CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Guodong Fang
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Established Name	Avanafil
(Proposed) Trade Name	
Therapeutic Class	PDE5 Inhibitor
Applicant	Vivus Inc.
Formulation(s)	$C_{23}H_{26}ClN_7O_3$
Dosing Regimen	50 mg. 100 mg. 200 mg
Indication(s)	Male Erectile dysfunction (ED)
Intended Population(s)	Adult Men with ED

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1 Recommendations/Risk Benefit Assessment

1.1 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.

1.2 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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no recommendation for postmarket risk evaluation and mitigation strategy (REMS).

1.4 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.

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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.

2 Introduction and Regulatory Background

Avanafil has undergone evaluation for the treatment of erectile dysfunction (ED) under IND 51,235, which was originally submitted on November 30, 2001, after a pre-IND meeting with the Division on November 07, 2001. With the opening IND, the Sponsor included a Protocol # TA-01, "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 between the Sponsor and DRUP. The sponsor proposed to conduct two, pivotal, Phase 3 studies (one in the broad ED population and one in diabetics only), one Phase 3 study in men with ED who had undergone radical prostatectomy, and one 12-month open label safety extension study. This proposal was considered generally acceptable for the clinical development plan. The Division also provided additional comments and recommendations (details see below Section 2.5).

During the Phase 3 clinical trial development, the Division responded with advice to the Sponsor's proposed "pivotal" clinical trials TA-301 (in the general ED population), TA-302 (in diabetic men) and TA-303 (in radical prostatectomy patients) through special protocol assessments (SPAs). The Division also reviewed the protocol for TA-314 (long-term safety and tolerability) (details see below Section 2.5). The Clinical Pharmacology team also had several comments as well (details see below Section 2.5).

Finally, the Sponsor advised that the radical prostatectomy study was accruing subjects slowly and would not be ready with the original NDA. The Sponsor requested the Division's concurrence that the NDA could be submitted without the radical prostatectomy study. The Division agreed that the NDA could be submitted without this study. The safety data from ongoing Study TA-303 was submitted with the 120-Day Safety Update.

2.1 Product Information

According to the Sponsor, avanafil is a potent and highly specific inhibitor of the cyclic guanosine monophosphate (cGMP) – specific type 5 phosphodiesterase (PDE5) and is highly selective for the PDE5 isoenzyme relative to other phosphodiesterases. Avanafil is formulated with excipients as an oral, oval, pale yellow, immediate release tablet at 50 mg, 100 mg, and 200 mg strengths; and is rapidly absorbed following oral administration and achieves maximum

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plasma concentrations from 30 to 45 minutes in the fasted state. Avanafil has a half-life ($t_{½}$) of approximately (b) (4) 5 hours. Avanafil tablets are manufactured at (b) (4) (b) (4)

Two avanafil immediate-release tablet formulations (Formulations I and II) were used in studies conducted in support of this NDA. (b) (4) Avanafil Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and it is the proposed commercial formulation.

Avanafil increases penile blood flow and erection in response to sexual stimulation. In men, sexual stimulation causes nitric oxide to be released by nerves and endothelial cells and diffused into smooth muscle cells in the walls of penile arteries and spongy erectile tissues. Nitric oxide stimulates the guanylate cyclase enzyme to synthesize cGMP, which leads to decreased Ca+2 concentrations in the smooth muscle cells of the erectile tissues, smooth muscle relaxation, and increased blood flow into the penis. In the erectile tissues, cGMP is degraded by the activity of the PDE5 enzyme. Through inhibition of PDE5, cGMP concentrations are increased, resulting in enhanced smooth muscle relaxation and greater blood flow to the erectile tissues in response to sexual stimulation.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.1 Currently Available Treatments with PDE 5 Inhibitors for ED

	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
Reported Side Effects	Nasal Congestion, Dyspepsia, Flushing, Headaches, Urinary Tract Infection, Blurred Vision	Headache, Flushing, Myalgia, Dyspepsia, Back Pain	Headache, Flushing, Dyspepsia, Nasal Congestion	Headache, Flushing, Nasal Congestion, Dyspepsia, Dizziness, Back pain
Contraindications	Any Nitrate-Based Medicine	Any Nitrate-Based Medicine	Any Nitrate-Based Medicine	Any Nitrate-Based Medicine

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2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is Avanafil API is manufactured by the [redacted] (b) (4) [redacted] (b) (4) with a DMF number of [redacted] (b) (4)

2.4 Important Safety Issues With Consideration to Related Drugs

All phosphodiesterase Type 5 inhibitors include a Contraindication with nitroglycerin-containing products due to a potential for life-threatenting hypotension. There are also precautions for use with alpha-blockers, significant amounts of alcohol, and anti-hypertensives. PDE5 inhibitors are known vasodilators and have a small but acute effect on lowering blood pressure. The adverse reactions associated with PDE5 inhibitors are well-known and include flushing, headache, dyspepsia, vision disturbance (including bluish tinge to vision), and back pain. Serious cardiovascular events have been reported in the postmarketing period in patients taking PDE5 inhibitors, but the direct relationship of these events to PDE5 inhibitors remains unclear.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Avanafil has undergone evaluation for the treatment of erectile dysfunction (ED) under IND 51,235, which was originally submitted on November 30, 2001, after a pre-IND meeting with the Division on November 07, 2001. With the opening IND, the Sponsor included a Protocol # TA-01, "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 between the Sponsor and DRUP. The sponsor proposed to conduct two, pivotal, Phase 3 studies and one 12-month open label safety extension study. This proposal was considered generally 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 [redacted] (b) (4), this information could be included in labeling.
3) Drug interaction studies, including nitroglycerin, alpha-blockers, and ketoconazole (400 mg QD) should be conducted.

