CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	April 24, 2012
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA#	202,276
Applicant	Vivus, Inc.
Date of Submission	June 29, 2011
PDUFA Goal Date	April 29, 2012
Proprietary Name / Established (USAN) names	STENDRA avanafil
Dosage forms / Strength	50 mg, 100 mg and 200 mg tablets
Proposed Indication(s)	Treatment of erectile dysfunction
Recommended:	***Approval***

1. Introduction

Erectile dysfunction (ED) is the consistent inability to achieve and maintain a penile erection adequate for sexual intercourse. Erectile dysfunction is multi-factorial, with the major reasons for the condition being impaired neurologic and vascular mechanisms of erection. Men with systemic neurologic and vascular diseases, such as men with diabetes mellitus, are prone to suffer from ED. The current mainstay of treatment for ED are the oral phosphodiesterase Type 5 inhibitors (PDE5 inhibitors), including Viagra (sildenafil), Levitra (vardenafil), and Cialis (tadalafil).

PDE5 inhibitors work by enhancing the effect of nitric oxide on cavernosal smooth muscle. The physiologic mechanism of penile erection involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), which promotes cavernosal smooth muscle relaxation and increased blood flow into the penis. PDE5 is responsible for degrading cGMP and causing penile detumescence. Through its inhibition of PDE5, avanafil inhibits degradation of cGMP and thus increases cGMP concentrations in the corpora, resulting in enhanced cavernosal smooth muscle relaxation and greater blood flow to the erectile tissues in response to sexual stimulation.

According to the Sponsor, avanafil is a potent and highly specific inhibitor of PDE5 and it is highly selective for PDE5 relative to other PDE isozymes. As previously mentioned, four (4) other PDE5 inhibitors are FDA-approved for the treatment of ED, as follows:

	VIAGRA	CIALIS	LEVITRA	STAXYN (Vardenafil ODT)
Manufacturer	Pfizer	Lilly Icos	Bayer	Bayer
Date Introduced	March 1998	Feb 2003	April 2003	June 2010
Dosage	50mg,100mg	5mg, 10mg, 20mg	2.5 mg, 5mg, 10mg, 20mg	Oral Dispersible Table (ODT), 10 mg
Average Approx. Absorption Rate	40 Minutes	20 Minutes	40 Minutes	rapidly dissolves on the tongue within seconds without water
Duration of Effectiveness	2-4 Hours	36 Hours	4-8 Hours	4-8 Hours

Labeling for all PDE5 inhibitors includes a contraindication with nitroglycerin-containing products due to a potential for life-threatening hypotension. There are also precautions for use in combination with alpha-blockers, significant amounts of alcohol, and anti-hypertensive medications. PDE5 inhibitors are known vasodilators unto themselves and have small but acute effects on lowering blood pressure. The adverse reactions associated with PDE5 inhibitors are well-known and include flushing, headache, dyspepsia, common-cold like symptoms (nasopharyngitis, rhinitis), vision disturbance (including bluish tinge to vision), and back pain.

Avanafil is another PDE5 inhibitor proposed for the treatment of ED. It is similar to the currently available PDE5 inhibitors, with the only possible difference being a modestly shorter time to maximum plasma concentration compared to Viagra, Levitra and Cialis. As part of the avanafil clinical trials, patients were instructed to attempt sexual intercourse at 30 minutes after dosing, compared to at 60 minutes for the other products. The half-life of avanafil is 3-5 hours, and the absorption and clearance profile leads to a rapid onset and relatively rapid decline in effect, similar to Viagra and Levitra. In vitro studies of avanafil show selectivity for PDE5 over the other PDE isozymes, but the side effect profile demonstrated in avanafil clinical studies, including headache, flushing, dyspepsia, back pain and nasopharyngitis, does not support complete clinical selectivity for PDE5, and is the same as for the other PDE5 inhibitors.

The safety and efficacy of avanafil was investigated in eighteen Phase 1 studies, two Phase 2a, proof-of-concept studies, a large Phase 2 dose-ranging study (Study TA-05), and two Phase 3 efficacy and safety studies (TA-301 and TA-302). Avanafil was also evaluated for safety for up to 52 weeks in a 40-week extension study to TA-301 and TA-302 (TA-314). Finally, safety data was submitted from a Phase 3 study in men who had ED status-post bilateral, radical retropubic prostatectomy (TA-314).

2. Background

2.1 DESCRIPTION OF PRODUCT

Avanafil is a potent and selective inhibitor of type 5 phosphodiesterase and is intended for the treatment of erectile dysfunction. Avanafil increases penile blood flow and erection in response to sexual stimulation.

Avanafil will be supplied as oval-shaped, yellow, immediate-release tablets, debossed on one side with the tablet strength. The proposed dosing regimen is one 100 mg tablet taken 30 minutes prior to initiation of sexual activity, and not more than once daily. The dose may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability

2.2 REGULATORY HISTORY

On November 7, 2001, a Pre-IND meeting was held to discuss the development of avanafil for the treatment of erectile dysfunction (ED).

On November 30, 2001, the original IND for avanafil for the treatment of ED was submitted to DRUP (IND #51,235). The opening IND contained the phase 2a protocol TA-01, entitled "*A double-blind, randomized, crossover evaluation of safety and efficacy of TA-1790 with visual sexual stimulation in patients with erectile dysfunction.*"

On November 02, 2005, an End of Phase 2 (EOP2) meeting was held. The sponsor proposed to conduct two Phase 3 studies (TA-301 and TA-302), one Phase 3, 12-month, open label safety extension study of the "pivotal" Phase 3 studies (TA-314), and one Phase 3 study in patients with ED after bilateral radical retropubic prostatectomy (TA-303) . This proposal was considered acceptable for the clinical development plan. The Division provided several comments and recommendations, including:

1) Superiority claims to other PDE5 inhibitors would require the demonstration of efficacy superiority and the demonstration of non-inferiority of pre-specified safety endpoints in two trials, in studies using multiple doses.

2) If clinical safety and clinical pharmacology data support the use of avanafil as needed up to a maximum frequency (b) (4) this information could be considered for inclusion in labeling.

3) Drug interaction studies, including with nitroglycerin, alpha-blockers, alcohol, and a strong CYP 3A4 inhibitor such ketoconazole 400 mg QD, should be conducted.

During the Phase 3 clinical trial development, the protocols for the "pivotal" clinical trials TA-301 (in the general ED population), TA-302 (in diabetic men) and TA-303 (in radical prostatectomy patients) were reviewed by DRUP under special protocol assessments (SPAs). The Division also reviewed the protocol for TA-314 (long-term safety and tolerability) before it was initiated.

On October 20, 2010, the Division met with the Sponsor for a Pre-NDA meeting. The following were important topics of discussion at the meeting:

1. Due to slower than expected enrollment, the Sponsor asked whether the NDA could be submitted without TA-303 (in radical prostatectomy patients). The Division stated that even without inclusion of TA-303, the Sponsor could submit the NDA because the summary data in the Pre-NDA submission appeared to support a submission for the proposed indication even without inclusion of Study TA-303.

2. The 200 mg dose appeared to provide benefit over 100 mg in diabetic patients in TA-302, but in TA-301, in the broad ED population, avanafil 200 mg did not provide much benefit over avanafil 100 mg. Avanafil 200 mg was, however, associated with an increased incidence of headache compared to 100 mg. Therefore, the NDA should contain justification for approval of the 200 mg dose in the non-diabetic (general) ED population.

3. [redacted] (b) (4)

4. Claims related to the [redacted] (b) (4) needed to be supported by substantial evidence. [redacted] (b) (4)
   The NDA should contain information supporting both these claims, if such claims are sought, and these will be review issues.

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

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

7. A single-dose sperm study was considered insufficient. A multiple-dose study, with assessment of WHO sperm parameters, including sperm concentration, was needed. There was discussion of conducting this study as a postmarketing requirement, and the Division was willing to consider such timing for this study.

8. The potential interaction of avanafil with alcohol, α-blockers, and anti-hypertensives would be a review issue. Substantial evidence would be needed to support claims of [redacted] (b) (4)

9. The NDA should include information to describe the effect of mild, moderate and strong CYP3A4 inhibitors on avanafil PK.

10. The impact of severe renal impairment and severe hepatic impairment on avanafil PK was not assessed. The Sponsor was requested to address this in the NDA submission.

11. The effect of age on avanafil exposure should be addressed in the NDA.

On June 29, 2011, the original NDA for avanafil was submitted NDA 202,276.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Guodong Fang, stated in his final review, dated April 17, 2012:

"Recommendation on Regulatory Action: In the opinion of this reviewer, from a clinical standpoint, avanafil, at doses of 50, 100, and 200 mg, should be approved for the indication 'treatment of erectile dysfunction.' The drug is effective in the proposed regimen and its risks are acceptable and can be managed adequately with labeling.

Risk Benefit Assessment: This submission has provided substantial evidence from two double blind, placebo controlled studies that avanafil is an effective treatment for men with erectile dysfunction. Avanafil was efficacious in achieving both primary and secondary efficacy endpoints. No significant safety issues were detected. Avanafil has been shown to be generally safe for its intended use as recommended in the label by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to those seen with other approved drugs in its class of PDE5 inhibitors. The most common adverse events (seen in >2% of subjects and more frequently than seen in placebo) were: headache, flushing, nasal congestion, dyspepsia, dizziness and back pain.

The overall risk/benefit profile for avanafil was assessed and determined to be favorable. In summary, the data that have been submitted by the Sponsor are adequate to allow the reasonable conclusion that avanafil is an effective and safe treatment for men with erectile dysfunction. The data also provide an adequate basis for labeling the product so that it can be used in a safe and effective manner.

Recommendations for Postmarket Requirements and Commitments: Based upon preclinical findings showing reversible changes in sperm motility and morphology, a multiple-dose sperm study of avanafil will be requested as a postmarket requirement. The single dose sperm study that Sponsor conducted, showing no effects on human sperm, is considered inadequate to assess this potential risk in humans.

In addition, a postmarketing requirement will be requested for a vision study, in which avanafil or placebo will be a given as a single dose, and multiple measures of vision performance, including but not limited to visual acuity, intraocular pressure, pupillometry, and color vision testing, will be assessed. Despite few reports of clinical vision adverse events, the specific vision investigations conducted as part of Studies HP-01 and TA-016 are considered inadequate to fully assess the effect of avanafil on vision."

Dr. Fang provided the following summary comments regarding Efficacy:

"*The efficacy results of avanafil mainly are constituted by pivotal two Phase 3 studies and one Phase 2 study, which are supported by two Phase 2 studies. The data in this NDA demonstrate that treatment with avanafil is effective in the treatment of erectile dysfunction. All three pre-defined co-primary efficacy endpoints were met across all three doses of avanafil (50 mg, 100 mg, and 200 mg) in general ED population, and at both doses studied in diabetic men with ED. Avanafil treatment resulted in clinically meaningful increases in the proportion of positive responses to the subject diary questions and improvements in the IIEF erectile function, orgasmic function, and intercourse satisfaction domain scores and overall IIEF satisfaction score.*

Efficacy, as measured by successful intercourse, was evidenced for all doses across multiple time intervals after dosing; however, the data are not sufficient (b) (4)

(b) (4) *The clinical study results further support the conclusion that in some individuals not satisfied with their response to the 100 mg recommended starting dose, an enhanced response may be achieved with the 200 mg dose. While not statistically significant, subgroup analysis demonstrates a better effect of the 200 mg dose compared to the 100 mg dose in geriatric men, men with diabetes, and men with severe ED or prolonged ED at baseline*."

Dr. Fang provided the following summary comments regarding Safety:

1. "*The exposure of avanafil to patients and other subjects including the long-term exposure complied with ICH standards.*
2. *Overall, the safety and tolerability profile of avanafil appear acceptable. Common adverse effects mainly consist of AE profile of other PDE5 inhibitors.*
3. *No additional formal risk management program (RMP) activities are recommended at this time.*
4. *A human sperm study should be conducted as a postmarketing requirement."*

Dr. Fang also recommended a second postmarketing requirement: a single-dose vision study to include (but not limited to) multiple parameters of visual function, such as visual acuity, intraocular pressure, pupillometry, and color discrimination.

3. CMC/Device

The Chemistry Review team, Hamid Shafiei and Moo Jhong Rhee, made the following recommendation in their final review dated April 17, 2012:

*"Therefore, this NDA is now recommended for **approval** from the ONQA perspective ".*

In the April 17, 2012, review, Drs. Shafiei and Rhee described the resolution of three key Chemistry issues that were unresolved at the time of their March 1, 2012, CMC review:

1. The executed batch record in the original NDA was from a small scale process and did not adequately reflect the proposed set points for the critical process parameters for commercial manufacturing. On March 19, 2012, the sponsor submitted an NDA amendment containing a master batch record that fully reflected the proposed set points for the critical process parameters for commercial manufacturing.

2. All CMC labeling issues, including all container/carton labeling, were resolved by NDA amendments on March 13, 2012 and April 11, 2012. The trade name issue was resolved by the sponsor and FDA accepting the trade name "Stendra".

3. On April 17, 2012, the Office of Compliance made an overall recommendation of Approval from the ONDQA perspective.

The CMC review contained the following items of note:

- *Avanafil is a white crystalline powder manufactured by* (b) (4)
- *The drug master file (DMF) in support of the drug substance was deemed acceptable.*

- *Avanafil tablets are oval-shaped, yellow, immediate-release tablets, debossed on one side with the tablet strength. The tablets are produced at 50mg, 100mg, and 200mg strengths. Each strength is presented in white HDPE bottles with child resistant screw top closures in quantities of 30 or 100 tablets. The product will also be presented as a 3-tablet, physician sample blister card. The drug product is also manufactured by* (b) (4)
- *The manufacturing process for the drug product is deemed well controlled and supportive by evidence from proper studies.*
- *In addition to avanafil, the drug product also includes mannitol, fumaric acid, hydroxypropylcellulose, calcium carbonate, magnesium stearate, and yellow ferric oxide.* (b) (4)
- *The proposed specification for release and stability testing was deemed acceptable.*
- *The proposed 24-month expiration dating is granted.*

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewers, Yangmee Shin and Lynnda Reid, made the following recommendation in their final review dated March 21, 2012:

> "*From a Pharmacology/Toxicology perspective, the nonclinical data submitted support the **approval** of avanafil for the treatment of erectile dysfunction at the proposed doses.*"

There were no additional nonclinical recommendations.

The following are notable comments from the March 21, 2012 and March 26, 2012, Pharmacology/Toxicology review and supervisory memo:

- Avanafil displayed high selectivity for PDE5 versus PDE6 (~100-fold) and other PDEs (>1000-fold). This selectivity in vitro may not translate into clinical meaningful selectivity vis a vis side effects.

  CDTL Comment: The side effect profile of avanafil is essentially the same as for the currently marketed, approved PDE5 inhibitors. The known side effects reflect either a lack of complete selectivity for PDE5, or PDE5 located in tissues other than the corpora cavernosa, or both.

- As expected from the pharmacologic activity of a PDE5 inhibitor, avanafil induced vasodilation in vitro and in vivo. Other cardiovascular effects in animals included increased heart rate (HR), reduced blood pressures (BP), and prolonged QT interval.

  CDTL Comment: Avanafil, like other PDE5 inhibitors, is a vasodilator with effects on lowering blood pressure and consequently increasing heart rate. Avanafil did not prolong the QT interval in humans at a dose of up to 800 mg in the thorough QT (TQT) study.

