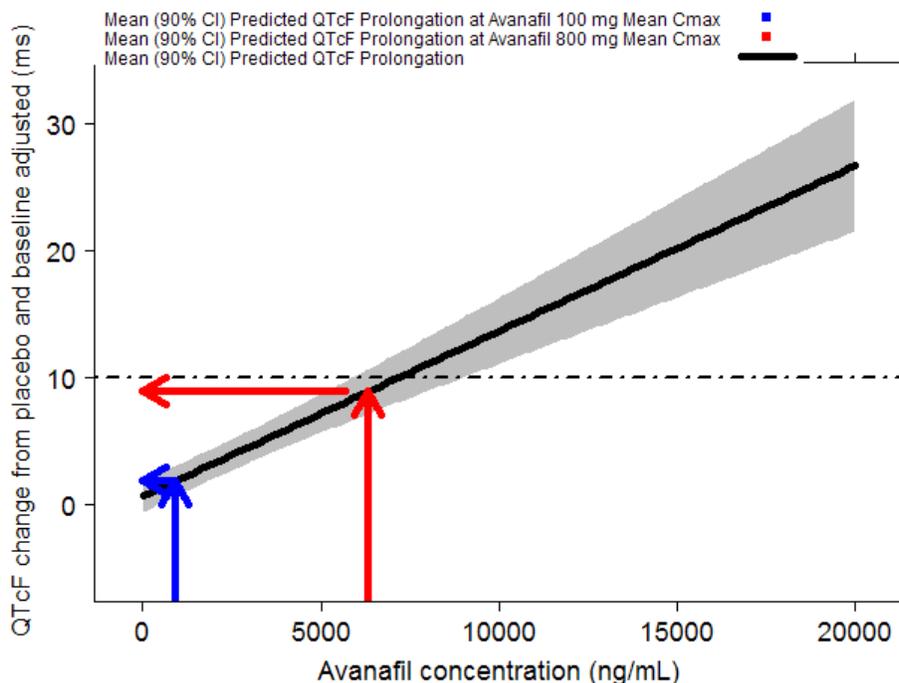
The predicted $\Delta\Delta$ QTcF at the geometric mean peak avanafil concentrations for 100 mg and 800 mg q.d. can be found in Table 19 and visualized in Figure 8. In addition, the anticipated $\Delta\Delta$ QTcF at the high exposure scenario was determined by interpolation (Table 19). High exposure scenario concentrations were determined using the reported avanafil accumulation ratio of 1.1, drug-drug interaction results with ketoconazole (3-fold increase in C_{max}), and reduced avanafil dose (50 mg every other day) as described in Section 6.1 (Highlights of Clinical Pharmacology).

Table 19: Predicted $\Delta\Delta$ QTcF Interval at Geometric Mean Peak Avanafil Concentration Using Model 1.

Treatment	C_{max}	Predicted $\Delta\Delta$ QTcF	90% CI
Avanafil 100 mg (single dose)	925 ng/mL	1.9	(0.6; 3.1)
Avanafil 800 mg (single dose)	6320 ng/mL	8.9	(7.1; 10.6)
Avanafil 50 mg q.o.d. (with potent CYP3A4 inhibitor)*	3100 ng/mL	4.7	(3.7; 6.3)

*Predicted based on sponsor's ketoconazole drug-drug interaction and multiple dose result