During the Phase 3 clinical trial development, the Division responded with advice to the Sponsor's proposed "pivotal" clinical trials TA-301 (in the general ED population), TA-302 (in diabetic men) and TA-303 (in radical prostatectomy patients) through special protocol assessments (SPAs). The Division also reviewed the protocol for TA-314 (long-term safety and tolerability)

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On October 20, 2010, the Division met with the Sponsor for a Pre-NDA meeting. The Clinical review team had several comments and recommendations:

1. Due to slower than expected enrollment, the Sponsor asked whether the NDA could be submitted without Study 303 (in radical prostatectomy patients). The Division stated that even without inclusion of Study 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 (treatment of ED). In addition, there appeared to be sufficient patient exposure to support safety even without inclusion of Study TA-303. (b) (4)

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

3. (b) (4)

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

5. All pooling of efficacy data in the ISE would be considered exploratory.

6. In addition to safety data presented by individual phase 1 study, the Division requested an overall narrative summary of safety from the seventeen phase 1 studies.

7. The Sponsor was asked to conduct a pre-defined analyses of safety data from the open-label, safety extension study TA-314 and to keep this analysis separate from the controlled studies in the ISS.

8. The Sponsor was asked to provide individual narratives for the targeted medical events (TMEs).

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

10. 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.

    The Sponsor acknowledged that avanafil is contraindicated in men taking any form of nitroglycerin. The Sponsor did conduct the requested nitroglycerin study and concluded that in a patient who has taken avanafil, where nitrate administration is deemed medically necessary in a life threatening situation, at least 12 hours should elapse after the last dose of avanafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

11. The Sponsor was informed to submit a request for pediatric waiver in the NDA submission, and it would be conveyed to the Pediatric Review Committee (PeRC). (b) (4)

12. 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.

The Clinical Pharmacology team had several comments as well:

1) The impact of severe renal impairment including End State Renal Disease (ESRD) on avanafil PK was not assessed. This would become a review issue and might become a post-marketing requirement (PMR) given that avanafil is an NME. The Sponsor was requested to address this in the NDA submission.

2) The impact of severe hepatic impairment on avanafil PK was not assessed. This would become a review issue. The Sponsor was requested to address this in the NDA submission.

3) The Pre-NDA meeting package stated that avanafil can be taken without regard to food. However, food appears to delay the time to maximum plasma concentration. Therefore, food effect would be a review issue.

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

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5) Regarding **Drug-Drug Interaction** (DDI) studies
   - [redacted] (b) (4) the NDA would need to include information supporting the previous DDI studies TA-016, TA-018, TA-015, TA-017, and TA-019.
   - The NDA should include information to address the effect of CYP 3A4 inducer (e.g., rifampin) co-administration on avanafil PK.
   - The NDA should include information to address the effect of avanafil on P-glycoprotein (e.g., digoxin).
   - The NDA should include information to describe the effect of mild, moderate and strong CYP3A4 inhibitors on avanafil PK.

6) The NDA would need to include information on the following additional clinical pharmacology issues:
   - The effect of age on avanafil exposure.
   - The starting dose of avanafil and how it was determined.
   - The safety of [redacted] (b) (4) administration of avanafil, if such a dosing regimen was requested.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Sponsor has in place standard operating procedures consistent with ICH Good Clinical Practice, which include archiving of source data, data validation of CRF data, internal audits, documentation of qualifications of investigators, and the use of central laboratory.

An assessment of the datasets and CRFs from the pivotal clinical studies by this reviewer did not reveal miscoding or discrepancies between data recorded on CRFs and the datasets.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all trials submitted to the NDA were conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. In support of this, the Applicant submitted samples of informed consent, documents of IRB approval, and required CRFs. No ethics or good clinical practice (GCP) issues have been identified.

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3.3 Financial Disclosures

Form FDA 3454 (10/09) ("Certification: Financial Interests and Arrangements of Clinical Investigators"), dated May 30, 2011, and signed by Malcolm McKay, V.P. Regulatory Affairs and Compliance Officer, Vivus, Inc., was included in this submission. Financial disclosure documents were submitted for clinical investigators (principal and sub-investigators) for clinical studies under IND 51,235 (for the three Phase 3 studies).

In accordance with 21 CFR Part 54.4, certification and disclosure requirements, forms of clinical investigator certification and financial disclosure provided by Vivus, Inc., were signed by individual investigators and submitted. To the extent investigators have provided financial disclosure information via questionnaires, they were asked to do so based on site-specific (or if shorter, their individual) study start and completion dates. A total of 226 investigators (43 PI's and 183 sub-PI's) from study sites all over the United States had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.4(a)(3)(i), 54.2 (a)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4 (a)(3)(ii), 54.2(f)], proprietary interest in the tested product [21 CFR 54.4(a)(3)(iii), 54.2(c)], or significant equity interest in the sponsor of the covered study product [21 CFR 54.4(a)(3)(iv), 54.2(b)].

Financial disclosures were made for all required studies submitted to the NDA. There is no evidence to suggest that a financial relationship had any impact on the study results.

Reviewer's Comment: The financial disclosure information is acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Reviewer believes that the proposed testing and acceptance criteria in the drug substance and drug product are considered adequate to assure its identity, strength, purity, and quality to support the NDA based on a review of chemistry, maufacturing, and control issues that pertain to avanafil tablets of all requested dosage strengths. The CMC reviewer recommends approval of NDA 202,276.

4.2 Clinical Microbiology

There are no clinical microbiology issues for this application.