- Microscopic changes in the heart included arteritis in a branch of the cardiac extramural coronary artery or vascular inflammation. The NOAEL in the 9-month dog

study resulted in exposures 3 times greater than systemic exposures in men at the maximum recommended human dose (MHRD). The LOAEL at which effects were observed was 9 times greater than then the systemic exposure at MHRD.

- CNS-related adverse events (ataxia, tremor, convulsion, prostration, hypoactivity) were observed in mice, pregnant rats, and dogs in multiple-dose studies at exposures approximately 5 to 8-fold greater than the mean C_{max} at the MHRD. No such signs were observed in animals after single, very large doses.

  CDTL Comment: CNS adverse events reported in the nonclinical studies were not observed in clinical studies.

- Treatment-related findings ion the liver were observed in all animal species tested at exposures 8-20 times the MHRD.

  CDTL Comment: Liver toxicity was not observed in clinical studies

- Avanafil was associated with increased reticulocytes, decreased red blood cell counts, and increased white blood cell counts in rats and dogs, as early as 1 week after multiple dosing. The NOAELs for these findings in dogs, rats and mice were approximately 1 – 5 times greater than the systemic exposure at MHRD

  CDTL Comment: In human trials, hematology parameters were not altered by avanafil. There was no evidence that the increased incidence of nasopharyngitis and upper respiratory infection reported in humans was related to any changes in the human hematologic or immune systems, but rather reflects a well known benign side effect of all PDE5 inhibitors, likely due to vasodilation in the nasopharynx.

- In reproductive toxicology studies, avanafil was determined to have low risk of causing major developmental abnormalities in humans and for labeling purposes, the recommended Pregnancy Category is C.

- Avanafil-treated rats had reduced fertility in both males and females at approximately 11- and 30-times, respectively, the exposure in men at MHRD. Male rats demonstrated reduced sperm motility and increases abnormal sperm morphology (e.g., broken sperm). The effects on the sperm were reversible at the end of a 9-week, off-treatment, period.

  CDTL Comment: In single-dose human studies, no effects of avanafil were observed on sperm motility or morphology. Spermatogenesis has been negatively affected in animal studies with other PDE5 inhibitors but not in human studies of these same moieties. In this case, it is considered appropriate to conduct multiple-dose human sperm studies as a postmarketing requirement and the sponsor has agreed. Labeling will note that the effect of avanafil on human spermatogenesis is unknown.

- According to the supervisory pharmacologist/toxicologist's March 26, 2012, memo, the exposure multiples quoted for all previous data should be considered as

"*conservative estimates*" and "*safety margins are expected to be much greater, based on the following factors"*:

- Exposure levels were calculated using bound plus unbound avanafil plasma concentrations. Only free, unbound avanafil is pharmacologically active. The concentrations of free avanafil are higher in animals (in vitro binding of 91-93%) compared to humans (in vitro binding of 99%).
- Animals were dosed daily for 6-9 months, providing continuous exposure to avanafil. The frequency of exposure in men is expected to be much less when used only on an as needed basis.

5. Clinical Pharmacology/Biopharmaceutics

A final review from the Clinical Pharmacology review team of LaiMing Lee, Hyunjin Kim, and Dennis Bashaw was received on March 9, 2012.

Clinical Pharmacology made the following recommendation:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 202276 for avanafil 50 mg, 100 mg, and 200 mg oral tablets submitted to the Agency on June 29, 2011. We have found this NDA* ***acceptable*** *from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."*

There were no postmarketing requirements listed.

In their "*Summary of Clinical Pharmacology and Biopharmaceutics Findings*", Clinical Pharmacology made the following key comments:

- Pharmacokinetics: The median T_{max} in single dose studies ranged from 30 to 75 minutes, but was generally observed at 30 minutes to 45 minutes after the 200 mg dose. In the majority of clinical pharmacology studies, the half-life was approximately 5 hours (range 4.5 to 6.4 hours). Avanafil is 99% bound to plasma proteins (43 % to gamma-globulin, and 66% to alpha-1 acid glycoprotein).

- Important clinical pharmacology studies conducted: Factors that could affect the PK of avanafil were evaluated in the following studies: renal impairment, hepatic impairment, age effect, food effect, drug interaction with ketoconazole, ritonavir, and erythromycin.

  The sponsor also conducted studies to evaluate the effect of avanafil on the PK and PD (pharmacodynamic) effects with other drugs, including nitrates (glyceryl trinitrate), alpha-blockers (doxazosin and tamsulosin), anti-hypertensive medications (enalapril and amlodipine), alcohol, and warfarin.

- Specific populations (renal, hepatic and elderly): Mild and moderate renal impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. No dose adjustment in patients with mild and moderate renal impairment is recommended. The sponsor did not evaluate the effect of severe or end stage renal impairment.

Mild and moderate hepatic impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. No dose adjustment in patients with mild and moderate hepatic impairment is recommended. The sponsor did not evaluate the effect of severe hepatic impairment on avanafil PK

The arithmetic mean $AUC_{0\text{-}inf}$ for avanafil was 1.1-fold higher in elderly subjects, compared to young subjects. Median tmax increased by approximately 11 minutes (from 34 minutes to 45 minutes) and mean $t_{1/2}$ decreased by approximately 1 hour from 6.5 to 5.6 hrs in elderly subjects, compared to young subjects. These overall differences were not significantly different and no adjustment is needed in the elderly.

- CYP3A4 inhibitors: Ketoconazole 400 mg inhibited avanafil metabolism, leading to an approximate 13-fold increase in mean $AUC_{0\text{-}inf}$ and 3.1-fold increase in C_{max}. Similarly, ritonavir 300-600 mg inhibited avanafil metabolism, leading to an approximate 13-fold increase in mean $AUC_{0\text{-}inf}$ and 2.4-fold increase in C_{max}. There was an increase in avanafil half-life to 8.5 hours and 8.8 hours following administration of ketoconazole and ritonavir, respectively. Increasing the maximum dosing interval from 24 to 48 hrs would address the increase in half-life and ensure that 4-5 half-lives elapse between doses. It is necessary, however, to administer a dose of approximately 15 mg to account for the 13-fold increase in exposure. A dose of not more than 25 mg every 48 hours would provide exposures approximately 63% greater than exposures observed in patients taking 200 mg. Irrespective of the final dose adjustment in patients taking strong CYP 3A4 inhibitors, there is currently no dose below 50 mg in this application. Therefore, use of avanafil is not recommended in patients taking strong inhibitors of CYP3A4, such as ketoconazole and ritonavir.

  Moderate inhibitors of CYP3A4, such as erythromycin, led to a 3.6-fold increase in avanafil mean $AUC_{0\text{-}inf}$ and 2.0-fold increase in C_{max}. For patients taking these drugs, a dose of 50 mg is recommended.

- Food: A high fat, high caloric meal decreased avanafil AUC and C_{max} by 1.5% and 40%, respectively, compared to fasting. Tmax was prolonged from 45 minutes when fasting to 2 hours after a high-fat, high caloric meal. No restrictions on food intake are recommended.

- Pharmacodynamic interactions: Avanafil demonstrated pharmacodynamic interactions with glyceryl trinitrate, the alpha-blockers doxazosin and tamsulosin, the anti-hypertensives enalapril and amlodipine, and with alcohol. Nitroglycerin had the largest interaction. The interactions observed with doxazosin and with alcohol were smaller than with nitroglycerin, and the interactions with tamsulosin and with the anti-hypertensives amlodipine and enalapril were smaller still. Both the clinical pharmacologist's and the medical officer's primary review contains details of these studies and their results. In addition, the results of these pharmacodynamic interaction studies are briefly summarized in Section 8.1.3 of this review (Special Safety Study results).

- Warfarin: Avanafil had no effect on the PK of a single 25 mg dose of warfarin; and multiple doses of avanafil had no effect on the pharmacodynamics of a single dose of warfarin.

6. Clinical Microbiology

A Microbiology consult was not requested for this NDA.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The "pivotal" clinical efficacy studies in the avanafil program were the Phase 3 studies **TA-301** and **TA-302**. In these two Phase 3 studies patients had mild to severe ED, while in the Phase 2 study **TA-05**, patients had mild to moderate ED.

In the Phase 3 studies, patients were randomized in TA-301 in a 1:1:1:1 ratio to placebo, avanafil 50, 100, and 200 mg, while those in TA -02 were randomized in a 1:1:1 ratio to placebo, avanafil 100, and 200 mg. In TA-301, subjects with diabetes and subjects with erectile dysfunction caused by spinal cord injury or radical prostatectomy were excluded. In TA-302, only subjects with type 1 or type 2 diabetes were enrolled. Both studies consisted of a 4-week non-treatment run-in period followed by a 12-week treatment period. Randomization was stratified by disease severity. During the treatment period, subjects were instructed to take 1 dose of study drug approximately 30 minutes prior to initiation of sexual activity. No restrictions were placed on the timing for consumption of food or alcohol. Subjects were to make at least 4 attempts at sexual intercourse per month. For each attempt, subjects were instructed to record information in a diary regarding the administration of study drug and the sexual experience.

The Sponsor also conducted a large Phase 2 study **TA-05**. TA -05 was a Phase 2, randomized, double-blind, parallel-design, placebo-controlled, multicenter study in adult male subjects with mild to moderate ED. Subjects with diabetes and subjects with erectile dysfunction caused by spinal cord injury or radical prostatectomy were excluded. Identical to the Phase 3 studies, the study consisted of a 4-week non-treatment run-in period followed by a 12-week treatment period. Eligible subjects were assigned randomly in a 1:1:1:1:1 ratio to one of the following treatments: placebo, avanafil 50 mg, 100 mg, 200 mg, or avanafil 300 mg. During the treatment period, subjects were instructed to take one dose of study drug approximately 30 minutes prior to initiation of sexual activity. For each attempt at sexual activity, subjects were instructed to record information in a diary regarding the administration of study drug and sexual experience.

There were two, small, "supportive", Phase 2 studies, studies **TA-01** and **TA-03**. TA-01, the IND opening study, was a single blind, randomized, crossover study to evaluate the safety and efficacy of 3 dose levels of avanafil given in conjunction with visual sexual stimulation and RigiScan monitoring in patients with mild to moderate ED. TA-03 was a double-blind, randomized, active-controlled, 3-way crossover study intended to evaluate the onset of effect of avanafil 200 mg administered at home, and to determine the effective duration of action of avanafil at-home.

In addition, **TA-314**, was a Phase 3, open-label extension study of subjects in Studies TA-301 and TA-302 to evaluate the long-term safety and tolerability of avanafil in patients with mild to severe ED. All eligible subjects were initially assigned to treatment with avanafil 100 mg. During the study, subjects could request to have their dose up-titrated to avanafil 200 mg or down-titrated to avanafil 50 mg based on their individual response to treatment. Subjects were

instructed to take one dose of study drug approximately 30 minutes prior to initiation of sexual activity.

7.2 DEMOGRAPHICS

Tables 1 and 2 provide a summary of demographic and baseline patient characteristics for the ITT populations in the Phase 3 studies TA-301 and TA-302, respectively.

The mean age of subjects in all three efficacy studies (TA-301, TA-302, and TA-05) was 56.6 years. Demographics are shown for all three studies based upon similarity of the patient populations. The majority of subjects were White (84.0%). The ED severity was mild for 32.5% of subjects, moderate for 36.3% of subjects, and severe for 31.2% of subjects. The mean baseline IIEF erectile function domain score was 12.9 (with a maximum total score of 30 patients, where 30 is the best function). At baseline, the mean duration of erectile dysfunction was 74.3 months. The randomized treatment groups were comparable with respect to demographic and baseline characteristics.

Table 1: Demographic and Baseline Characteristics in TA-301

	Placebo (N=162)	Avanafil 50 mg (N=161)	Avanafil 100 mg (N=161)	Avanafil 200 mg (N=162)	Total (N=646)
Age (years)					
n	162	161	161	162	646
Mean (SD)	55.4 (11.1)	55.4 (10.8)	56.5 (10.3)	55.7 (11.3)	55.7 (10.9)
Minimum - Maximum	23 - 77	29 - 83	23 - 88	24 - 80	23 - 88
Age category n (%)					
<50 years	52 (32.1)	50 (31.1)	46 (28.6)	45 (27.8)	193 (29.9)
≥50 years & <65 years	74 (45.7)	81 (50.3)	76 (47.2)	78 (48.1)	309 (47.8)
≥65 years	36 (22.2)	30 (18.6)	39 (24.2)	39 (24.1)	144 (22.3)
Race n (%)					
White	131 (80.9)	135 (83.9)	137 (85.1)	150 (92.6)	553 (85.6)
Black	28 (17.3)	25 (15.5)	21 (13.0)	11 (6.8)	85 (13.2)
Asian	2 (1.2)	1 (0.6)	2 (1.2)	1 (0.6)	6 (0.9)
Multiple	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)
Ethnicity n (%)					
Hispanic or Latino	26 (16.0)	28 (17.4)	20 (12.4)	29 (17.9)	103 (15.9)
Not Hispanic or Latino	136 (84.0)	133 (82.6)	141 (87.6)	133 (82.1)	543 (84.1)
Weight (kg)					
n	162	161	161	162	646
Mean (SD)	90.2 (17.6)	91.7 (17.7)	91.3 (15.2)	91.3 (16.6)	91.1 (16.8)
Height (cm)					
n	162	161	161	162	646
Mean (SD)	178.4 (7.5)	178. 1 (7.4)	177.8 (7.4)	178.4 (7.5)	178.2 (7.4)
Body mass index (kg/m^2)					
n	162	161	161	162	646
Mean (SD)	28.3 (4.93)	28.8 (4.80)	28.9 (4.45)	28.7 (4.75)	28.7 (4.73)
ED severity n (%)					
Mild	57 (35.2)	56 (34.8)	56 (34.8)	56 (34.6)	225 (34.8)
Moderate	52 (32.1)	53 (32.9)	52 (32.3)	53 (32.7)	210 (32.5)
Severe	53 (32.7)	52 (32.3)	53 (32.9)	53 (32.7)	211 (32.7)
ED duration (months)					
n	162	161	161	162	646
Mean (SD)	74.5 (66.6)	79.3 (71.4)	87.5 (92.8)	68.3 (52.3)	77.4 (72.4)
ED duration category n (%)					
<24 months	30 (18.5)	24 (14.9)	22 (13.7)	20 (12.3)	96 (14.9)
≥24 & < 60 months	54 (33.3)	55 (34.2)	62 (38.5)	64 (39.5)	235 (36.4)
≥60 months	78 (48.1)	82 (50.9)	77 (47.8)	78 (48.1)	315 (48.8)

Table 2: Demographic and Baseline Characteristics in TA-302

	Placebo (N=130)	Avanafil 100 mg (N=129)	Avanafil 200 mg (N=131)	Total (N=390)
Age (years)				
n	130	129	131	390
Mean (SD)	58.2 (8.6)	58.2 (9.6)	57.5 (9.0)	58.0 (9.1)
Minimum, maximum	39, 78	30, 78	35, 77	30, 78
Age category n (%)				
<50 years	23 (17.7)	30 (23.3)	26 (19.8)	79 (20.3)
≥50 years and <65 years	72 (55.4)	61 (47.3)	73 (55.7)	206 (52.8)
≥65 years	35 (26.9)	38 (29.5)	32 (24.4)	105 (26.9)
Race n (%)				
White	103 (79.2)	111 (86.0)	100 (76.3)	314 (80.5)
Black	24 (18.5)	16 (12.4)	27 (20.6)	67 (17.2)
Asian	1 (0.8)	2 (1.6)	3 (2.3)	6 (1.5)
Multiple	1 (0.8)	0 (0.0)	1 (0.8)	2 (0.5)
Unknown	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Ethnicity n (%)				
Hispanic or Latino	20 (15.4)	33 (25.6)	26 (19.8)	79 (20.3)
Not Hispanic or Latino	110 (84.6)	96 (74.4)	105 (80.2)	311 (79.7)
Weight (kg)				
n	130	129	130	389
Mean (SD)	100.0 (19.9)	98.6 (18.1)	99.6 (18.7)	99.4 (18.9)
Height (cm)				
n	130	129	131	390
Mean (SD)	178.2 (7.0)	177.6 (7.5)	177.2 (7.7)	177.7 (7.4)
Body mass index (kg/m^2)				
n	130	129	130	389
Mean (SD)	31.5 (5.9)	31.3 (5.4)	31.8 (5.5)	31.5 (5.6)
ED severity n (%)				
Mild	29 (22.3)	28 (21.7)	28 (21.4)	85 (21.8)
Moderate	40 (30.8)	40 (31.0)	42 (32.1)	122 (31.3)
Severe	61 (46.9)	61 (47.3)	61 (46.6)	183 (46.9)
ED duration (months)				
n	130	129	131	390
Mean (SD)	78.7 (66.6)	73.8 (53.1)	64.6 (44.7)	72.3 (55.7)
ED duration category n (%)				
<24 months	19 (14.6)	17 (13.2)	19 (14.5)	55 (14.1)
≥24 months and <60 months	41 (31.5)	49 (38.0)	52 (39.7)	142 (36.4)
≥60 months	70 (53.8)	63 (48.8)	60 (45.8)	193 (49.5)

7.3 DISPOSITION OF SUBJECTS

Tables 3 and 4 provide a summary of the subject disposition for the ITT Population in studies TA-301 and TA-302.