Figure 8: Mean (90% CI) Predicted $\Delta\Delta$ QTcF at Geometric Mean C_{max} . Predicted C_{max} for the High Exposure Scenario was Interpolated from the Sponsor's Highlights of Clinical Pharmacology (orange)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 98% of the ECGs were annotated in the primary lead II, with less than 0.04% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Five subjects had a PR >200 ms at baseline. Post-baseline values were < 10% over baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Avanafil 100 mg no more than once a day; may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability.	
Maximum tolerated dose	Avanafil 800 mg single dose was the highest studied. It was well tolerated (HP-01 and TA-140).	
Principal adverse events	Headache, flushing, nasal congestion, nasopharyngitis, and back pain were reported by $\geq 2\%$ of patients treated with avanafil (Section 2.7.4). There was no dose limiting adverse event.	
Maximum dose tested	Single Dose	800 mg (HP-01 and TA-140)
	Multiple Dose	200 mg q12h for 7 days (TA-07); 200 mg daily (QD) for 14 days (TA-02)
Exposures Achieved at Maximum Tested Dose	Single Dose	800 mg: avanafil C_{max} = 6800 ng/mL (42%), avanafil $AUC_{(0-\infty)}$ = 27900 ng·hr/mL (41%) (in-text Table 5 of TA-140 CSR)
	Multiple Dose	200 mg q12h for 7 days: avanafil C_{max} = 3490 ng/mL (34%), avanafil $AUC_{(0-12)}$ = 8180 ng·hr/mL (33%) (in-text Table 11.4.1.2:1 of TA-07 CSR) 200 mg QD for 14 days: avanafil C_{max} = 2180 ng/mL (29%), avanafil $AUC_{(0-24)}$ = 4110 ng·hr/mL (37%) (in-text Table 11.4.1.2:2 of TA-02 CSR)
Range of linear PK	Single dose: C_{max} and AUC increased dose-proportionally from 12.5 to 600 mg and from 12.5 to 800 mg, respectively (HP-01). QD for 14 days: C_{max} increased dose-proportionally from 50 to 200 mg (TA-02).	
Accumulation at steady state	50 mg QD for 14 days: 1.28 (38%) (in-text Table 11.4.1.2:2 of TA-02 CSR) 100 mg QD for 14 days: 1.09 (56%) (in-text Table 11.4.1.2:2 of TA-02 CSR) 200 mg QD for 14 days: 1.09 (30%) (in-text Table 11.4.1.2:2 of TA-02 CSR) 200 mg q12h for 7 days: 1.24 (22%) (in-text Table 11.4.1.2:1 of TA-07 CSR)	
Metabolites	<p>Two major circulating metabolites, M4 (mono hydroxyl avanafil) and M16 (open pyrrolidine ring carboxylic acid avanafil), were identified in humans (TA-010).</p> <ul style="list-style-type: none"> • Avanafil IC_{50} for PDE₅ = 4.3 – 5.2 nM (Section 2.6.2) • M4 IC_{50} for PDE₅ = 51 nM (Section 2.6.2) • M16 IC_{50} for PDE₅ = 4.1 μM (Section 2.6.2) <p>The metabolite/parent ratios for M4 (22 to 37%) and M16 (about 32%) across clinical pharmacology studies generally remained comparable (Section 2.7.2) and were not dose-dependent or affected by hepatic impairment (TA-012), renal impairment (TA-013) or age (M4 only) (TA-014). The ratios of M16/avanafil were slightly lower in young subjects (32%) compared to elderly subjects (50 to 56%) (TA-014).</p>	

Absorption	Absolute/Relative Bioavailability	not studied
	Tmax	<ul style="list-style-type: none"> • Avanafil: 0.50 (0.50 - 2.0) hours for one 50 mg tablet and 0.75 (0.47 - 2.0) hours for 2x100 mg tablets (in-text Table 2 of TA-020 CSR) • M4: 0.51 (0.50 - 2.0) hours for one 50 mg avanafil tablet and 0.75 (0.47 - 2.0) hours for 2x100 mg avanafil tablets (in-text Table 7 of TA-020 CSR) • M16: 0.75 (0.50 - 2.0) hours for one 50 mg avanafil tablet and 0.75 (0.47 - 2.0) hours for 2x100 mg avanafil tablets (in-text Table 8 of TA-020 CSR)
Distribution	Vd/F or Vd	Day 1 (in-text Table 11.4.1.2:1 of TA-02 CSR) - 50 mg: 89 L (16%) 100 mg: 102 L (33%) 200 mg: 94 L (48%) Day 14 (in-text Table 11.4.1.2:2 of TA-02 CSR) - 50 mg: 158 L (36%) 100 mg: 147 L (73%) 200 mg: 105 L (43%)
	% bound	Avanafil: 99% (0.20%) (Section 2.6.5.5B) M4: 97% (0.37%) (Section 2.6.5.5B) M16: 81% (1.8%) (Section 2.6.5.5B) • Independent of total concentrations in plasma, subjects' age, renal and hepatic function (Section 2.7.2).
Elimination	Route	<ul style="list-style-type: none"> • Fecal excretion was the primary route of elimination; 62% of the administered radioactivity was recovered in feces (in-text Table 9 of TA-010 CSR). • Renal elimination was a minor route; 21% of the dose was recovered in the urine (in-text Table 8 of TA-010 CSR).
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Avanafil: 2.8 (61%)¹ hours for 50 mg tablet and 5.1 (57%) hours for 2x100 mg tablets (in-text Table 2 of TA-020 CSR) • M4: 3.1 (48%) hours for one 50 mg avanafil tablet and 5.8 (36%) hours for 2x100 mg avanafil tablets (in-text Table 7 of TA-020 CSR) • M16: 2.4 (34%) hours for one 50 mg avanafil tablet and 6.0 (42%) hours for 2x100 mg avanafil tablets (in-text Table 8 of TA-020 CSR)
	CL/F or CL	Day 1 following 200 mg: 27 L/hr (29%) ² (in-text Table 11.4.1.2:1 of TA-07 CSR) Steady state following 200 mg q12h for 7 days: 27 L/hr (34%) ² (in-text Table 11.4.1.2:1 of TA-07 CSR)