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4.3 Preclinical Pharmacology/Toxicology

Based on a completed nonclinical package submitted by the Sponsor that included general and safety pharmacology and pharmacokinetics / ADME assessments, single- and repeated dose toxicology studies, and a single-dose phototoxicity study, the Pharmacology/Toxicology Reviewer believes that the toxicity profile for avanafil is similar to that observed for other PDE5 inhibitors. The PharmTox reviewer commented upon nonclinical findings of CNS toxicity and impaired fertility, which occurred at low exposure multiples compared to clinical exposures. Signs of CNS toxicity were not reported in clinical studies and no adverse effects were observed after a single dose sperm study. Effects of avanafil on human sperm after multiple doses were not assessed. The Pharm/Tox Reviewer determined the nonclinical data submitted by the Sponsor support the approval of aavanafil for the treatment of erectile dysfunction at the proposed doses. Based on adverse effects on sperm motility and sperm morphology and fertility in animals, a post-marketing clinical study will be requested to further evaluate potential effects on spermatogenesis in men following repeat-dose administration.

4.4 Clinical Pharmacology

The Clinical Pharmacology Reviewer believes that this NDA is 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. The reader is referred to the Clinical Pharmacologist's review for details; in particular, in regard to clinical relevant drug interactions with avanafil, and use of avanafil in specific populations.

4.4.1 Mechanism of Action

The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cGMP, which leads to decreased calcium (Ca^{+2}) concentrations in the smooth muscles of erectile tissues, smooth muscle relaxation, and increased blood flow into the penis . The PDE5 enzyme is responsible for the degradation cGMP. Through the inhibition of PDE5, avanafil inhibits cGMP degradation and thereby increasing cGMP concentrations, which results in enhanced smooth muscle relaxation and greater blood flow to the erectile tissues in response to sexual stimulation.

4.4.2 Pharmacodynamics

Avanafil acts as a vasodilator and has effects on blood pressure and pulse, and shows drug-drug interaction with nitrate, alpha-blockers, other anti-hypertersensives, and with alcohol.

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4.4.3 Pharmacokinetics

Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes. Avanafil's pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly CYP3A4). The concomitant use of potent CYP3A4 inhibitors is associated with increased plasma exposure of avanafil; avanafil has a terminal half life of about (b) (4) 5 hours. The reader is referred to the Clinical Pharmacologist's review for more information.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The principal analyses of efficacy and safety included in this NDA include data from 3 efficacy and safety clinical studies, 3 supportive clinical studies, and 17 Phase 1 studies.

- Efficacy and safety clinical studies (N = 3): TA-05 (Phase 2), TA-301 (Phase 3), and TA-302 (Phase 3);
- Supportive studies (N = 3): TA-01 (Phase 2), TA-03 (Phase 2), and TA-314 (open-label, safety extension, Phase 3);
- Phase 1 clinical pharmacology studies (N = 17); HP-01, TA-02, TA-04, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, and TA-140.

Reviewer's comment: There are only two Phase 3 studies, TA-301 and TA-302. The Phase 2 study TA-05 enrolled only subjects with mild and moderate ED, no subjects with severe ED were enrolled.

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Table 5.1.1 Efficacy and Safety Clinical Studies (n=3)

Protocol	Primary end points	Treatment groups /doses/patients	N	Subjects
Phase 2 studies				
TA-05	Dose-ranging, safety and efficacy (9-12 weeks)	Randomized, active-controlled, double-blind, 3-way crossover	295	Mild to moderate ED
Phase 3 studies				
TA-301	Efficacy and safety in general ED (12 weeks)*	Randomized, placebo-controlled, double-blind, parallel with doses (50, 100, 200, 300 mg)	646	Mild to severe ED
TA-302	Efficacy and safety in diabetic patients (12 weeks)	Randomized, placebo-controlled, double-blind, parallel with doses (100, 200 mg)	390	Mild to severe ED

*patients with diabetes, as well as patients ED caused by spinal cord injury or radical prostatectomy were excluded from Study TA-301. Diabetics were studied separately in TA-302. Radical prostatectomy patients were studied separately in TA-303

Table 5.1.2 Supportive Clinical Studies (n=3)

Protocol	Primary end points	Treatment groups /doses/patients	N	Subjects
Phase 2 studies				
TA-01	Preliminary safety and efficacy (3 dose levels) using RigiScan™ monitoring	Randomized, single-blind; randomized, placebo, and active (sildenafil, SIL)–controlled, crossover (TA1970 50, 100, 200 mg), single dose	89	Mild to moderate ED
TA-03	(1) Onset of effect of 200 mg dose; (2) effective duration of action	Randomized, active -controlled, double-blind, 3-way crossover (TA1970 200 mg, SIL 100 mg) 9-12 weeks	51	Mild to moderate ED
Phase 3 studies				
TA-314	Long-term safety and efficacy (52 weeks)	Open-label extension (TA1970 50, 100, 200, mg)	712	Completed TA-301,302

Table 5.1.3 Phase 1 Clinical Pharmacology studies (n=17)