For TA-301, 646 subjects were assigned randomly to treatment. Of the 646 randomized subjects, 550 (85.1%) completed the study and 96 (14.9%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was similar across the treatment groups. The most common reasons for discontinuation from the study were protocol non-compliance (which also includes subjects who withdrew consent) (8.2%), loss to follow-up (3.4%), and adverse event (2.6%).

For TA-302, 390 subjects were assigned randomly to treatment. Of the 390 randomized subjects, 333 (85.4%) subjects completed the study and 57 (14.6%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was similar across the treatment groups. The reasons for discontinuation from the study were protocol non-compliance (9.2%, also includes subject withdrawal of consent), subject lost to follow-up (3.8%), adverse event (1.0%), and requirement for an excluded medical treatment (0.5%).

Table 3: Subject Disposition in Study TA-301

	Placebo n (%)	**Avanafil 50 mg n (%)**	**Avanafil 100 mg n (%)**	**Avanafil 200 mg n (%)**
Randomized	162 (100.0)	161 (100.0)	161 (100.0)	162 (100.0)
Completed study	137 (84.6)	131 (81.4)	141 (87.6)	141 (87.0)
Discontinued from study	25 (15.4)	30 (18.6)	20 (12.4)	21 (13.0)
Protocol non-compliance [1]	16 (9.9)	16 (9.9)	10 (6.2)	11 (6.8)
Subject lost to follow-up	4 (2.5)	9 (5.6)	4 (2.5)	5 (3.1)
Adverse event	5 (3.1)	3 (1.9)	5 (3.1)	4 (2.5)
Requirement for restricted medication	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)

[1] The category of protocol non-compliance includes subjects who withdrew consent.

Table 4: Subject Disposition in Study TA-302

	Placebo n (%)	**Avanafil 100 mg n (%)**	**Avanafil 200 mg n (%)**
Enrolled			
Randomized	130 (100.0)	129 (100.0)	131 (100.0)
Completed study	110 (84.6)	109 (84.5)	114 (87.0)
Discontinued from study	20 (15.4)	20 (15.5)	17 (13.0)
Protocol non-compliance [2]	15 (11.5)	15 (11.6)	6 (4.6)
Subject lost to follow-up	4 (3.1)	2 (1.6)	9 (6.9)
Adverse event	0 (0.0)	2 (1.6)	2 (1.5)
Requirement for excluded treatment	1 (0.8)	1 (0.8)	0 (0.0)

[1] The category of protocol non-compliance also includes subject withdrawal of consent.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

In both Phase 3 studies, the primary efficacy assessment measures were the same. There were three co-primary efficacy endpoints:

1) Change from baseline in the IIEF erectile function (EF) domain score from baseline to end of treatment (a 30-point domain)

2) Change from baseline in the percentage of sexual attempts resulting in successful vaginal penetration (Sexual Encounter Profile Question 2 [SEP2])

3) Change from baseline in the percentage of sexual attempts resulting in successful intercourse (SEP3).

These are the current standard for primary efficacy endpoints in Phase 3 ED trials.

In addition to these primary efficacy endpoints, the studies included other domains of the IIEF questionnaire, including, among others, orgasmic function, sexual desire, intercourse satisfaction, as secondary endpoints.

7.4.1.1 Primary Efficacy Analysis

In phase 3 studies TA-301 and TA-302, all three avanafil doses (50 mg, 100 mg and 200 mg) demonstrated statistically significant improvement on all three co-primary endpoints compared with placebo using the pre-specified
hierarchal testing procedure.

In study TA-301, relative to placebo, the placebo-subtracted changes-from-baseline in the avanafil 50 mg, 100 mg and 200 mg groups for the co-primary endpoints were:

- 2.6, 5.5 and 6.7 points, respectively, for the IIEF EF domain,
- 11.1%, 20.1% and 22.7%, respectively, for the percentage of sexual attempts having successful vaginal penetration (SEP2), and
- 13.8%, 29.3% and 30.2%, respectively, for the percentage of sexual attempts having successful intercourse (SEP3).

In study TA-302, relative to placebo, the placebo-subtracted changes-from-baseline in the avanafil 100 mg and 200 mg groups for the co-primary endpoints were:

- 2.9 and 4.1 points, respectively, for the IIEF EF domain,
- 9.0% and 11%, respectively, for the percentage of sexual attempts having successful vaginal penetration (SEP2), and
- 15.6% and 16.4%, respectively, for the percentage of sexual attempts having successful intercourse (SEP3).

These data are shown in the following set of tables:

Tables 5a and 5b: Change from Baseline in IIEF Erectile Function Domain Score in Studies TA-301 and TA-302

TA-301 IIEF Domain Score

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	152	12.4 (5.1)	15.3 (7.8)	2.9 (6.4)	2.9 (0.6)	<0.0001
Avanafil 50 mg	152	12.6 (5.2)	18.1 (7.9)	5.4 (7.5)	5.4 (0.6)	<0.0001
Avanafil 100 mg	156	12.6 (5.4)	20.9 (7.9)	8.3 (7.7)	8.3 (0.6)	<0.0001
Avanafil 200 mg	155	12.8 (5.0)	22.2 (7.7)	9.5 (7.0)	9.5 (0.6)	<0.0001
Treatment Comparison				**Difference (Tmt 1 – Tmt 2) [4]**		
				LS Mean (SE)	**95% CI**	**P-value**
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				6.7 (0.80)	(5.1, 8.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				5.5 (0.80)	(3.9, 7.0)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)				2.6 (0.80)	(1.0, 4.2)	0.0014

TA-302 IIEF Domain Score

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	125	11.4 (5.0)	13.2 (7.7)	1.8 (6.2)	1.8 (0.6)	0.0066
Avanafil 100 mg	125	11.2 (4.8)	15.8 (8.3)	4.6 (7.0)	4.5 (0.6)	<0.0001
Avanafil 200 mg	125	12.0 (5.1)	17.3 (8.6)	5.3 (7.5)	5.4 (0.7)	<0.0001
Treatment Comparison				**Difference (Tmt 1 – Tmt 2) [4]**		
				LS Mean (SE)	**95% CI**	**P-value**
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				3.6 (0.87)	(1.9, 5.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				2.8 (0.87)	(1.1, 4.5)	0.0017

1. n is the number of subjects with values at both time points.
2. Baseline values were calculated from all subject diary entries available from the 4-week, non-treatment run-in period.
3. End of treatment values were calculated from all subject diary entries beginning with the first dose of study drug and ending with the last study visit.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, erectile dysfunction severity category, and study as factors and baseline response as the covariate for the change from baseline response.

CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; Tmt = treatment;

Tables 6a and 6b: Change from Baseline in Percentage of Sexual Attempts in Which Subjects Were Able to Achieve Successful Vaginal Penetration (SEP2) in Studies TA-301 and TA-302

TA-301 SEP2

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	155	46.7 (36.3)	53.8 (37.9)	7.1 (32.1)	7.1 (2.3)	0.0025
Avanafil 50 mg	154	45.4 (36.7)	64.3 (37.2)	18.9 (35.5)	18.2 (2.3)	<0.0001
Avanafil 100 mg	157	46.6 (38.2)	73.9 (32.3)	27.3 (35.2)	27.2 (2.3)	<0.0001
Avanafil 200 mg	156	48.3 (38.2)	77.3 (31.4)	29.0 (35.9)	29.8 (2.3)	<0.0001
Treatment Comparison				**Difference (Tmt 1 – Tmt 2) [4]**		
				LS Mean (SE)	**95% CI**	**P-value**
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				22.7 (3.3)	(16.3, 29.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				20.1 (3.3)	(13.6, 26.5)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)				11.1 (3.3)	(4.6, 17.6)	0.0009

TA-302 SEP2

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	127	36.0 (36.6)	42.0 (39.3)	5.9 (31.2)	7.5 (2.9)	0.0088
Avanafil 100 mg	126	32.5 (35.2)	54.0 (39.4)	21.5 (37.2)	21.5 (2.9)	<0.0001
Avanafil 200 mg	126	41.5 (37.7)	63.5 (38.7)	22.0 (35.0)	25.9 (2.9)	<0.0001
Treatment Comparison				**Difference (Tmt 1 – Tmt 2) [4]**		
				LS Mean (SE)	**95% CI**	**P-value**
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				18.4 (3.95)	(10.6, 26.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				14.0 (3.94)	(6.3, 21.8)	0.0004

1. n is the number of subjects with values at both time points.
2. Baseline values were calculated from all subject diary entries available for the non-treatment run-in period.
3. End of treatment values were calculated from all subject diary entries beginning with the first dose of study drug and ending with the last study visit.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, erectile dysfunction severity category, and study as factors and baseline response as the covariate for the change from baseline response.

CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; Tmt = treatment;

Tables 7a and 7b: Change from Baseline in Percentage of Sexual Attempts in Which Subjects Were Able to Maintain an Erection to Have Successful Intercourse in Studies TA-301 and TA-302

TA-301 SEP3

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	155	12.6 (17.8)	27.0 (31.4)	14.4 (27.6)	14.1 (2.6)	<0.0001
Avanafil 50 mg	154	13.5 (18.6)	41.3 (35.9)	27.8 (33.9)	27.8 (2.6)	<0.0001
Avanafil 100 mg	157	13.9 (18.9)	57.1 (36.0)	43.2 (33.9)	43.4 (2.6)	<0.0001
Avanafil 200 mg	156	12.4 (18.5)	57.0 (37.8)	44.6 (35.7)	44.2 (2.6)	<0.0001
Treatment Comparison				**Difference (Tmt 1 – Tmt 2) [4]**		
				LS Mean (SE)	**95% CI**	**P-value**
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				30.2 (3.63)	(23.0, 37.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				29.3 (3.63)	(22.2, 36.5)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)				13.8 (3.64)	(6.6, 20.9)	0.0002

TA-302 SEP3

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	127	10.0 (16.4)	20.5 (29.1)	10.5 (27.7)	13.6 (2.8)	<0.0001
Avanafil 100 mg	126	8.2 (17.4)	34.4 (36.4)	26.2 (33.7)	28.7 (2.8)	<0.0001
Avanafil 200 mg	126	8.0 (14.9)	40.0 (36.3)	32.1 (32.9)	34.0 (2.8)	<0.0001
Treatment Comparison				**Difference (Tmt 1 – Tmt 2) [4]**		
				LS Mean (SE)	**95% CI**	**P-value**
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				20.4 (3.84)	(12.9, 28.0)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				15.2 (3.84)	(7.6, 22.7)	<0.0001

1. n is the number of subjects with values at both time points.
2. Baseline values were calculated from all subject diary entries available for the non-treatment run-in period.
3. End of treatment values were calculated from all subject diary entries beginning with the first dose of study drug and ending with the last study visit.

4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment, erectile dysfunction severity category, and study as factors and baseline response as the covariate for the change from baseline response.

Results from the secondary efficacy assessments, such as the IIEF domains for orgasmic function, intercourse satisfaction, and overall satisfaction all showed statistically significant improvements from baseline when compared to placebo, for all three doses, further supporting the clinical meaningfulness of the primary endpoint results.

7.4.1.2 Dose Selection Rationale

The results from the pivotal double-blind studies, the Phase 2 study TA-05, and the open-label extension study TA-314 support the efficacy of avanafil 50 mg, 100 mg, and 200 mg for the treatment of erectile dysfunction. The proposed dosing regimen is the same as that used in the double-blind and open-label studies: that is, 1 tablet to be taken as needed 30 minutes prior to initiation of sexual activity. The proposed initial starting dose of avanafil is 100 mg; the dose may be increased to 200 mg for insufficient efficacy or reduced to 50 mg for tolerability reasons. This treatment algorithm is the same as that used in the open-label extension study. During the review of the application, discussions were held regarding the need for the three dose strengths from an efficacy perspective.

In Study TA-302, conducted in diabetics with ED, there was a clear numeric improvement in erectile function for both the 100 mg and 200 mg doses over placebo; and importantly, there was also a clear numeric improvement in erectile function for the 200 mg dose as compared to the 100 mg dose. The reader is referred to Table 5b, 6b and 7b for the efficacy results in diabetics. The review team further assessed whether the dose of 200 mg was needed in the non-diabetic population.

In this regard, the Sponsor observed that avanafil provided consistently greater mean point estimates for the 200 mg dose compared to the 100 mg, and that an analysis of the double-blind studies in conjunction with the data from the open-label study TA-314 support conclusions of a dose response from 50 mg through 200 mg.

The Sponsor provided evidence to support the rationale for the 200 mg dose by showing the need for a higher dose in several, clinically relevant sub-populations, such as subjects with diabetes, subjects ≥ 65 years, subjects with severe ED at baseline, and subjects with prolonged history of ED (duration ≥ 60 months). This analysis is shown in the table that follows:

Table 8: Change from baseline in mean IIEF-EF domain and SEP3 scores

Treatment	Diabetics		Age ≥ 65 years		Severe ED at Baseline		ED Duration ≥ 60 months	
	IIEF	SEP 3	IIEF	SEP 3	IIEF	SEP 3	IIEF	SEP 3
Placebo	1.8	10.5	–0.4	1.0	2.1	6.5	1.4	6.6
50 mg	—	—	3.7	20.0	6.0	20.7	2.7	20.2
100 mg	4.6	26.2	4.7	25.5	7.0	27.6	6.1	33.5
200 mg	5.3	32.1	6.1	31.5	8.2	31.9	7.5	35.9

The Sponsor had the following additional justifications:

- During the final month of the pivotal, Phase 3 study TA-301 or TA-302, the SEP3 and SEP2 success rates were lower among 100 mg subjects that entered the open label TA-314 and requested an escalation to the 200 mg dose compared to those subjects who were satisfied with the starting dose of 100 mg. This indirectly supports the conclusion that for some individuals, 100 mg is satisfactory, but other individuals do not find 100 mg to be completely satisfactory, and go on to receive additional benefit from the 200 mg dose.