Intrinsic Factors	Age	<ul style="list-style-type: none"> • Avanafil: the geometric mean ratios for C_{max} and $AUC_{(0-\infty)}$ were similar between elderly (≥ 65 years) and young (18 - 45 years) subjects (in-text Table 4 of CSR-014). • M4: the mean ratios for C_{max} and $AUC_{(0-\infty)}$ were similar between the two cohorts (in-text Table 9 of CSR-014). • M16: the geometric mean ratios for C_{max} and $AUC_{(0-\infty)}$ were 51% and 70% higher for elderly subjects as compared to young subjects (in-text Table 14 of CSR-014)
	Sex	Avanafil is indicated for the treatment of erectile dysfunction and thus, only male subjects were studied
	Race	not studied
	Hepatic & Renal Impairment	<ul style="list-style-type: none"> • Hepatic impairment (Section 2.7.2)- Mild: no effect on exposure to avanafil and M4, with M16 C_{max} and AUC increased 30 - 50% Moderate: a 28 – 57% decrease in C_{max} of avanafil, M4, and M16, with no effect on AUC • Renal impairment (Section 2.7.2)- Mild: little effect on the exposure to avanafil and M4; a 33 and 48% increase in M16 C_{max} and AUC, respectively. Moderate: little effect on the exposure to avanafil and M4; a 25% and 135% increase in M16 C_{max} and AUC, respectively.
Extrinsic Factors	Drug interactions	<p>Other drugs to affect avanafil PK:</p> <ul style="list-style-type: none"> • Potent CYP3A4 inhibitors, such as ketoconazole (400 mg daily) and ritonavir (600 mg BID), increased 50 mg avanafil C_{max} 2 – 3 fold and AUC 13 - 14 fold (TA-011). • Moderate CYP3A4 inhibitors, such as erythromycin (500 mg BID), increased 50 mg avanafil C_{max} 2-fold and AUC 3-fold (TA-011). • Amlodipine (5 mg daily), a CYP3A4 substrate, increased 200 mg avanafil C_{max} 28% and AUC 60% (TA-019). <p>Avanafil to affect other drugs (Section 2.7.2):</p> <ul style="list-style-type: none"> • Co-administration of 200 mg avanafil did not alter C_{max} and AUC of rosiglitazone (CYP2C8 substrate), R- and S-warfarin (CYP2C9 substrate), desipramine (CYP2D6 substrate), or amlodipine (CYP3A4 substrate). A 17% and 12% increase in omeprazole (CYP2C19 substrate) C_{max} and AUC, respectively, was observed.
	Food Effects	Ingestion 2x100 mg tablets with a high-fat meal resulted in a 39% reduction in avanafil C_{max} and a median delay of T_{max} by 1.25 hours with no effect on avanafil $AUC_{(0-\infty)}$ (in-text Tables 2 and 3 of TA-020 CSR). Similar food

		effects were also observed for M4 and M16 (in-text Tables 7 and 8 of TA-020 CSR). The inter-subject variability in the systemic exposure to avanafil (geometric CV% of 30-40%) was consistent with or without food (TA-020).
Expected High Clinical Exposure Scenario	Avanafil metabolism is mainly mediated by CYP3A4. Therefore, avanafil C _{max} and AUC could be increased up to 3- and 14- fold, respectively, in patients taking concomitant potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, and telithromycin). In the presence of a potent CYP3A4 inhibitor, the maximum recommended dose of avanafil is 50 mg, not to exceed once every 48 hours. The predicted dose equivalent for C _{max} would be 150 mg and for AUC would be 700 mg. The supratherapeutic dose in the TQT study was 800 mg.	

¹This is most likely due to an artifact of insufficient detectable concentration-time points during the terminal elimination phase following the 50 mg dose.

²Data presented were from Study TA-07 that used a validated bioanalytical method with LLOQ of 1.00 ng/mL for avanafil. The CL/F data were also available for 50, 100 and 200 mg from Study TA-02. However, Study TA-02 used a different validated bioanalytical method with high LLOQ of 125 ng/mL to determined plasma concentrations of avanafil and subsequently, CL/F values were higher, ranging from 57.7 – 61.7 L/hr.