Protocol	Primary end points	Treatment groups /doses/patients	N	Subjects
HP-01	Safety, tolerability, PK profile, metabolites, food effect	Randomized, double-blind, placebo-controlled, single ascending dose, parallel (12.5, 25, 50, 100, 200, 400, 600, 800 mg)	65	Healthy male
TA-02	PK of single and multiple doses; safety, tolerability,	Randomized, double-blind, single- and multiple-dose, paralleldoses (50, 100, 200 mg) (72 hr to 17 days)	48	Healthy male
TA-04	hemodynamic effects of sublingual glyceryl trinitrate on avanafil relative to sildenafil	Randomized, placebo-controlled, double-blind, 3-way crossover (200 mg) (sildenafil 100 mg, placebo) single dose	106	Healthy male
TA-07	PK of single and steady –state; bid dose	Non-radomized, open-label (200 mg single D); washout 48 hrs, per 12 hr dose of 200 mg x 7 days	15	Healthy male
TA-010	[^{14}C] TA-1790 Mass balance & absorption, distribution, metabolism, excretion profile	Single-dose, non-randomized, open-label, mass balance study (600 mg suspension oral)	6	Healthy male
TA-011	Safety and PK co-administered with ketoconazole, ritanovir, or erythromycin	Randomized, open-label, 1-sequence, 3-parallel group (various doses on different days with single dose TA-1790 50-200 mg)	44	Healthy male
TA-012	PK+tolerability in hepatic impairment	Non-randomized, open-label, single-dose, parallel-group, matched-control (200 mg)	24	Male of normal, or hepatic impairment mild to moderate
TA-013	PK+tolerability in renal impairment	Non-randomized, open-label, single-dose, parallel-group, match-controlled, (200 mg)	24	Male of normal, or renal impairment mild to moderate
TA-014	Age effect, semen exposure, acute effect on sperm; age on the PK, safety in young/elderly	Open-label, non-randomized, 2-cohort, single-dose (200 mg)	32	Healthy male (young & elderly)
TA-015	Hemodynamic interactions of concomitant TA-1790+alcohol	Randomized, double-blind, placebo-controlled, 3-period, 3-way crossover (200 mg) single dose	15	Healthy male
TA-016	Effects of daily avanafil dosing on the PK & PD of a single dose of warfarin.	Randomized, double-blind, placebo-controlled, 2-way crossover (200 mg) single dose	24	Healthy male
TA-017	Effects of the co-administration of avanafil on the hemodynamic effects of 2 α-adrenergic blockers doxazosin (DOX) or tamsulosin (TAM)	Randomized, double-blind, placebo-controlled, 2-cohort, 2-period, crossover; various doses of DOX (Cohort A) and TAM (Cohort B) or placebo with TA-1790 (200 mg single dose)	48	Healthy male
TA-018	effect of a single dose of avanafil on the single - dose PK of desipramine (DESI) and rosiglitazone (ROSI) and multiple-dose PK of omeprazole	All open-label, crossover; doses of OME, single dose of ROSI, DESI , with single dose of TA-1790 (200 mg); Cohort A: Non-randomized, 1-sequence; Cohort B and C: randomized, 2-period;	60	Healthy male
TA-019	PK and hemodynamic effects of the co-administration of avanafil with 2 BP medications enalapril (ENAL) or amlodipine (AML)	Randomized, double-blind, placebo-controlled, 2-cohort, 2-period crossover; Cohort A: ENAL + TA-1790 (200 mg single dose); Cohort B: AML + TA-1790 (200 mg single D)	48	Healthy male
TA-020	Effect of food on the PK; relative BA of 2 formulations; and dose-proportionality of avanafil	Randomized open-label, 4-period crossover (2x100 mg formulation II fasted or fed; 2x100 mg formulation I, 1x50 mg formulation II, fasted; single dose)	24	Healthy male, BW ≥50 kg BMI 18-30 kg/m^2
TA-021	Acute effect on sperm, semen exposure; safety & tolerability in young male	Double-blind, placebo-controlled, randomized, 2-period crossover; 200 mg, single dose	17	Healthy male, BW ≥50 kg BMI 18-30 kg/m^2
TA-140	Thorough QT study with therapeutic and supra-therapeutic dose of avanafil vs. placebo vs moxifloxacin (MOX)	Randomized, double-blind, placebo- & active controlled (MOX 400 mg), 4-arm crossover, avanafil 100 mg, 800 mg; single dose	57	Healthy male, 18- 45 years of age BMI 19-28 kg/m^2

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5.2 Review Strategy

This review is based on the following information:

- The ”pivotal studies” that support efficacy: Phase 3 studies (TA-301 and TA-302), as well as Phase 2 study (TA-05) (efficacy and safety data)
- The Phase 3 long term safety study (TA-314)
- The safety data from study TA-303 in patients with ED status post radical prostatectomy.
- Two smaller, “supportive” Phase 2 studies (TA-01 and TA-03)
- A host of Phase 1 studies, including a thorough QT (TQT) study (TA-140), a single dose study on the effects on sperm (TA-021), and vision investigations on two Phase 1 studies (HP-01 and TA-016).

5.3 Discussion of Individual Studies/Clinical Trials

The main “pivotal” clinical studies are Phase 3 studies **TA-301** and **TA 302**. In the two Phase 3 studies patients had mild to severe ED, while in the Phase 2 study, TA-05, patients had mild to moderate ED. Disease severity was determined by the International Index of Erectile Function (IIEF) erectile function domain score (mild=IIEF score of 17 to 25; moderate=IIEF score of 11 to 16; severe=IIEF score ≤10) at the randomization visit. In the 12-week, 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 from participation; in TA -302, subjects with mild to severe erectile dysfunction and 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 at the randomization visit using a centralized, computer-generated randomization system. 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 regarding the administration of study drug and sexual experience in a subject diary.

The Sponsor classified Study **TA-05** as another one of the “pivotal” clinical trials, even though TA -05 was a Phase 2 study. TA-05 was a Phase 2, randomized, double-blind, parallel-design, placebo-controlled, multicenter study in adult male subjects with mild to moderate ED of ≥ 6 months duration and who were in a monogamous heterosexual relationship for at least 3 months. Subjects with diabetes and subjects with erectile dysfunction caused by spinal cord injury or radical prostatectomy were excluded from participation. 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

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attempt at sexual activity, subjects were instructed to record information regarding the administration of study drug and sexual experience in a diary.