- In another analysis, among subjects who took at least 4 doses of avanafil 100 mg and at least 4 doses of avanafil 200 mg during the pivotal, Phase 3 study TA-301 or TA-302 and/or study TA-314, the successful percentages of SEP3 and SEP2 were significantly higher with avanafil 200 mg treatment than with avanafil 100mg treatment (69.9% vs. 54.7%). Of note, this effect was seen among subjects in the "general" ED population as well as subjects with diabetes.

- An augmentation of response with the increase in dose from avanafil 100 mg to 200 mg is also evident on an individual level in study TA-314, the open-label extension of the double-blind studies TA-301 and TA-302, designed to assess the long-term safety, tolerability, and efficacy of avanafil (up to 52 weeks).

- Safety results specific to the 200 mg dose within the double-blind cohort of Studies TA-05, TA-301 or TA-302, and TA-314 study do not suggest any new types or substantially increased rates of common AEs compared to the 100 mg dose. Rates of SAEs were also low and comparable between the 100 mg and 200 mg doses and overall, few subjects discontinued study drug due to an adverse event.

CDTL Comment: There is adequate rationale for all three avanafil doses.

7.4.1.3 Timing Between Dose and Sexual Activity

In the Phase 3 studies, patients were instructed to take avanafil approximately 30 minutes prior to anticipated sexual activity. In order to analyze the efficacy associated with different times of dosing prior to anticipated sexual activity (b) (4) patients were asked to record in a diary the time they took avanafil prior to sexual activity. The study protocols mentioned that such analyses would be conducted. As part of the Clinical review team's assessment of labeling, the Division assessed the data in support of different times.

(b) (4)

n the Sponsor's study reports, time between dose administration and sexual attempts were re-categorized into the following intervals: ≤15 minutes; > 15 minutes and ≤ 30 minutes; > 30 and ≤ 45 minutes; > 45 and ≤ 60 minutes; > 60 and ≤ 120 minutes; > 120 and ≤ 240 minutes; > 240 and ≤ 360 minutes; and > 360 minutes. The Sponsor provided the following data from Study 301, using the SEP Question 3 as a marker of successful intercourse, (b) (4)

Table 9: Summary of Attempts in Which Subjects Successfully Maintained an Erection of Sufficient Duration to Have Successful Intercourse by Time Interval (SEP3) in Study 301.

Time Interval From Dose to Attempt Statistics	Placebo	Avanafil 50 mg	Avanafil 100 mg	Avanafil 200 mg
≤15 minutes				
Number of attempts	74	61	110	55
Successful erections [1] n (%)	20 (27.0)	39 (63.9)	74 (67.3)	39 (70.9)
>15 minutes and ≤30 minutes				
Number of attempts	973	1014	1008	1071
Successful erections [1] n (%)	301 (30.9)	526 (51.9)	616 (61.1)	616 (57.5)
>30 minutes and ≤45 minutes				
Number of attempts	648	825	953	776
Successful erections [1] n (%)	154 (23.8)	377 (45.7)	585 (61.4)	477 (61.5)
>45 minutes and ≤60 minutes				
Number of attempts	500	499	537	494
Successful erections [1] n (%)	193 (38.6)	194 (38.9)	320 (59.6)	304 (61.5)
>60 minutes and ≤120 minutes				
Number of attempts	347	336	447	386
Successful erections [1] n (%)	91 (26.2)	130 (38.7)	266 (59.5)	258 (66.8)
>120 minutes and ≤240 minutes				
Number of attempts	73	88	107	100
Successful erections [1] n (%)	21 (28.8)	33 (37.5)	59 (55.1)	65 (65.0)
>240 minutes and ≤360 minutes				
Number of attempts	8	18	12	23
Successful erections [1] n (%)	2 (25.0)	10 (55.6)	4 (33.3)	16 (69.6)
>360 minutes				
Number of attempts	12	22	23	23
Successful erections [1] n (%)	3 (25.0)	13 (59.1)	18 (78.3)	19 (82.6)

Number of attempts is the number of diary entries for the specified time interval and is used as the denominator in the corresponding calculation of the proportion of successes.
[1] Successful intercourse is defined as a YES response to the diary question "Did your erection last long enough for you to have successful intercourse?"

CDTL Comment: (b) (4) [redacted]

Statistician's Conclusion

In their final memo for this NDA, dated April 9, 2012, the Statistical Review team of Jia Guo and Mahboob Sobhan concluded the following:

> "*The purpose of this review was to evaluate the efficacy data in support of Avanafil in the treatment of erectile dysfunction in men. Based on reviewer's analyses, the results support the efficacy of Avanafil 50 mg, 100 mg and 200 mg in the improvement of all three*

protocol specified co-primary endpoints. The treatment effects of Avanafil 100 mg and 200 mg on all three co-primary endpoints are statistically significantly better than Avanafil 50 mg. Although Avanafil 200 mg is not statistically more effective than Avanafil 100 mg, numerical improvement was seen in diabetic subjects.

From a statistical perspective, all doses of Avanafil (50 mg, 100 mg and 200 mg) are effective in treating ED."

The Statistical review focused on the Phase 3 studies TA-301 (in the general ED population) and TA-302 (in the diabetic ED population). The study designs, endpoints and results have already been discussed. TA-301 studied three doses (50 mg, 100 mg and 200 mg) versus placebo, while TA-302 studied only two doses (100 mg and 200 mg) versus placebo. The Statistics review team confirmed that all doses in both studies met all 3 co-primary endpoints at a p value < 0.05 using an appropriate ANCOVA model for the analysis.

One statistical review issue was comparing the effect of avanafil across doses in these fixed-dose studies. In TA-301, the Statistics review team stated that using the Hochberg procedure to compare dose groups, avanafil 100 mg and 200 mg were statistically significantly better than 50 mg but not different from each other. The statistician states, however, that "*numerical benefit is seen for avanafil 200 mg over 100 mg, especially in the diabetic subjects* [in TA-302]".

Finally, the statistician conducted efficacy analysis in subgroups, and efficacy was demonstrated in all important subgroups. Definitive conclusions could not be drawn from an analysis by ethnicity in white versus non-white subjects due to the limited number of non-white subjects

7.4.2 Overall Assessment of Efficacy

In three, randomized, double-blind, placebo-controlled studies (both Phase 3 studies TA-301 and TA-302, as well as the Phase 2 study TA-05), avanafil, at doses of 50 mg, 100 mg and 200

mg, demonstrated efficacy in the treatment of ED. The treatment effect is highly statistically significant compared to placebo and is clinically meaningful.

In regard to dose selection, 50 mg appears to be the least effective dose, and doses above 200 mg provide no increase in efficacy compared to lower doses. In the diabetic population compared to the non-diabetic population, a slightly higher dose is required (100 mg and 200 mg compared to 50 – 200 mg in the broad ED population). In diabetics, 200 mg provides clear numeric improvement over the 100 mg dose, although the difference was not statistically significant. In non-diabetics, a numeric benefit of the 200 mg dose over the 100 mg is observed in certain subpopulations; specifically, ED patients with severe disease, ED patients with a long history of the condition, and geriatric ED patients. Therefore, the doses proposed by the Sponsor (b) (4) (50 mg, 100 mg and 200 mg) are considered scientifically and clinically justified. The 100 mg dose is an appropriate starting dose, with potential for increase to 200 mg (b) (4) , and potential to decrease dose to 50 mg (b) (4) .

In regard to dosing instructions, the Phase 3 data support instructions to take avanafil approximately 30 minutes prior to anticipated sexual activity, (b) (4) Discussion of this labeling issue was ongoing at the time of filing this review.

8. Safety

8.1 SAFETY DATA

The safety data submitted in this NDA come from:

1. Two 12-week, Phase 3, controlled efficacy and safety studies (TA-301 and TA-302); one, large, Phase 2 study (TA-05); and a third, 12-week, controlled efficacy and safety study in men with ED status-post bilateral, nerve-sparing, radical prostatectomy (TA-303).
2. A 40-week, open-label, safety extension study to studies TA-301 and TA-302 (TA-314).
3. Phase 1 studies of pharmacokinetics (pK), clinical pharmacology, and tolerability. These studies included: investigations of single and multiple dose pK, food effect, metabolic drug interactions (e.g, inhibitors of CYP3A4, warfarin, rosiglitazone, etc), and avanafil pK in specific populations (e.g., renal and hepatic impaired).
4. A number of special safety studies, as follows:
    a. a thorough QT study (TA-140)
    b. a single-dose "sperm" study (TA-014)
    c. investigations of effects on vision (HP-01 and TA-016)
    d. interaction studies with nitroglycerin (TA-04), alpha blockers (doxazosin and tamsulosin, TA-017), anti-hypertensives (enalopril and amlodipine, TA-019), and alcohol (TA-015).

In total, 1923 subjects were exposed to avanafil during the clinical development program: 621 subjects received avanafil in Phase 1 studies, 360 subjects received avanafil in Phase 2 studies, and 942 subjects received avanafil in Phase 3 studies.

A total of 712 subjects were exposed to avanafil in the long-term safety study TA-314. In total, 493 subjects were exposed to avanafil for ≥ 6 months (26 weeks) and 153 subjects were exposed to avanafil for ≥ 12 months (52 weeks). In this long-term safety study, >500 subjects received the 200 mg dose.

8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

Deaths

One subject died. Subject # 108-020 in study TA-301 (avanafil 100 mg group), died from a self-inflicted gunshot wound; the event was considered by the investigator to be not related to study drug. There appeared to be mitigating social factors that may have played a role in the patient's suicide.

Serious Adverse Events (SAEs)

The incidence of serious adverse events (SAEs) in the Phase 3 studies TA-301 and TA-302 was 1.0% (n=3) subjects in the placebo group, 0.6% (n=1) subject in the avanafil 50 mg group, 2.1% (n=6) subjects in the avanafil 100 mg group, and 2.4% (n=7) subjects in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group.

One subject in the avanafil 300 mg group in the Phase 2 study TA-05 reported two SAE's (abdominal injury and head injury) due to a motor vehicle accident.

Eleven subjects reported an SAE during the open-label extension study TA-314. No subject in TA-314 had an SAE that was considered by the investigator to be related to study drug (and the reviewing medical officer agreed). The SAE resulted in discontinuation of study drug in Study TA-314 for 6 subjects: 1 with acute psychosis, 1 with femoral artery occlusion, 1 with coronary artery disease, 1 with aortic valve stenosis, 1 with cervical vertebral fracture, and 1 with congestive cardiac failure.

In the post-radical prostatectomy study TA-303, no subject died and none reported an SAE.

The primary medical officer's review contains narratives for each and every SAE in the Phase 3 studies TA-301, TA-302 and TA-314. For all but two of the SAEs in these three studies, the medical officer agreed with Sponsor that the event was either not related or probably not related to treatment with avanafil. In the two remaining cases, the medical officer stated that a relationship between the event and avanafil could not be excluded. These two SAEs were:

> Subject 130-012 in Study TA-301was an 80-year-old White male with a history of ED, tobacco use, hyperlipidemia, hypertension, peripheral artery disease, renal artery stenosis, status-post renal artery stent placement, atherosclerotic heart disease status-post right and left coronary angioplasty, and peripheral vascular disease. The subject was randomized to avanafil 200 mg dose on 21-Apr-2009. The last dose of study drug was taken on (b) (6) On (b) (6), the subject presented to the emergency department with bitemporal headache and retrosternal and left-sided chest discomfort radiating to the left side of the neck into the left jaw with associated nausea. The subject was emergently treated with hydromorphone and nitroglycerin with resolution of chest pain and headache. Cardiac monitoring revealed normal sinus rhythm and no evidence of gross

ischemia. A 12-lead electrocardiogram revealed normal sinus rhythm, normal axis, first degree atrioventricular block, and non-specific ST-T changes. Laboratory results revealed a troponin of 0.15 ng/mL (normal range [NR] 0.00-0.06 ng/mL) and creatine phosphokinase of 414 (NR and units not provided). A chest x-ray revealed no changes from previous x-ray on 20-Oct-2008. Cardiac catheterization with left ventriculography and coronary angiography was performed which revealed moderate non-obstructive coronary artery disease with heavy calcification in the right coronary artery and 40-50% stenosis in the proximal and midportion, heavy calcification of the left anterior descending coronary artery with 30-40% stenosis, calcification in the left main coronary artery with 30-40% ostial tapering, and 30-60% stenosis of the circumflex artery. A follow-up electrocardiogram revealed sinus bradycardia with first degree AV block. The subject was diagnosed with non-obstructive coronary artery disease. Medical management was advised. Additional treatment for the event included aspirin, isosorbide mononitrate, and metoprolol. The subject recovered from the event of moderate non obstructive coronary artery disease and headache on (b) (6) The investigator considered the event as not related to study drug; nonetheless, the subject was withdrawn from the study due to the SAE.

Subject 203-031 in Study TA-302 was a 54-year-old White male with a history of ED, diabetes, coronary artery disease status-post right coronary artery angioplasty with stent insertion, and history of heart attack. The subject was randomized to avanafil 200 mg on 12-Aug-2009. The last dose of study drug was taken on (b) (6) On (b) (6), the subject experienced chest pain and discomfort without radiation or shortness of breath and was hospitalized for evaluation and treatment. On (b) (6) a cardiac catheterization revealed a 20% distal discrete lesion of the left anterior descending artery, a 20% mid luminal irregular lesion of the circumflex artery, and an 80% lesion proximal to the previous stent in the right coronary artery. A stent was placed in the lesion in the right coronary artery. The subject was subsequently diagnosed with unstable angina. Laboratory results revealed a troponin of 0.27 and a creatine phosphokinase MB (CK-MB) of 4.2 (units and normal ranges not provided). Treatment medications included aspirin, hydrochlorothiazide, and Plavix. The subject was discharged and recovered from the event on (b) (6) The investigator considered the event of unstable angina as not related to study drug; but nonetheless, the subject was withdrawn from the study due to the SAE.

CDTL Comment: Because these events occurred within 24 hours of taking avanafil, the CDTL agrees with the medical officer that it is not possible to exclude a relationship between avanafil and the SAE in these two subjects; however, it is notable that both subjects had significant pre-existing coronary artery disease, and both had previously undergone coronary artery angioplasty. It is also notable that these are the only two SAEs in Phase 3 studies in which the role of avanafil could not be excluded.

Discontinuations due to Adverse Events

In total, 22 (2.1%) subjects in the Phase 3 double-blind cohort had an adverse event that resulted in study drug discontinuation. The incidences of discontinuations due to AEs in each group were: 1.7% (n=5) subjects in the placebo group, 1.9% (n=3) subjects in the avanafil 50 mg group, 2.8% (n=8) subjects in the avanafil 100 mg group, and 2.0% (n=6) subjects in the avanafil 200 mg group. No specific adverse event led to study drug discontinuation in more than 3 subjects in any treatment group.

In the open-label extension study TA-314, adverse events that led to discontinuation were considered by the investigators to be related to study drug in 10 subjects: 1 subject with back pain and headache; 2 subjects with dizziness; 1 subject with pigmentation disorder; 1 subject

with chest discomfort; 1 subject with palpitations, increased heart rate, and dizziness; 1 subject with dyspepsia, headache, and diarrhea; 1 subject with headache; 1 subject with erection increased; and 1 subject with pruritis and eye swelling.