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

/s/

NITIN MEHROTRA

11/23/2011

Jeff Florian is the primary author

JEFFRY FLORIAN

11/23/2011

MOH JEE NG

11/23/2011

JOANNE ZHANG

11/28/2011

MONICA L FISZMAN

11/28/2011

NORMAN L STOCKBRIDGE

11/30/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 202276	NDA Supplement #: S-
Efficacy Supplement Type SE-	
Proprietary Name: (b) (4) (proposed) Established/Proper Name: avanafil Dosage Form: Tablet Strengths: 50 mg, 100 mg and 200 mg	
Applicant: VIVUS, Inc. Agent for Applicant (if applicable):	
Date of Application: June 29, 2011 Date of Receipt: June 29, 2011 Date clock started after UN: N/A	
PDUFA Goal Date: April 29, 2012 (Sunday)	Action Goal Date (if different): April 27, 2011
Filing Date: August 28, 2011	Date of Filing Meeting: August 10, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1	
Proposed indication: treatment of erectile dysfunction	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 51235				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? <i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears																			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 30%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 20%;">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act</i>				

section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				This NDA is all electronic. Field Office has access to EDR.

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		X		

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			It's an NME. Consult will be sent to PeRC.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				Request for full waiver included.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			DMEPA found the proposed name (b) (4) unacceptable on 7/22/11. New proposal submitted 8/9/11 for (b) (4) (b) (4) as alternate).
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			Several revisions to the format will be requested via 74-Day letter (See RPM review of SRPI in

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

				DARRTS dated 8/24/2011)
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			Consult to IRT-QT for Final Study Report TA-140 sent on 8/18/2011
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting?	X			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Date: 11/28/2005				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA meeting?	X			
Date: 10//20/2010				
<i>If yes, distribute minutes before filing meeting</i>				

<p>Any Special Protocol Assessments (SPAs)? Date(s): Stability SPA – 11/02/2009 Clinical SPA – 2/1/2007 Carcinogenicity SPA – 12/18/2003 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>				
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ATTACHMENT

MEMO OF FILING MEETING

DATE: August 10, 2011

NDA: 202276

PROPRIETARY NAME: none at the moment

ESTABLISHED/PROPER NAME: avanafil

DOSAGE FORM/STRENGTH: 50, 100 and 200 mg tablets

APPLICANT: VIVUS, Inc.

PROPOSED INDICATION: treatment of erectile dysfunction

BACKGROUND: Avanafil is another PDE5 inhibitor being developed for erectile dysfunction. VIVUS submitted the NDA on June 29, 2011. PDUFA Goal date is April 29, 2012.

Relevant IND: 51235

REVIEW TEAM:

Discipline/Organization	Present at filing meeting? (Y or N)	
Regulatory Project Management	DeGuia	Y
	Mercier	Y
Cross-Discipline Team Leader (CDTL)	Y	
Clinical	Fang	Y
	Hirsch	Y
Social Scientist Review (<i>for OTC products</i>)	N/A	
	N/A	
OTC Labeling Review (<i>for OTC products</i>)	N/A	
	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	N/A	
	N/A	
Clinical Pharmacology	Reviewer: Lee	Y
	TL: Kim	Y

Biostatistics	Reviewer:	Guo	Y
	TL:	Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shin	N
	TL:	Reid	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Shafeie	Y
	TL:	Christner	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Townsend (PM) Denise Baugh	Y N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:	Shawna Hutchins	N
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Blay	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Dr. Julie Beitz, Office Director Maria Walsh, ADRA		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug is not the first in its class.

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Beitz	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments: Review milestones will be posted in the eRoom.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)

<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

/s/

EUFRECINA P DEGUIA
08/25/2011

JENNIFER L MERCIER
08/26/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202276

Name of Drug: avanafil

Applicant: VIVUS, Inc.

Labeling Reviewed

Submission Date: June 29, 2011

Receipt Date: June 29, 2011

Background and Summary Description

See attached Selected Requirements for Prescribing Information (SRPI) for details.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review.

During the preliminary review of the submitted labeling, the following labeling format issues were identified and will be communicated to the applicant via 74-day letter on or before September 11, 2011.

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.”

Conclusions/Recommendations

From a regulatory perspective, there is no action indicated at this time. In the 74-day letter, a request will be made to the applicant to re-submit a revised labeling within two to three weeks addressing the issues above for review and discussion.

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- 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.

- 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.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

EUFRECINA P DEGUIA
08/24/2011

JENNIFER L MERCIER
08/24/2011