Reviewer's comment: Study TA-05 is a Phase 2 study that excluded patients with severe ED.

The supportive studies include 2 Phase 2 studies. One of the 2 Phase 2 studies is Study **TA-01**, which was a single blind, randomized, crossover study to evaluate the safety and efficacy of 3 dose level of avanafil given in conjunction with visual sexual stimulation (and RigiScan monitoring) in patients with mild to moderate ED. The other Phase 2 study was Study **TA-03**, which was a double-blind, randomized, active-controlled, 3-way crossover study to evaluate the onset of effect of avanafil 200 mg administered at home in patients with ED; and to determine the effective duration of action of avanafil in the at-home setting.

In addition, **TA-314**, was a Phase 3, open-label extension study 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. All Patients in Study TA-314 had completed a previous Phase 3 avanafil study; either TA-301 or TA-302.

The remaining 17 Phase 1 studies include:

- A biopharmaceutics study – Study **TA-020** comparing avanafil Formulations I and II,
- A food effect arm in the first-in-human study (**Study HP-01**) to determine the effect of food on the avanafil PK and the dose proportionality.
- Pharmacokinetics studies:
  - To evaluate absorption, distribution, metabolism, and excretion – Studies TA-020, HP-01, and **TA-010**
  - Single dose and steady-state PK of avanafil – **TA-07**
- To evaluate drug-drug interaction:
  - Effect of other drugs on the PK of avanafil – co-administered with ketoconazole and ritonavir in **TA-011**; co-administered with erythromycin in **TA-019**
  - Effect of avanafil on the pharmacokinetics of other drugs – co-administered with omeprazole (a CYP2C19 substrate), rosiglitazone (a CYP2C8 substrate) or desipramine (a CYP2D6 substrate) in **TA-018**, and with amlodipine (a CYP3A4 substrate) in TA-019
  - Effect of avanafil on warfarin (S-warfarin is a 2C9 substrate), including on the prothrombin time (PT) and international normalized ratio (INR) or collagen-induced platelet aggregation in **TA-016**,
- In special populations:
  - Renal impairment – **TA-013**
  - Hepatic impairment – **TA-012**

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  - Age – **TA-014**
- Pharmacodynamics: Effects on blood pressure and heart rate – avanafil alone in **TA-02**; with nitrates in **TA-04**; with alpha blockers in **TA-017**; with anti-hypertensives, including ACE inhibitors and calcium channel blockers in TA-019**,** and with alcohol in **TA-015;**
- Effect on sperm function – **TA-021**
- TQT study – **TA-140**

6 Review of Efficacy

Efficacy Summary

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) 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.

6.1 Indication

Avanafil is a PDE 5 inhibitor indicated for the treatment of erectile dysfunction (ED).

6.1.1 Methods

The NDA 202,276 was entirely electronically submitted. The following pivotal studies were reviewed in detail:

- Phase 3 study TA-301
- Phase 3 study TA-302

Phase 2 study TA-05 was also reviewed as part of efficacy analysis.

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The Sponsor proposed to present the summary of clinical efficacy with presentations of individual study results as well as an integrated analysis of data pooled across studies. The integrated efficacy analyses include data from the two Phase 3 double-blind studies (TA-301 and TA-302) and the Phase 2 double-blind study (TA-05). Study TA-314 is presented separately because it is an open-label extension to the pivotal studies TA-301 and TA-302. The Phase 2 crossover studies, TA-01 and TA-03, are also presented individually due to their unique study designs. The Sponsor believed that rationale for inclusion of studies in the integrated efficacy dataset is as follows:

- The study populations consisted of adult men with mild to severe erectile dysfunction, the target population for the proposed indication.
- The doses studied were consistent with the planned proposed commercial doses.
- The study designs were similar with respect to a 4-week non-treatment run-in period, 12-week treatment period, dosing instructions, and basic visit structure.
- Efficacy data were collected using a uniform standard across studies that allowed for proper pooling.

Reviewer's comment: Both Phase 3 studies were designed as randomized, placebo-controlled, double-blind, parallel studies with appropriate doses (50, 100, 200 mg in Study TA-301 and 100, 200 mg in Study TA-302), and treatment periods of 12 weeks in subjects with mild to severe ED. The Phase 2 study TA-05 was designed as a randomized, active-controlled, double-blind, 3-way crossover study with a 9-12 week treatment period in subjects with mild to moderate ED. Obviously they were not the same design; therefore, the Reviewer recommends the analysis for efficacy be carried out separately for Studies TA-301 and TA-302 versus TA-05. In addition, avanafil 300 mg was a randomized treatment group in study TA-05 only and is not one of the proposed doses for marketing.

The long-term, open-label, Phase 3, safety study TA-314, and the early Phase 2 studies TA-01 and TA-03 were reviewed, but in less detail.

6.1.2 Demographics

Table 6.1.2.1 summarizes demographic and baseline characteristics for the ITT population. The mean age of subjects in studies TA-301, TA-302, and TA-05 was 56.6 years. The majority of subjects were White (84.0%).