In the radical prostatectomy study, 1 (1.0%) subject in the placebo group discontinued due to AEs ("*lumbar spinal stenosis*"); 3 (3.0%) subjects in the avanafil 100 mg group discontinued due to AEs ("*abdominal pain upper*", "*vomiting/dyspepsia*" and "*vision blurred/headache/nausea*"), and 2 (2.0%) subjects in the avanafil 200 mg group discontinued due to adverse events ("*hypertension*" and "*psychomotor hyperactivity/inappropriate affect (laughing)/headache*")

8.1.2 Other Adverse Events

Overall Adverse Events

In the Phase 3 studies TA-301 and TA-302, the incidences of the following TEAEs were higher in the avanafil groups than in the placebo group:

- Headache (placebo, 1.4%; avanafil 50 mg, 4.4%; avanafil 100 mg, 5.9%; and avanafil 200 mg, 10.2%);
- Flushing (placebo, 0.0%; avanafil 50 mg, 3.8%; avanafil 100 mg, 4.2%; and avanafil 200 mg, 3.8%);
- Dyspepsia (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 0.3%; and avanafil 200 mg, 1.4%), and
  Diarrhea (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 0.3%; and avanafil 200 mg, 1.4%);
- Sinus congestion (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 1.7%; and avanafil 200 mg, 0.3%), and
  Upper respiratory infection (placebo, 0.3%; avanafil 50 mg, 1.9%; avanafil 100 mg, 0.7%; and avanafil 200 mg, 0.3%).

The list of AEs reported by ≥ 1% of subjects in any treatment group in the Phase 3 studies TA-301 and TA-302 is shown in the table below.

Table 10: Summary of Treatment-Emergent Adverse Events (TEAEs) reported ≥1% of Subjects in Any Treatment Group, by System Organ Class and PT – Phase 3 Double-Blind Cohort (TA-301+TA-302)

System Organ Class Preferred Term (PT)	Placebo (N=291) n (%)	Avanafil		
		50 mg (N=160) n (%)	100 mg (N=288) n (%)	200 mg (N=293) n (%)
Infections and infestations	**19 (6.5)**	**13 (8.1)**	**29 (10.1)**	**28 (9.6)**
Nasopharyngitis	8 (2.7)	1 (0.6)	6 (2.1)	10 (3.4)
Sinusitis	3 (1.0)	0 (0.0)	5 (1.7)	3 (1.0)
Bronchitis	1 (0.3)	3 (1.9)	1 (0.3)	4 (1.4)
Influenza	0 (0.0)	1 (0.6)	5 (1.7)	1 (0.3)
Upper respiratory tract infection	1 (0.3)	3 (1.9)	2 (0.7)	1 (0.3)
Nervous system disorders	**9 (3.1)**	**9 (5.6)**	**22 (7.6)**	**34 (11.6)**
Headache	4 (1.4)	7 (4.4)	17 (5.9)	30 (10.2)
Musculoskeletal & connective tissue disorders	**14 (4.8)**	**11 (6.9)**	**16 (5.6)**	**11 (3.8)**
Back pain	4 (1.4)	4 (2.5)	6 (2.1)	4 (1.4)
Pain in extremity	2 (0.7)	0 (0.0)	2 (0.7)	3 (1.0)
Gastrointestinal disorders	**7 (2.4)**	**9 (5.6)**	**12 (4.2)**	**15 (5.1)**
Diarrhea	0 (0.0)	1 (0.6)	1 (0.3)	4 (1.4)
Dyspepsia	0 (0.0)	1 (0.6)	1 (0.3)	4 (1.4)
Nausea	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.0)
Constipation	1 (0.3)	3 (1.9)	0 (0.0)	0 (0.0)
Stomach discomfort	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.3)
Vascular disorders	**1 (0.3)**	**7 (4.4)**	**18 (6.3)**	**11 (3.8)**
Flushing	0 (0.0)	6 (3.8)	12 (4.2)	11 (3.8)
Hypertension	0 (0.0)	1 (0.6)	4 (1.4)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	**5 (1.7)**	**4 (2.5)**	**14 (4.9)**	**15 (5.1)**
Nasal congestion	2 (0.7)	1 (0.6)	7 (2.4)	4 (1.4)
Sinus congestion	1 (0.3)	1 (0.6)	2 (0.7)	5 (1.7)
Injury, poisoning, and procedural complications	**10 (3.4)**	**3 (1.9)**	**8 (2.8)**	**4 (1.4)**
Skin laceration	0 (0.0)	1 (0.6)	3 (1.0)	0 (0.0)
Skin & subcutaneous tissue disorders	**4 (1.4)**	**3 (1.9)**	**3 (1.0)**	**4 (1.4)**
Rash	1 (0.3)	2 (1.3)	0 (0.0)	1 (0.3)

The profile of adverse events commonly reported in the phase 3 Study TA-303 was the same as in the Phase 3 studies TA-301 and TA-302, but the incidences were somewhat higher in TA-303. The AEs reported in ≥ 2% of patients treated with avanafil 100 mg and 200 mg in Study TA-303 are shown in the table below:

Table 11: Treatment Emergent Adverse Events Reported by ≥ 2% of Patients Treated with Avanafil 100 mg or Avanafil 200 mg in Study TA-303 in Patients Who Underwent Bilateral Nerve-Sparing Radical Prostatectomy

Adverse Reaction	Placebo (N = 100)	AVANAFIL 100 mg (N = 99)	AVANAFIL 200 mg (N = 99)
Headache	1.0%	8.1%	12.1%
Flushing	0.0%	5.1%	10.1%
Nasopharyngitis	0.0%	3.0%	5.1%
Upper respiratory infection	0.0%	2.0%	3.0%
Nasal congestion	1.0%	3.0%	1.0%
Back pain	1.0%	3.0%	2.0%
Electrocardiogram abnormal	0.0%	1.0%	3.0%
Dizziness	0.0%	1.0%	2.0%

The profile of adverse events commonly reported in the Phase 3, 40-week, open-label extension study TA-314 was the same as in the 12-week, placebo-controlled, phase 3 studies, with slightly lower incidences. The AEs reported in ≥ 2% of patients treated with a dose-optimization regimen of avanafil 50 mg, 100 mg and 200 mg in Study TA-314 are shown in the table below:

Table 12: Treatment Emergent Adverse Events Reported by ≥ 2% of Patients Treated With a Dose Optimization Regimen of Avanafil 50 mg, 100 mg, or 200 mg in Study TA-314, a 40-week, Open-Label Extension Trial

Adverse Reaction	AVANAFIL (N = 711)
Headache	5.6%
Flushing	3.5%
Nasopharyngitis	3.4%
Nasal congestion	2.1%

Adverse reactions reported by greater than or equal to 1%, but less than 2% of patients in Study TA-314 included: upper respiratory infection (URI), influenza, sinusitis, bronchitis, dizziness, back pain, arthralgia, hypertension, and diarrhea.

8.1.3 Special Safety Studies

8.1.3.1 Thorough QT (TQT) Study (TA-140)

On November 30, 2011, Jeffry Florian, Moh Jee Ng, Joanne Zhang, Monica Fiszman, and Norman Stockbridge of the Interdisciplinary Review Team – QT (IRT-QT) finalized their consultative report concerning the TQT study conducted for avanafil. The consultants concluded:

"*The upper bound of 90%CI for ΔΔQTcF 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."

The study design and results are summarized herein:

The avanafil TQT study was a randomized, double-blind, 4-arm crossover study. Fifty-seven healthy, young, male volunteers were enrolled to receive therapeutic avanafil (100 mg single dose), supratherapeutic avanafil (800 mg single dose), placebo, and moxifloxacin 400 mg. Dosing was conducted in the fasted condition. Each subject received each treatment. An overall summary of the study results is presented in the table below:

Table 13: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Therapeutic and Supratherapeutic Avanafil and the Largest Lower Bound for Moxifloxacin (IRT-QT Analysis)

Treatment	Time (h)	ΔΔQTcF (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.

No subject's absolute corrected QT interval was > 500 milliseconds and no subject had a change from baseline of > 60 milliseconds. One moxifloxacin subject had a corrected QT value > 450 msec, while no avanafil subject met that criterion. Two moxifloxacin subjects had a change from baseline in corrected QT > 30 milliseconds, while no avanafil subject met that criterion. According to the IRT-QT report, when the QT interval was corrected for changes in heart rate using the individualized correction method (QTcI), the upper bounds of the 90% confidence for change-from-baseline in placebo-corrected QTc were "well less than 5 milliseconds". While the reviewer states that the Fridericia-corrected QT interval was the more appropriate measurement tool compared to the QTcI, the reviewer also stated "*These data do not support any effect of avanafil on cardiac repolarization*".

The supratherapeutic dose (800 mg) produced 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 TQT 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 Cmax and AUC, respectively. To address this drug-drug interaction, the label will recommend that avanafil dose be reduced to 50 mg in patients taking moderate inhibitors of CYP3A4 (e.g., erythromycin) and avanafil use will not be recommended in patients taking strong inhibitors of CYP3A4. All together, the supratherapeutic dose of 800 mg produced serum avanafil concentrations sufficient to cover the steady state high exposure scenario anticipated in patients taking avanafil 50 mg along with a moderately potent inhibitor of CYP3A4, and would even be sufficient to cover exposures produced in patients taking a strong CYP3A4 inhibitor (i.e., ketoconazole) and 50 mg avanafil every other day.

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.

CDTL Comment: Therefore, the avanafil doses employed in the TQT study were appropriate and the results of this study do not demonstrate an effect of avanafil, at therapeutic and supratherapeutic plasma concentrations, on increasing the corrected QT interval.

8.1.3.2 Pharmacodynamic Interaction with Nitroglycerin (TA-04)

The magnitude of the interaction between sublingual nitroglycerin and avanafil, and the timepoint at which sublingual nitroglycerin can be safely administered after a dose of avanafil were assessed in Study TA-04. The results of the study are provided herein:

Study TA-04 was a single center, double blind, randomized, 3-way crossover study in healthy male subjects aged 30 to 60 years. Subjects were divided into 5 study groups, differing only by the time interval between treatment with avanafil 200 mg, sildenafil 100 mg, or placebo and with glyceryl trinitrate (0.4 mg) (0.5 hrs, 1 hr, 4 hrs, 8 hrs and 12 hrs).

A single oral dose of avanafil 200 mg was shown to potentiate the hypotensive effect of glyceryl trinitrate (0.4 mg tablet administered sublingually). The maximum interaction between avanafil and glyceryl trinitrate was observed at the **0.5-hour time point** for BP and pulse rate. The mean maximum decreases from pre-dose to post-dose in sitting systolic BP were **19.2 and 14.3 mmHg** in subjects given avanafil and placebo, respectively, followed by glyceryl trinitrate 0.5 hr later. The mean maximum decreases from pre-dose to post-dose in sitting diastolic BP were **16.7 and 14.3 mmHg** in subjects given avanafil and placebo, respectively, followed by glyceryl trinitrate 0.5 hr later. The mean maximum increase from pre-dose to post-dose in standing pulse rate were **19.8 and 16.8 bpm** in subjects given avanafil and placebo, respectively, followed by glyceryl trinitrate 0.5 hr later.

The incidence of symptomatic hypotension AEs in this study was 24% for avanafil and 11% for placebo.

The time at which a dose of nitroglycerin may be safely administered after a dose of avanafil was not well defined from this study, as there were sporadic statistically significant differences between avanafil and placebo groups at various timepoints after the 0.5-hr timepoint.

CDTL Comment: Avanafil, like all other PDE5 inhibitors has a significant pharmacodynamic interaction with nitroglycerin and these drugs should not be taken together. The timepoint at which nitroglycerin can be safely administered after a dose of avanafil was not clearly defined in this study; therefore, based upon an abundance of caution, the label should recommend 12 hours, and even then, with careful monitoring.

8.1.3.3 Interactions with Alpha Blockers (TA-017)

Men with ED commonly have BPH-related lower urinary tract symptoms. Therefore, it is expected that avanafil will be taken by men taking treatments for BPH symptoms, including alpha blockers. The magnitude of the potential interaction between avanafil and the alpha blockers doxazosin (a less selective alpha blocker) and tamsulosin (a more selective alpha blocker) were assessed in study TA-017. The results of the study are provided herein:

Doxazosin was given once daily in the morning, as follows: 1 mg on the first day, 2 mg on Days 2-3, 4 mg on Days 4-7, and 8 mg on Days 8-18. A single dose of either 200 mg avanafil or placebo was administered after the doxazosin dose on Days 15 and 18, respectively.

Tamsulosin 0.4 mg was administered once daily in the morning for 11 consecutive days. A single dose of either 200 mg avanafil or placebo was administered 3.3 hours after the tamsulosin dose on Days 8 and 11, respectively.

Overall, BP decreased and pulse rate increased soon after the administration of avanafil with either doxazosin or tamsulosin. The interaction between avanafil and doxazosin was larger compared to the interaction with tamsulosin. The clinical effect appeared to diminish within several hours.

For doxazosin, the maximum decreases in *supine* BP and increases in pulse rate are shown in the table below.

Table 14: Maximum Changes in Supine BP and Pulse Rate: Doxazosin with Avanafil vs. Placebo with Avanafil in Study TA-017

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Doxazosin + Avanafil	Doxazosin + Placebo	Mean Difference		
Max decrease systolic (mmHg)	-13.21	-7.21	-6.00	-9.07 - -2.93	0.0005
Max decrease diastolic (mmHg)	-10.58	-7.00	-3.58	-5.63 - -1.53	0.0015
Max increase pulse rate (bpm)	+17.12	+13.37	+3.75	-2.92 - +10.42	0.2564

For doxazosin, the decreases in *standing* BP and increases in standing pulse are shown in the three figures that follow:

Figure 1: Mean (SD) change from baseline in standing systolic BP in doxazosin cohort in Study TA-017

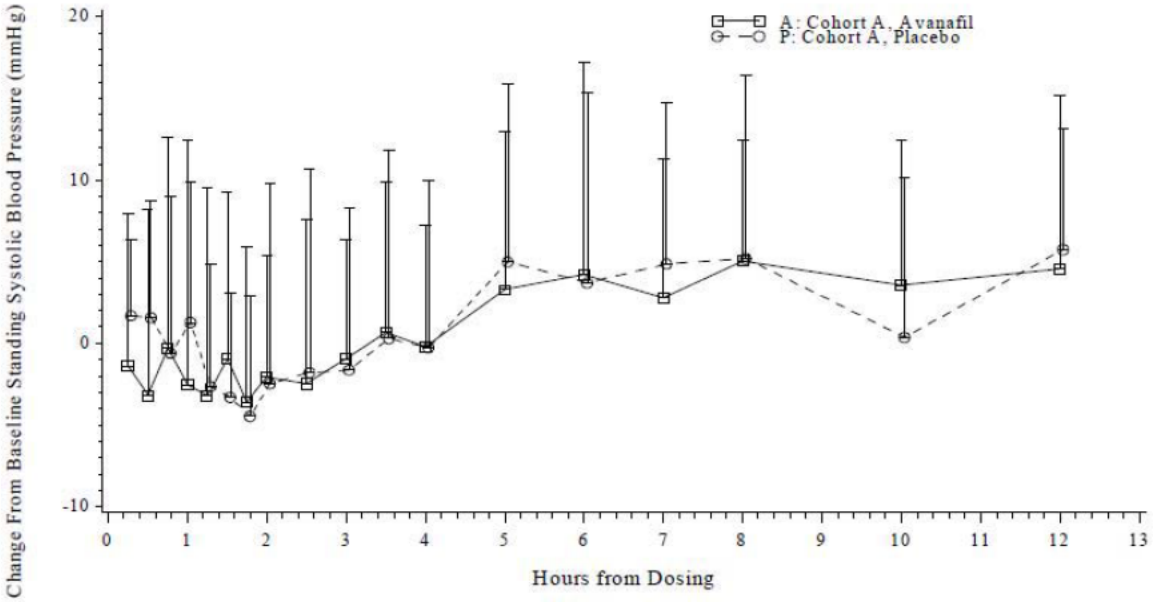


Figure 2: Mean (SD) change from baseline in standing diastolic BP in doxazosin cohort in Study TA-017

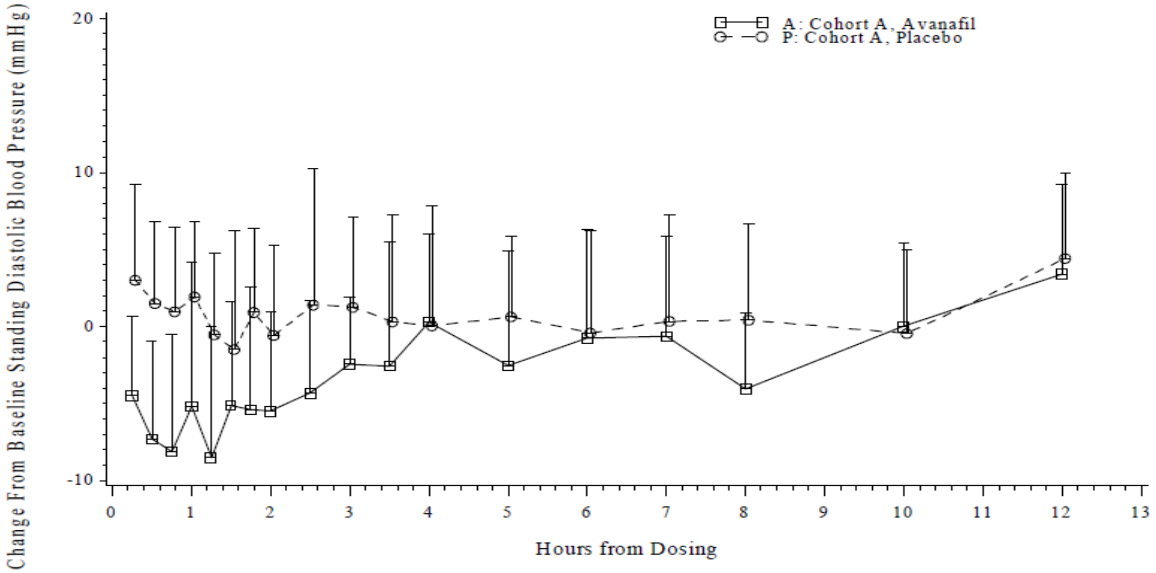
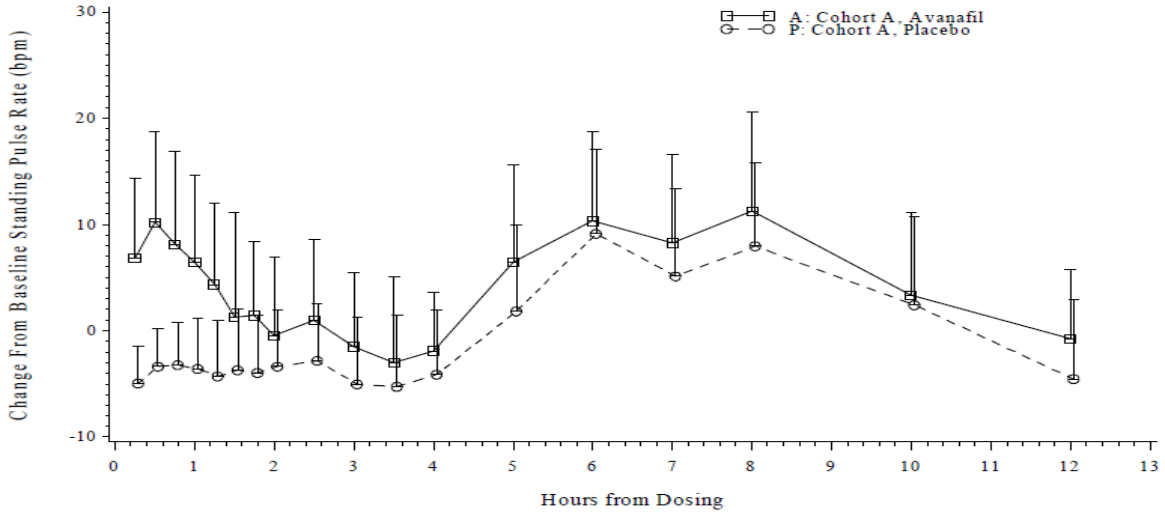


Figure 3: Mean (SD) change from baseline in standing pulse in doxazosin cohort in Study TA-017



A total of seven subjects experienced potentially clinically important absolute values or changes from baseline in standing SBP or DBP, with all but one event occurring after administration of avanafil. All of the potentially clinically important values began and resolved within the first 1.25 hours postdose, with the exception of one subject who had a single isolated potentially clinically important event at Hour 6.0. No subjects experienced potentially clinically important supine hemodynamic events.

For tamsulosin, the maximum decreases in *supine* BP and increases in pulse rate are shown in the table below.

Table 15: Maximum Changes in Supine BP and Pulse Rate: Tamsulosin with Avanafil vs. Placebo with Avanafil in Study TA-017

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Tamsulosin + Avanafil	Tamsulosin + Placebo	Mean Difference		
Max decrease systolic (mmHg)	-11.00	-7.88	-3.13	-6.37 - +0.12	0.0580
Max decrease diastolic (mmHg)	-10.04	-6.71	-3.33	-6.49 - -0.18	0.0392
Max increase pulse rate (bpm)	+20.75	+16.08	+4.67	+0.37 - +8.96	0.0344

For tamsulosin, the decreases in *standing* BP and increases in standing pulse are shown in the three figures that follow:

Figure 4: Mean (SD) change from baseline in standing systolic BP in tamsulosin cohort in Study TA-017

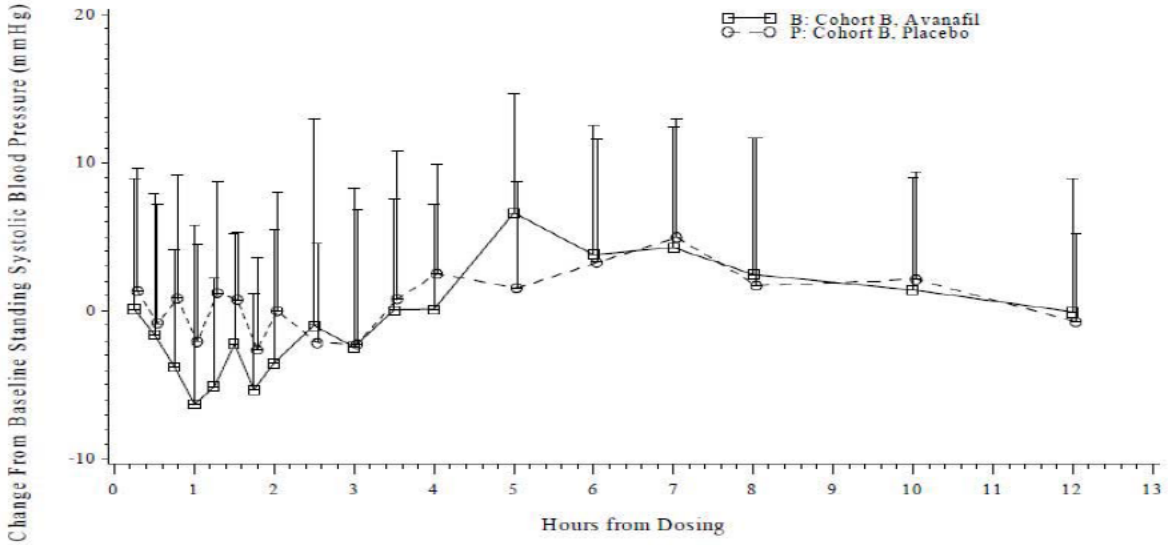


Figure 5: Mean (SD) change from baseline in standing diastolic BP in tamsulosin cohort in Study TA-017

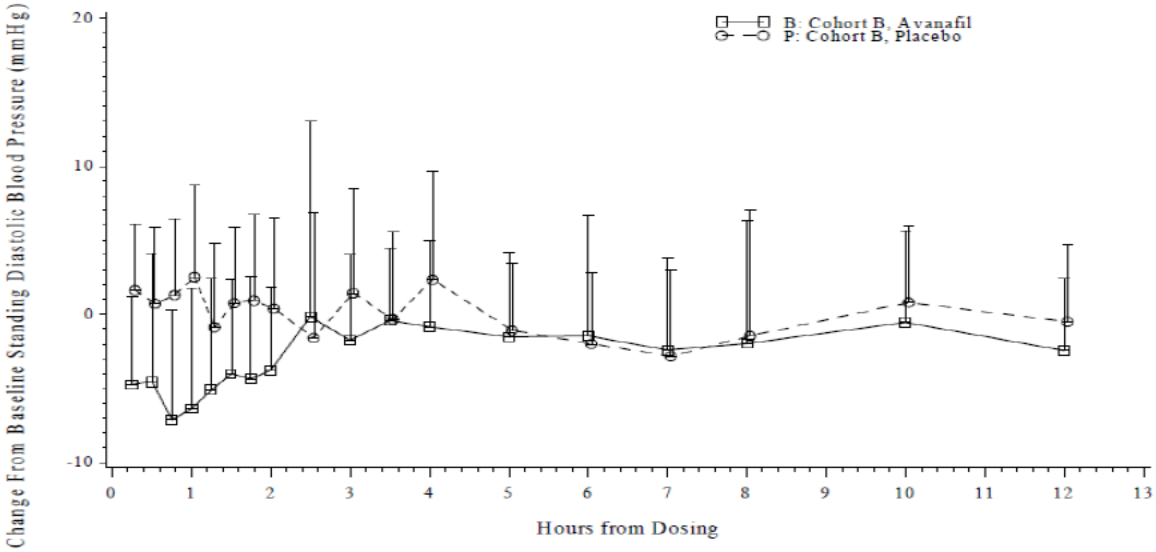
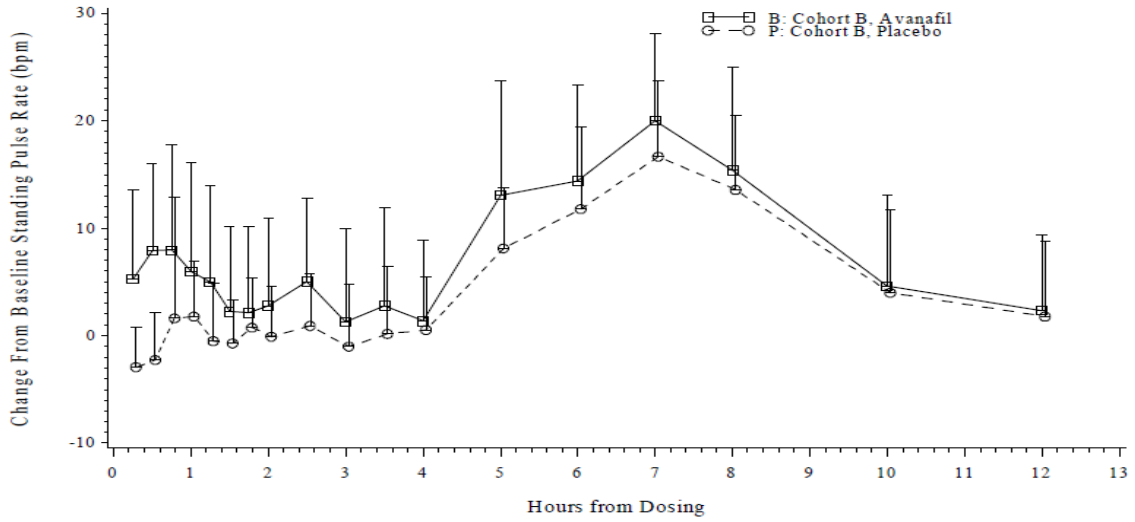


Figure 6: Mean (SD) change from baseline in standing pulse in tamsulosin cohort in Study TA-017



A total of five subjects experienced potentially clinically important absolute values or changes from baseline in standing SBP or DBP, with all but one event occurring after administration of avanafil. Three of the subjects experienced events beginning and resolving within 1.25 hours post-dose following avanafil. Of the two remaining subjects, one had a single isolated event at Hour 2.5 following placebo, and the other had a series of events at various postdose time points following avanafil, including at time points farther removed from the time of dosing (Hours 7.0, 8.0, and 24.0). No patient experienced a supine hemodynamic event that was reasonably temporally related to avanafil or placebo.

> ***CDTL Comment*:** Avanafil, like all other PDE5 inhibitors, has an interaction with alpha blockers, with more of an interaction with doxazosin, a less selective alpha-blocker, compared to with tamsulosin, a more selective alpha blocker. The label should advise cautious use of avanafil with alpha blockers.

8.1.3.4 Interactions with Anti-Hypertensives (TA-019)

Men with ED commonly have concomitant hypertension. Therefore, it is expected that avanafil will be taken by men taking anti-hypertensive medications. The magnitude of the potential interaction between avanafil and the anti-hypertensives enalapril (an ACE inhibitor) and amlodipine (a calcium channel blocker) were assessed in study TA-019. The results of the study are provided herein:

For enalapril, a single 200 mg dose of avanafil was given to subjects who received 10 mg doses of enalapril twice daily for 11 days.

For amlodipine, a single 200 mg dose of avanafil was given to subjects who received 5 mg doses of amlodipine once daily for 18 days.

Overall, the addition of avanafil incurred minor additional reductions in BP and increases in pulse rate in patients taking enalopril or amlodipine, without significant increase in symptomatic hypotension events.

For enalapril, the mean maximum changes from baseline in supine systolic/diastolic BP and in pulse rate after avanafil compared to after placebo were -1.8/-3.4 mmHg and +1 bpm, respectively. Differences between groups in changes from baseline in standing BP and pulse rate were even smaller.

For amlodipine, the mean maximum changes from baseline in supine systolic/diastolic BP and after avanafil compared to after placebo was -1.2/+1.5 mmHg. The mean maximum changes from baseline in standing systolic/diastolic BP and after avanafil compared to after placebo was -1.6/-1.4 mmHg and +5.4 bpm, respectively.

CDTL Comment: Avanafil, like all other PDE5 inhibitors, has a minor pharmacodynamic interaction with commonly used anti-hypertensives (in this case, enalapril and amlodipine). The label should include this information.

8.1.3.3 Interactions with Alcohol (TA-015)

The potential risks associated with combining alcohol with avanafil were assessed in Study TA-015. The results of this study are provided herein:

Study TA-015 was a Phase 1, single center, double-blind, randomized, placebo-controlled, three-period, three-way crossover study in young male subjects. The three treatment groups were (A) a single dose of 200 mg avanafil plus an alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kilogram of body weight); (B) a single placebo tablet plus an alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kilogram of body weight); and (C) a single dose of 200 mg avanafil plus a placebo drink mixed with fruit juice. A total of 15 subjects were enrolled with 14 subjects completing the study.