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Table 6.1.2.1 Demographic and Baseline Characteristics – Phase 3 pivotal Studies TA-301, TA-302, (Intent-to-Treat Population, ITT)
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) [1]					
n	162	161	161	162	646
Mean (SD)	55.4 (11.13)	55.4 (10.81)	56.5 (10.32)	55.7 (11.33)	55.7 (10.89)
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 (17.58)	91.7 (17.73)	91.3 (15.26)	91.3 (16.64)	91.1 (16.80)
Height (cm)					
n	162	161	161	162	646
Mean (SD)	178.4 (7.52)	178. 1 (7.35)	177.8 (7.36)	178.4 (7.52)	178.2 (7.43)
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)
Erectile dysfunction 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)
Erectile dysfunction duration (months) [1]					
n	162	161	161	162	646
Mean (SD)	74.5 (66.55)	79.3 (71.38)	87.5 (92.78)	68.3 (52.33)	77.4 (72.37)
Erectile dysfunction 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)

1. Age and duration of erectile dysfunction were calculated according to the date of informed consent.
2. The Hispanic category under race applied only to study TA-05.
3. Ethnicity applied only to studies TA-301 and TA-302.
4. Baseline for erectile dysfunction severity and IIEF erectile function domain score was the observation at the end of the run-in period.

IIEF = International Index of Erectile Function; SD = standard deviation.

TA-302

	Placebo (N=130)	Avanafil 100 mg (N=129)	Avanafil 200 mg (N=131)	Total (N=390)
Age (years) [1]				
n	130	129	131	390
Mean (SD)	58.2 (8.62)	58.2 (9.62)	57.5 (8.99)	58.0 (9.07)
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 (19.87)	98.6 (18.16)	99.6 (18.68)	99.4 (18.88)
Height (cm)				
n	130	129	131	390
Mean (SD)	178.2 (7.01)	177.6 (7.54)	177.2 (7.69)	177.7 (7.41)
Body mass index (kg/m^2)				
n	130	129	130	389
Mean (SD)	31.5 (5.86)	31.3 (5.36)	31.8 (5.47)	31.5 (5.56)
Erectile dysfunction 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)
Erectile dysfunction duration (months) [1]				
n	130	129	131	390
Mean (SD)	78.7 (66.59)	73.8 (53.08)	64.6 (44.69)	72.3 (55.67)
Erectile dysfunction 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)

Overall, including Study TA-05, 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

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domain score was 12.9. At baseline, the mean duration of erectile dysfunction was 74.3 months. The treatment groups were comparable with respect to demographic and baseline characteristics.

Reviewer's comment: The demographic figures for Studies TA-301 and TA-302 show a largely White study population (approximately 12-15% Black); with mild, moderate and severe ED reported by approximately 1/3 of study subjects, respectively; and the age of about 75% of the study population was ≥ 50. All of these demographics are acceptable for the target indication.

6.1.3 Subject Disposition

Table 6.1.3.1 summarizes subject disposition for the ITT Population in Studies TA-301 and TA-302.

For Study TA-301, 1509 subjects were enrolled, and 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 Study TA-302, 1378 subjects were enrolled in the study and 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%).

In total, TA-301, TA-302, with study TA-05 together, 1228 subjects were randomized to treatment in these 3 studies. Of the 1228 randomized subjects, 1081 (88.0%) subjects completed the study and 147 (12.0%) subjects discontinued from the study. The primary reasons for discontinuation from the study were protocol non-compliance (5.9%, which includes subject withdrawal of consent, improper enrollment, and withdrawal due to lack of efficacy for studies TA-301 and TA-302), subject lost to follow-up (2.1%); adverse event (1.8%), and subject or partner request for withdrawal (1.5%, category used only for study TA-05).

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Table 6.1.3.1 Subject Disposition – Integrated Analysis of Studies TA-301, TA-302, – Intent-to-Treat Population (ITT)

TA-301

	Placebo n (%)	Avanafil 50 mg n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Enrolled [1]					1509
Randomized	162 (100.0)	161 (100.0)	161 (100.0)	162 (100.0)	646 (100.0)
Completed study	137 (84.6)	131 (81.4)	141 (87.6)	141 (87.0)	550 (85.1)
Discontinued from study	25 (15.4)	30 (18.6)	20 (12.4)	21 (13.0)	96 (14.9)
Protocol non-compliance [2]	16 (9.9)	16 (9.9)	10 (6.2)	11 (6.8)	53 (8.2)
Subject lost to follow-up	4 (2.5)	9 (5.6)	4 (2.5)	5 (3.1)	22 (3.4)
Adverse event	5 (3.1)	3 (1.9)	5 (3.1)	4 (2.5)	17 (2.6)
Requirement for restricted medication	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.3)
Death	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Safety Population	161 (99.4)	160 (99.4)	161 (100.0)	162 (100.0)	644 (99.7)
Intent-to-Treat Population	155 (95.7)	154 (95.7)	157 (97.5)	156 (96.3)	622 (96.3)
Evaluable Population	147 (90.7)	141 (87.6)	152 (94.4)	154 (95.1)	594 (92.0)

Percentages are based on the number of randomized subjects in a treatment group.
1. Subjects who enrolled in the study include all subjects who signed the informed consent form.
2. The category of protocol non-compliance includes subjects who withdrew consent.