At most time points from 30 minutes to 4 hours post-dosing, there were larger mean blood pressure decreases (SBP and DBP) and larger mean pulse rate increases following Treatment A (alcohol + avanafil) compared to following Treatment C (avanafil alone) or Treatment B (alcohol alone). In this study, the differences between groups were more pronounced for changes in supine diastolic BP and pulse rate compared to supine systolic BP. By Hour 4, mean BP and pulse measurements were near baseline values for all treatments, but differences were still present between Treatment A (avanafil + alcohol) and Treatment B (alcohol alone). Results from this trial are shown in the table and three figures that follow:

Table 16: Mean Hemodynamic Changes From Baseline in Study TA-015

Parameter	Mean ± SD		
	Treatment A (N = 14)	Treatment B (N = 14)	Treatment C (N = 14)
Max decrease systolic (mmHg)	-14.5 ± 10.78	-10.9 ± 5.70	-11.8 ± 6.58
Max decrease diastolic (mmHg)	-14.6 ± 7.93	-9.6 ± 6.97	-11.4 ± 5.57
Max increase pulse rate (bpm)	+19.3 ± 9.38	+10.2 ± 10.82	+15.4 ± 7.20

Treatment A = single dose of 200 mg avanafil tablet plus an oral alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kilogram of body weight)
Treatment B = single oral dose of placebo plus an oral alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kilogram of body weight)
Treatment C = single dose of 200 mg avanafil tablet plus an oral placebo drink mixed with fruit juice

Figure 7: Mean (SD) change from baseline in supine systolic BP in Study TA-015

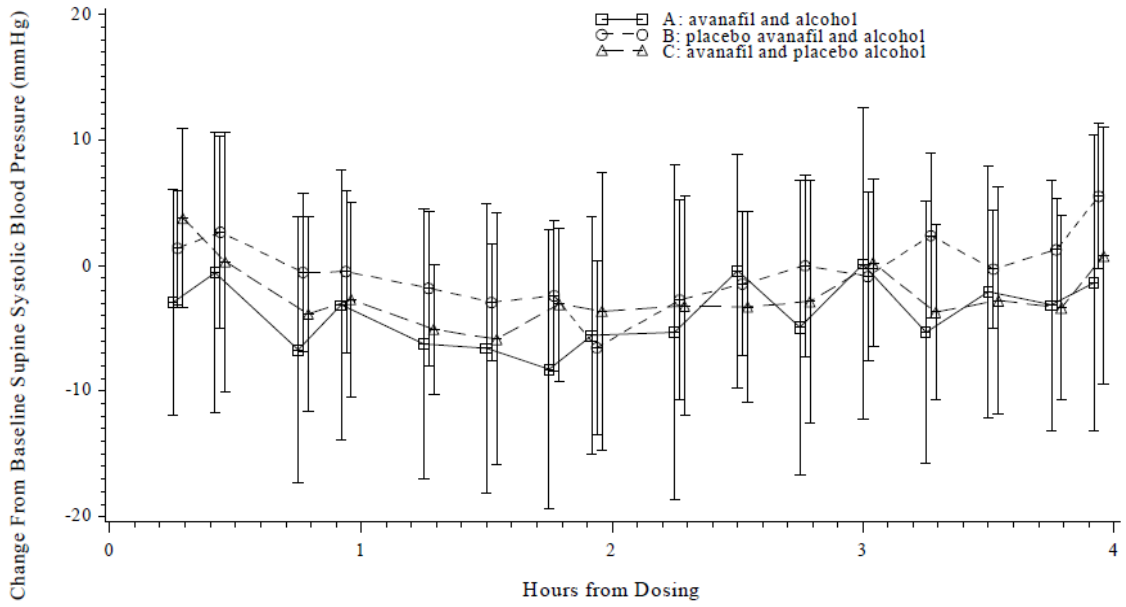


Figure 8: Mean (SD) change from baseline in supine diastolic BP in Study TA-015

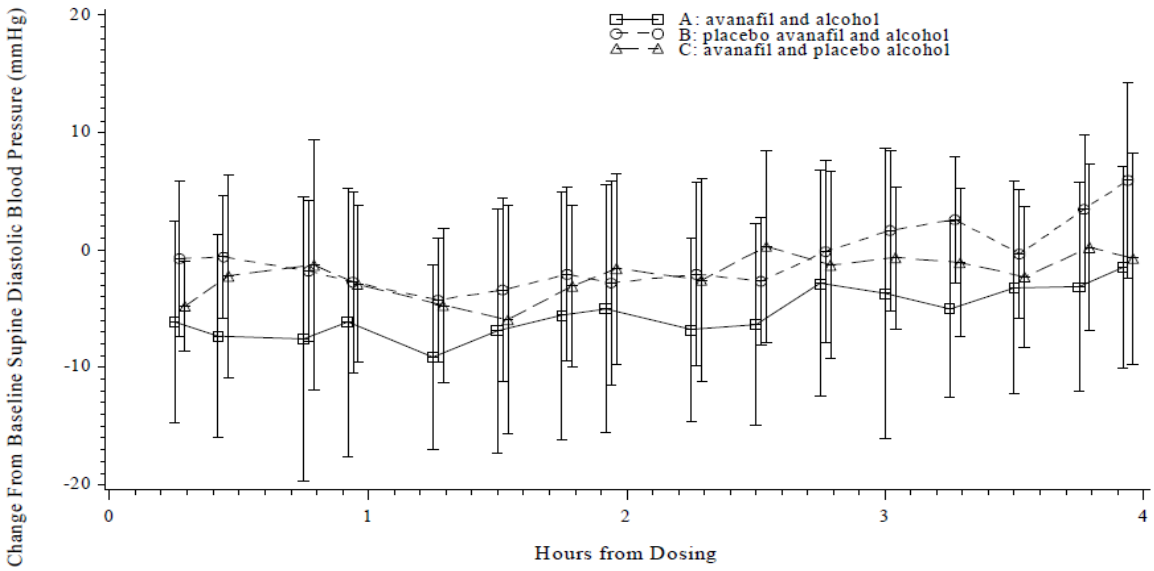
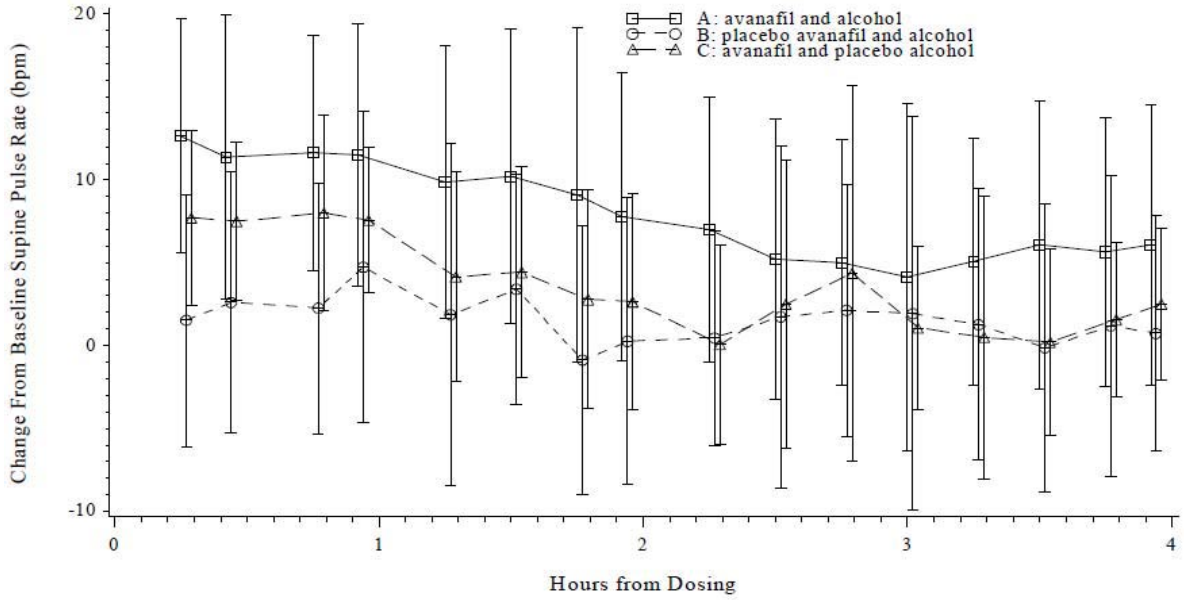


Figure 9: Mean (SD) change from baseline in pulse rate in Study TA-015



From the data in this study, there appears to be, at minimum, a further decrease of 3.5/4.5 mm Hg in systolic and diastolic BP, respectively, and additional increase of approximately 9 beats per minutes when avanafil is added to a 0.5 gm/kg bolus of alcohol. Differences between groups are observed soon after dosing, with the largest differences observed at approximately 1 - 1.25 hours after dosing. The differences between groups persist for 4 hours.

> ***CDTL Comment***: Avanafil, like all other PDE5 inhibitors, has a pharmacodynamic interaction with alcohol. The avanafil label should advise against excessive intake of alcohol (e.g., > 3 glasses of wine, or 3 shots of whisky) in combination with avanafil use.

8.1.3.4 Sperm Assessments

Effects of avanafil on human sperm were tested as part of the Phase 1 study TA-014, and also in the single-dose sperm study TA-021. The results of these limited investigations are provided herein.

Study TA-014 was a single dose (200 mg), non-randomized, open-label, 2-cohort study in healthy male subjects, which assessed the effect of age on the PK of avanafil. Subjects in the young group were men, 19 to 43 years of age, while the subjects in the elderly group were men, 65-80 years of age. Avanafil semen exposure and the acute effect of avanafil on sperm function in the young subjects were also evaluated. In regard to the exposure in semen and the effect on sperm, the Sponsor concluded

- Mean total amount of avanafil in seminal fluid collected at 1 hour post-dose was minimal (<0.0002% of the 200 mg administered);
- Mean sperm motility remained within the reference range and did not change by >20% from baseline. There was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress.
- Two subjects, however, showed notable decreases in sperm motility and decreases in sperm count compared to their baseline values. At Hour 1, Day 1, Subjects #11 and #13 showed

sperm motility of 34% and 24%, respectively, and sperm concentrations of 19 million/mL and 12 million/mL, respectively.

Study TA-021 was a single dose (200 mg), randomized, double-blind, placebo-controlled, 2-period crossover study which assessed the effect of a single dose of avanafil on sperm function in healthy, young male subjects. The results of the study showed:

- A single 200 mg dose of avanafil had no acute effect on sperm motility in a group of healthy male subjects.
- Mean values for all semen parameters (sperm concentration, sperm motility, forward progression, total sperm count, sperm morphology, and total motile sperm count) were within normal limits at the Day 1 post-dose assessment for avanafil treatment group.
- There were no subjects in either treatment group who experienced a ≥ 50% decrease from baseline in total motility, forward progression, or WHO calculated forward progression.
- There was no statistically significant difference ($p > 0.05$) in the least-squares (LS) mean changes from baseline for total motility, forward progression, or WHO calculated forward progression percentages between the avanafil and placebo treatments.

***CDTL Comment*:** Both Studies TA-014 and TA-021 were single-dose studies, and the potential adverse effects of avanafil on human sperm after longer-term use are currently unknown. The Sponsor has agreed to conduct a randomized, double-blind, placebo-controlled, multiple-dose sperm study to assess the potential effects of avanafil on human sperm.

8.1.3.3 Vision Assessments

Effects of avanafil on color discrimination were tested as part of two phase 1 studies, HP-01 and TA-016. The results of these limited vision investigations are provided herein.

Study HP-01 was a double-blind, single-ascending dose study of the safety, tolerability and pharmacokinetics of avanafil in healthy male volunteers. The study included a test of color discrimination following placebo or avanafil single doses of 12.5 mg to 800 mg. Modification of color vision (using the Farnsworth-Munsell 100-Hue Test), was assessed at screening, pre-dose and 1.5 hour after drug administration. Based on the plots of error scores for each panel of color at each evaluation time, the investigator stated "yes" for any defective color vision test or "no" if color vision defects were not observed. Subjects presenting at least one abnormal test for each panel of color, whatever the time after dosing, were counted as "yes".

The Sponsor reported that:

- One subject in the 12.5 mg group presented an abnormal result on one panel at one timepoint.
- One subject in the placebo group had defective color vision for two panels at 1.5 hour after administration. This patient's abnormality was observed on his left eye and was consistent with the same finding at screening on his right eye. The investigator believed that this defect in this subject was not related to the study drug.

Therefore, as only one subject in one dose group (12.5 mg) presented an abnormality in color vision discrimination at one timepoint, this abnormality in the 12.5 mg group was considered as not related to study drug by the investigator.

Study TA-016 was a Phase 1, single-center, double-blind, randomized, placebo-controlled, 2-way crossover study to assess the potential interaction of avanafil on the pharmacokinetics and pharmacodynamics of warfarin in healthy male volunteers. There was at least a 21-day washout

between treatment periods. Each subject participated in two sessions in which they were randomized to receive either 200 mg of avanafil or matching placebo for 9 days. On Day 3 of each period, subjects received a single dose of warfarin (25 mg). Following the warfarin dose, PK and PD sampling was taken over a period of 7 days. Potential for color vision impairment with avanafil was part of the PD assessment. The Farnsworth-Munsell 100-Hue Test was performed at screening, on Day -2 (Period 1 only), on Day -1 (both periods), and at approximately 0.667 hours post-dose on Day 1 (both periods). The analytical parameters assessed in the Farnsworth-Munsell 100-Hue Test included total error score (a measure of the gross errors), square root transformed total error score, the C index (Confusion index, a measure of severity of a color loss), the S-index (Scatter index, a measure of degree of randomness or selectivity in observers' arrangement), and the Angle score (a measure of type of a color loss).

Results of the Farnsworth-Munsell 100-Hue test in this study were summarized using descriptive statistics (N, arithmetic mean, SD, median, minimum, and maximum). Post-dose (0.67 hour) values as well as change from baseline (postdose minus Day -1 baseline) were respectively compared between treatments (Treatment A [warfarin + avanafil] vs Treatment B [warfarin + placebo]) using a Wilcoxon Signed Rank Test. Any difference was considered significant if the p-value was less than 0.05.

The results reported by the Sponsor showed that there were generally no statistically significant differences between groups in the post-dose values between the two treatments. The p-value for the comparison of groups for total error score was 0.056 (see table below). A statistically significant p-value was observed in mean change in square root transformed total error score in an analysis that excluded an outlier. That p-value for that comparison was 0.047 when comparing change from transformed total error score of 0.9640 for warfarin + avanafil to 0.0163 for warfarin + placebo (p-value = 0.047 when Subject 14 was excluded – see table below).

Table 17: Total Error Scores from the Farnsworth-Munsell 100-Hue Test from Study TA-016 (Outliers Excluded)

Time Point	Measurement Results		Changes from Pre-dose		p-value
	Treatment A	Treatment B	Treatment A	Treatment B	
Total Error					
Day –1 pre-dose	33.3±17.6	39.5±21.7			
Day 1 0.67 hr	45.3±19.8	39.2±19.1	12.0±19.3	–0.3±14.8	0.056
Total Error Square Root					
Day –1 pre-dose	5.6±1.5	6.03±1.8			
Day 1 0.67 hr	6.6±1.6	6.05±1.6	0.96±1.5	0.02±1.2	0.047

Treatment A: warfarin + avanafil; Treatment B: warfarin + placebo.

The Sponsor believes that the data from Study TA-016 do not suggest an effect of avanafil on color discrimination.