TA-302

	Placebo n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Enrolled [1]				1378
Randomized	130 (100.0)	129 (100.0)	131 (100.0)	390 (100.0)
Completed study	110 (84.6)	109 (84.5)	114 (87.0)	333 (85.4)
Discontinued from study	20 (15.4)	20 (15.5)	17 (13.0)	57 (14.6)
Protocol non-compliance [2]	15 (11.5)	15 (11.6)	6 (4.6)	36 (9.2)
Subject lost to follow-up	4 (3.1)	2 (1.6)	9 (6.9)	15 (3.8)
Adverse event	0 (0.0)	2 (1.6)	2 (1.5)	4 (1.0)
Requirement for excluded treatment	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.5)
Safety Population [3]	130 (100.0)	127 (98.4)	131 (100.0)	388 (99.5)
Intent-to-Treat Population [4]	127 (97.7)	126 (97.7)	126 (96.2)	379 (97.2)
Evaluable Population [5]	121 (93.1)	119 (92.2)	122 (93.1)	362 (92.8)

1. Subjects who enrolled in the study include all subjects who signed the informed consent form.
2. The category of protocol non-compliance also includes subject withdrawal of consent.
3. The Safety Population includes all subjects who received at least one dose of study drug and had any safety data available.
4. The Intent-to-Treat Population includes all subjects who were randomized, reported taking at least one dose of study drug, and had at least one post-dose efficacy assessment.
5. The Evaluable Population includes all Intent-to-Treat subjects who reported using at least 6 doses of study drug during the treatment period and had at least 4 attempts at intercourse during the non-treatment run-in period.

Reviewer's comment: It is notable that 88% of study subjects completed the 3 studies, and just 1.8 % of subjects discontinued the studies due to adverse events. All these are acceptable.

6.1.4 Analysis of Primary Endpoint(s)

There were **three co-primary efficacy endpoints:**

1) Change in IIEF erectile function (EF) domain score from baseline to end of treatment;
2) Changes in percentage of sexual attempts resulting in successful vaginal penetration (SEP2);
3) Change in percentage of sexual attempts resulting in successful intercourse (SEP3).

Co-Primary Endpoint 1 (EF Domain Score)

Table 6.1.4.1 Change in IIEF Erectile Function Domain Score From Baseline to End of Treatment –ITT Population – Individual Phase 3 Studies TA-301 and TA-302

TA-301 Primary Efficacy Endpoint (1)

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 (5.11)	15.3 (7.79)	2.9 (6.38)	2.9 (0.57)	<0.0001
Avanafil 50 mg	152	12.6 (5.20)	18.1 (7.94)	5.4 (7.54)	5.4 (0.57)	<0.0001
Avanafil 100 mg	156	12.6 (5.39)	20.9 (7.90)	8.3 (7.67)	8.3 (0.56)	<0.0001
Avanafil 200 mg	155	12.8 (5.00)	22.2 (7.73)	9.5 (7.03)	9.5 (0.56)	<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 Primary Efficacy Endpoint (1)

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 (5.01)	13.2 (7.72)	1.8 (6.24)	1.8 (0.64)	0.0066
Avanafil 100 mg	125	11.2 (4.78)	15.8 (8.26)	4.6 (7.00)	4.5 (0.64)	<0.0001
Avanafil 200 mg	125	12.0 (5.10)	17.3 (8.65)	5.3 (7.50)	5.4 (0.66)	<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 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;

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TA-05 Primary Efficacy Endpoint (1)

Treatment	N		Baseline Score (SD)	Score At End pt (SD)	Change from Baseline (SD)	LS Mean (SE)	p-value [1]
Placebo	55		15.8 (4.0)	16.9 (7.3)	1.1 (6.4)	0.9 (0.95)	–
Avanafil 50 mg	56		16.1 (3.5)	19.4 (7.5)	3.2 (7.6)	3.2 (0.94)	0.0915
Avanafil 100 mg	60		16.2 (4.1)	22.3 (7.0)	6.1 (6.7)	6.1 (0.90)	0.0001
Avanafil 200 mg	56		16.5 (3.8)	22.4 (7.4)	5.9 (7.1)	6.0 (0.94)	0.0002
Avanafil 300 mg	57		16.5 (3.8)	22.5 (7.2)	6.0 (7.9)	6.1 (0.94)	0.0001

Adult male subjects 35 to 70 years of age with mild to moderate erectile dysfunction;
N = 295 (249 completed, 84.4%)
1. Two-sided p-value from treatment comparison of avanafil with placebo.

Co-Primary Endpoint 2 (SEP2)

Table 6.1.4.2 Change in % of Sexual Attempts in Which Subjects Were Able to Achieve Successful Vaginal Penetration (SEP2) Between the Run-in Period and the Treatment Period – – ITT Population- Individual Phase 3 Studies TA-301 and TA-302

TA-301 Primary efficacy Endpoint (2)

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 (36.34)	53.8 (37.88)	7.1 (32.07)	7.1 (2.33)	0.0025
Avanafil 50 mg	154	45.4 (36.72)	64.3 (37.21)	18.9 (35.51)	18.2 (2.34)	<0.0001
Avanafil 100 mg	157	46.6 (38.24)	73.9 (32.26)	27.3 (35.17)	27.2 (2.32)	<0.0001
Avanafil 200 mg	156	48.3 (38.22)	77.3 (31.44)	29.0 (35.90)	29.8 (2.33)	<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 (3.30)	(16.3, 29.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				20.1 (3.29)	(13.6, 26.5)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)				11.1 (3.31)	(4.6, 17.6)	0.0009

TA-302 Primary Efficacy Endpoint (2)

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 (36.63)	42.0 (39.34)	5.9 (31.16)	7.5 (2.85)	0.0088
Avanafil 100 mg	126	32.5 (35.19)	54.0 (39.40)	21.5 (37.19)	21.5 (2.85)	<0.0001
Avanafil 200 mg	126	41.5 (37.66)	63.5 (38.67)	22.0 (35.00)	25.9 (2.90)	<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;

TA-05 Primary Efficacy Endpoint (2)

Treatment	N	Baseline Mean (SD)	Mean at End pt (%)	Change from Baseline (%)	LS Mean (SE)	p-value [1]
Placebo	55	56.3 (36.0)	60.5 (36.6)	4.2 (35.8)	-0.2 (3.53)	–
Avanafil 50 mg	56	67.8 (29.7)	76.1 (30.0)	8.4 (31.2)	11.5 (3.51)	0.0200
Avanafil 100 mg	60	61.7 (34.7)	79.2 (26.5)	17.5 (30.5)	16.7 (3.37)	0.0006
Avanafil 200 mg	56	66.8 (31.0)	79.8 (27.9)	13.0 (34.1)	15.4 (3.50)	0.0019
Avanafil 300 mg	57	62.8 (32.6)	83.7 (20.5)	20.9 (33.8)	20.8 (3.46)	<0.0001

Adult male subjects 35 to 70 years of age with mild to moderate erectile dysfunction;
N = 295 (249 completed, 84.4%)
1. Two-sided p-value from treatment comparison of avanafil with placebo.