CDTL Comment: The purpose of this study was to compare the effects on color vision beween warfarin + avanafil and warfarin + placebo. From this design, no conclusions can be reached as to whether avanafil itself has effects on color vision. Nevertheless, a difference was observed between avanafil and placebo in total error score and square root of the total error score (when an outlier was excluded). To resolve the potential effect of avanafil on vision, the Sponsor has agreed to conduct a dedicated postmarketing vision

study to evaluate effects of avanafil on, but not limited to, visual acuity, intraocular pressure, pupillometry and color vision discrimination.

8.1.4 Overall Assessment of Safety Findings

In this NDA, the controlled safety data comes from two, 12-week, Phase 3, efficacy and safety studies (TA-301 and TA-302); one, large, Phase 2 study (TA-05); and a third, 12-week, efficacy and safety study in men with ED status-post bilateral, nerve-sparing, radical prostatectomy (TA-303). Long-term safety data comes from a 40-week, open-label, safety extension study to studies TA-301 and TA-302 (TA-314). There are also a number of special safety studies, including a thorough QT study (TA-140), a single-dose "sperm" study (TA-014), investigations of effects on vision (HP-01 and TA-016), and interaction studies with nitroglycerin (TA-04), alpha blockers (doxazosin and tamsulosin, TA-017), anti-hypertensives (enalopril and amlodipine, TA-019), and alcohol (TA-015).

In total, 1923 subjects were exposed to avanafil during the clinical development program: 621 subjects received avanafil in Phase 1 studies, 360 subjects received avanafil in Phase 2 studies, and 942 subjects received avanafil in Phase 3 studies. A total of 712 subjects were exposed to avanafil in the long-term safety study TA-314. In total, 493 subjects were exposed to avanafil for ≥ 6 months (26 weeks) and 153 subjects were exposed to avanafil for ≥ 12 months (52 weeks). In the long-term safety study, >500 subjects received the 200 mg dose.

Overall, then, the studies conducted during the avanafil development program and the extent of exposure were acceptable to assess the safety of avanafil for the treatment of ED.

The safety results demonstrate the same adverse event profile as previously demonstrated for the marketed PDE5 inhibitors. The most commonly reported adverse reactions to avanafil are: headache, flushing, nasopharyngitis/nasal congestion, dyspepsia, and back pain. Most, but not all, reports were mild or moderate in severity. These adverse events were generally dose-related, and the incidences were consistent with the incidences reported for the marketed PDE5 inhibitors. The incidences reported in study TA-303 in radical prostatectomy patients were slightly higher in study TA-303 (radical prostatectomy) compared to study TA-301 (broad ED) and TA-302 (diabetic ED). The incidence ranges are as follows:

- headache: **placebo** 1%-1.4%; **50 mg** 4.4%; **100 mg** 5.9%-8.1%; **200 mg** 10.2%-12.1%
- flushing: **placebo** 0%; **50 mg** 3.8%; **100 mg** 4.2%-5.1%; **200 mg** 3.8%-10.1%
- nasopharyngitis: **placebo** 0%; **50 mg** 0.6%; **100 mg** 2.1%-3.0%; **200 mg** 3.4%-5.1%
- dyspepsia: **placebo** 0%; **50 mg** 0.6%%; **100 mg** 0.3%; **200 mg** 1.4%
- back pain: **placebo** 1.0%; **100 mg** 3.0%; **200 mg** 2.0%

The known adverse reactions did not increase in frequency in the long-term safety study. Notable adverse events reported by fewer than 2% of subjects but greater than in the placebo groups included: nausea, diarrhea, constipation, sinusitis, bronchitis, influenza, upper respiratory infection, dizziness, hypertension, and rash.

Only one death was reported in the program (a suicide by gunshot), and few serious adverse events for which a role of avanafil could not be excluded. In two cases, men with serious background coronary artery disease, including previous angioplasty in both, reported non-

obstructive coronary artery disease and unstable angina, respectively, on the day following the most recent avanafil dose. It was not possible to exclude a role of avanafil in these two SAEs, although the significant background of preexisting CAD in these two cases makes attribution difficult.

The special safety studies demonstrates the expected PDE5-class interactions with nitroglycerin, alpha blockers, anti-hypertensives and alcohol. Nitroglycerin should not be used with avanafil. In an urgent situation, it is prudent to wait at least 12 hours before using nitroglycerin and then with monitoring. It is also prudent to use alpha blockers with caution; e.g., start at the lowest alpha blocker or avanafil dose, and titrate up carefully. The vision investigations were not adequate to rule out an effect of avanafil and in at least one analysis, a difference from placebo was shown in color vision discrimination. The single dose sperm human study was not notable for an effect of avanafil, but a single dose study is not adequate as an assessment of the potential effect of avanafil on spermatogenesis.

The Sponsor has agreed to conduct a dedicated vision parameters clinical trial and a multiple-dose sperm clinical trial as postmarketing requirements.

9. Advisory Committee Meeting

Avanafil is similar to the existing phosphodiesterase Type 5 inhibitors, with comparable efficacy and safety profiles. There were no unresolved review issues. Therefore, an Advisory Committee was not held for this application.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies because the disease/condition (erectile dysfunction) does not exist in the pediatric population. The Division agreed. During a meeting of the PERC on February 29, 2012, the PeRC agreed with the Division to grant the full waiver. On March 27, 2012, in an eMAIL from George Greeley of the Pediatric and Maternal Health Staff, DRUP was notified that the PeRC agreed to grant the full waiver. (b) (4)

11. Other Relevant Regulatory Issues

Division of Drug Advertising, Marketing and Communication (DDMAC)

In their final consult report dated April 18, 2012, Jessica Cleck Derenick and Jina Kwak provided comments on various sections of the label, including Highlights, Dosage and Administration (D &A), Warnings & Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology, Nonclinical Toxicology, Clinical Studies and Patient Counseling. The DDMAC team also provided several comments on the Patient Information.

All the DDMAC comments and recommendations were carefully considered. Some were addressed through internal discussions amongst the primary review team and through successful negotiations with Sponsor. Several DDMAC recommendations were not taken, but these were relatively minor grammatical or formatting edits, or suggestions to add information that was not available for this application.

Office of Scientific Investigation (OSI)

At the request of DRUP, OSI audited three clinical investigative sites: Dr. Ronald Surowitz (Jupiter, FL), Dr. David Cook (Winston-Salem, NC) and Dr. Jeffrey Rosen (Coral Gables, FL), each of whom participated in both Phase 3 studies TA-301 and TA-302. These three investigational sites were selected for inspection because of their relatively large enrollment and significant primary efficacy results pertinent to decision-making. Some of the sites also had a high rate of drop-outs.

In addition to these three clinical investigative sites, the Sponsor was also inspected for administrative record-keeping, adverse event reporting, CRF handling, etc.

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. OSI stated that omission of these components of the physical examinations would not appear to affect the overall safety evaluations of these studies.

OSI concluded: "*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*".

In regard to the Sponsor site inspection, 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. For the Sponsor's site, OSI concluded: "*The studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication*".

Financial Disclosure

Financial disclosure documents were submitted for principal and sub-investigators for clinical studies for the Phase 3 studies. A total of 226 investigators (43 PI's and 183 sub-PI's) provided disclosures and none had any relevant financial disclosure information to declare. There was no missing financial disclosure information for investigators in the studies noted.

Office of Medical Policy Initiatives/ Division of Medical Policy Programs (DMPP)

On April 17, 2012, Shawna Hutchins, Melissa Hulett and LaShawn Griffiths of DMPP provided a final consult regarding the Sponsor's proposed Patient Package Insert (PPI). DMPP concluded:

> "*The PPI is acceptable with our recommended edits.*"

DMPP pointed out that their review of the PPI was based on the "*draft STENDRA Prescribing Information received June 29, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on April 13, 2012.*"

DMPP provided a number of edits to the PPI, most of which were intended to update the document to be consistent with current standards of PPI formatting and terminology (e.g., proper order of sections, use of the term "healthcare provider" consistently throughout the document, etc). DRUP added some text to the DMPP-revised PPI, to include, among other items, recommendations to use the lowest dose that works for the individual patient, as well as a list of specific drugs to avoid when taking STENDRA. DMPP accepted the DRUP edits.

All edits to the original PPI were conveyed to Sponsor, and all were ultimately agreed upon by Sponsor.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

Container/Carton/Package Insert Labeling

On January 26, 2012, Lubna Merchant and Carol Holquist from DMEPA provided a final review of the 30- and 100-count bottle container labeling, the container and carton labeling for physician samples, and the Package Insert labeling. DMEPA's review of these materials was intended to evaluate areas of vulnerability in labeling that could lead to medication errors.

DMEPA had the following comments and recommendations:

- The established name, strength, net quantity, NDC number, and the statement "*Protect from Light*" were not sufficiently prominent.
- The strengths were not well differentiated from each other and this issue could lead to selection errors.
- The strength of each tablet in the physician samples was not made clear.
- The labeling contained error-prone abbreviations, symbols and acronyms.

DMEPA made a number of recommendations to correct these deficiencies; for example, for the *bottle container label*, the three different strengths should be differentiated using markedly different colors, the proprietary name should appear not as all upper case letters but rather as title case, the established name should be made more prominent, and the net quantity should be relocated away from the dose. For the *physician sample container*, 100 mg should be displayed next to each of the 3 tablets, so that a patient realizes that each tablet is 100 mg. For the *physician's sample carton*, many of the same issues that applied to the bottle container were applicable (e.g., revising presentation of the proprietary and established names, etc). Finally, for the Package Insert, DMEPA recommended against use of symbols and abbreviations such as $<$, $>$, $\geq$, and $\leq$.

DMEPA's recommendations for revisions were conveyed to Sponsor who made the requested changes and returned revised container/carton labeling on April 11, 2012. These items were found acceptable by the Office of New Drug Quality Assurance. At the time of filing this review, DMEPA remained in discussions with Sponsor concerning the physician sample blister card and sample carton labeling. While the sample pack required removal of both

cardboard and foil to reach the tablet, DMEPA was requesting more prominence of the Warning that the sample pack did not contain a child resistant closure.

Trade name

During the course of this NDA review, DMEPA was asked to conduct proprietary name reviews for 4 different proposals: (b) (4) and "Stendra". Of these, (b) (4) were all rejected by DMEPA. The reasons for these DMEPA decisions are provided herein:

On *July 22, 2011*, in their first review, Denise Baugh, Todd Bridges, Kelly Taylor and Carol Holquist stated:

(b) (4)

On *November 1, 2011*, in their second review, Denise Baugh, Lubna Merchant and Carol Holquist stated:

(b) (4)

On *March 5, 2012*, in their third review, Zachary Oleszczik and Carol Holquist stated:

(b) (4)

(b) (4)

On *April 24, 2012*, in their fourth and final review, Zachary Oleszczik and Carol Holquist stated:

> "*The proposed proprietary name [STENDRA] is acceptable from both a promotional and safety perspective.*"

DMEPA acknowledged the existence of the tradename "Tendra" for an approved wound care product line, but upon further investigation, DMEPA found that the wound care line is only dispensed by the tradename "Mepitel" or "Mepilex Lite", and not simply by a prescription for 'Tendra".

Office of Compliance

On April 17, 2012, the Office of Compliance provided an "Acceptable" recommendation via EES for the facilities involved in the NDA.

12. Labeling

Labeling discussions have proceeded as per standard practice. Two key labeling issues to Sponsor are 1) the recommended time between taking avanafil and expected sexual activity and 2) the effect of avanafil on vision. (b) (4) The discussion of this labeling issue was ongoing at the time of filing this review. The Sponsor also has some concern regarding the Division's interpretation of vision study results and this labeling issue also was under discussion at the time of filing this review.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this new drug application be Approved.

13.2 Risk Benefit Assessment

In three, randomized, double-blind, placebo-controlled studies (both Phase 3 studies TA-301 and TA-302, as well as the Phase 2 study TA-05), avanafil, at doses of 50 mg, 100 mg and 200 mg, demonstrated efficacy in the treatment of ED. The treatment effect is highly statistically significant compared to placebo and is clinically meaningful. The dose regimen will be one tablet at approximately 30 minutes prior anticipated sexual activity. The starting dose will be 100 mg, and the dose can be down titrated to 50 mg for tolerability reasons, or increased to 200 mg for inadequate efficacy. The label will emphasize use of the lowest effective dose for by an individual patient. The rationale for dose selection is acceptable. The 30 minute time between dosing and anticipated sexual activity is supported by Phase 3 data, (b) (4)

[redacted] (b) (4) At the time of filing this review, the exact timing of avanafil dosing to anticipated sexual activity was under continued discussion as part of labeling negotiations with Sponsor.

The studies conducted, and the extent of patient exposure to avanafil, were acceptable to assess the safety of avanafil for the treatment of ED. The safety results demonstrate the same adverse event profile as previously demonstrated for the marketed PDE5 inhibitors. The most commonly reported adverse reactions to avanafil are: headache, flushing, nasopharyngitis/nasal congestion, dyspepsia, and back pain. Most, but not all, reports were mild or moderate in severity. These adverse events were generally dose-related, and the incidences were consistent with the incidences reported for the marketed PDE5 inhibitors. Only one death was reported in the program (a suicide by gunshot), and there were few serious adverse events in which a role of avanafil could not be excluded. In two cases, men with serious background coronary artery disease (CAD) including previous angioplasty in both, reported non-obstructive CAD and unstable angina, respectively, on the day following the most recent avanafil dose. It was not possible to exclude a role of avanafil in these two SAEs, although the significant background of pre-existing CAD in these two cases makes attribution difficult.

The special safety studies conducted for avanafil demonstrate the expected PDE5-class interactions with nitroglycerin, alpha blockers, anti-hypertensives and alcohol. Labeling will inform prescribers of these interactions and how to minimize their risks. There is also a notable interaction with strong CYP3A4 inhibitors, and no currently available dose for adjustment. Therefore the label will advise against use with strong CYP3A4 inhibitors. The vision investigations were not adequate to rule out an effect of avanafil and in at least one analysis, a difference from placebo was observed in color vision discrimination. The single dose sperm study was not notable for an adverse effect of avanafil, but was inadequate to rule out an effect, because any effect on spermatogenesis requires at least 3 months to detect. Therefore, the Sponsor has agreed to conduct a dedicated vision parameters clinical trial as well as a multiple-dose sperm clinical trial as postmarketing requirements.

There are no deficiencies in the avanafil efficacy and safety data that preclude approval.

13.3 Recommendation for Postmarketing Risk Management Activities

There are no specific recommendations for postmarketing risk management activities.

13.4 Recommendation for other Postmarketing Study Commitments

The Division requested, and the Sponsor agreed to conduct two (2) postmarketing clinical trials, both as postmarketing requirements. These human trials will be:

1. A randomized, double-blinded, placebo-controlled, multiple-dose trial to assess the potential effect of avanafil on human sperm and spermatogenesis. Single dose trials were not indicative of an effect but were too short to rule out potential adverse effects.

2. A randomized, double-blinded, placebo-controlled, single-dose trial to assess the potential effect of avanafil on multiple parameters of human vision, to include, but not limited to visual acuity, intraocular pressure, pupillometry, and color vision discrimination. The two human vision investigations that Sponsor conducted under Studies HP-01 and TA-016, were indicative of a potential problem with color vision, but were not robustly designed to provide definitive conclusions and also did not assess other parameters of vision, such as visual acuity.

13.5 Recommended Comments to Applicant

There are no additional comments for Sponsor at this time.

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/s/

MARK S HIRSCH
04/25/2012

AUDREY L GASSMAN
04/25/2012
I concur