Co-Primary Endpoint 3 (SEP3)

Table 6.1.4.3 Change in the Percentage of Sexual Attempts in Which Subjects Were Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse Between the Run-in Period and the Treatment Period Resulting in Successful Intercourse (SEP3) – ITT Population – Individual Phase 3 Studies TA-301 and TA-302

TA-301 Primary efficacy Point (3)

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 (17.82)	27.0 (31.41)	14.4 (27.63)	14.1 (2.57)	<0.0001
Avanafil 50 mg	154	13.5 (18.58)	41.3 (35.94)	27.8 (33.86)	27.8 (2.58)	<0.0001
Avanafil 100 mg	157	13.9 (18.87)	57.1 (36.05)	43.2 (33.86)	43.4 (2.56)	<0.0001
Avanafil 200 mg	156	12.4 (18.52)	57.0 (37.78)	44.6 (35.67)	44.2 (2.57)	<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 Primary Efficacy Endpoint (3)

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 (16.41)	20.5 (29.10)	10.5 (27.73)	13.6 (2.77)	<0.0001
Avanafil 100 mg	126	8.2 (17.42)	34.4 (36.37)	26.2 (33.71)	28.7 (2.78)	<0.0001
Avanafil 200 mg	126	8.0 (14.91)	40.0 (36.34)	32.1 (32.94)	34.0 (2.76)	<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.

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

TA-05 Primary Efficacy Endpoint (3)

Treatment	N	Baseline Mean (SD)	Mean at End pt (%)	Change from Baseline (%)	LS Mean (SE)	p-value [1]
Placebo	55	16.9 (19.6)	28.9 (30.2)	12.1 (29.9)	11.2 (4.21)	–
Avanafil 50 mg	56	21.2 (19.6)	53.4 (33.9)	32.2 (33.8)	34.4 (4.19)	0.0001
Avanafil 100 mg	60	19.0 (20.4)	58.6 (33.6)	39.6 (34.7)	40.0 (4.03)	<0.0001
Avanafil 200 mg	56	20.4 (18.9)	62.1 (33.0)	41.7 (33.6)	43.0 (4.18)	<0.0001
Avanafil 300 mg	57	18.1 (20.1)	64.3 (32.3)	46.1 (34.3)	46.0 (4.14)	<0.0001

Adult male subjects 35 to 70 years of age with mild to moderate erectile dysfunction;
N = 295 (249 completed, 84.4%)
1. Two-sided p-value from treatment comparison of avanafil with placebo.

Reviewer's comment: The results showed that avanafil was effective in the treatment for ED as demonstrated by all three co-primary endpoints.

Table 6.1.4.4 Changes in the Three Co-Primary Efficacy Endpoints Between the Run-in Period and the Treatment Period – Individual Studies TA-301, TA-302, and TA-05 – Intent-to-Treat Population (ITT)

Treatment	Study TA-301			Study TA-302			Study TA-05		
	Baseline [1] Mean (SD)	During Treatment [2] Mean (SD)	Change [3] LS Mean (SE)	Baseline [1] Mean (SD)	During Treatment [2] Mean (SD)	Change [3] LS Mean (SE)	Baseline [1] Mean (SD)	During Treatment [2] Mean (SD)	Change [3] LS Mean (SE)
Percentage of Attempts Resulting in Successful Intercourse (SEP3)									
Placebo	12.6 (17.82)	27.0 (31.41)	14.1 (2.57)	10.0 (16.41)	20.5 (29.10)	13.6 (2.77)	16.9 (19.62)	28.9 (30.16)	11.2 (4.21)
Avanafil 50 mg	13.5 (18.58)	41.3 (35.94)	27.8 (2.58)*	–	–	–	21.2 (19.61)	53.4 (33.89)	34.4 (4.19)
Avanafil 100 mg	13.9 (18.87)	57.1 (36.05)	43.4 (2.56)*	8.2 (17.42)	34.4 (36.37)	28.7 (2.78)*	19.1 (20.38)	58.6 (33.61)	40.0 (4.03)*
Avanafil 200 mg	12.4 (18.52)	57.0 (37.78)	44.2 (2.57)*	8.0 (14.91)	40.0 (36.34)	34.0 (2.76)*	20.4 (18.92)	61.9 (32.99)	43.0 (4.18)*
Avanafil 300 mg	–	–	–	–	–	–	18.6 (20.51)	64.3 (32.28)	46.0 (4.14)*
Percentage of Attempts Resulting in Successful Vaginal Penetration (SEP2)									
Placebo	46.7 (36.34)	53.8 (37.88)	7.1 (2.33)	36.0 (36.63)	42.0 (39.34)	7.5 (2.85)	56.6 (36.06)	60.5 (36.55)	-0.2 (3.53)
Avanafil 50 mg	45.4 (36.72)	64.3 (37.21)	18.2 (2.34)*	–	–	–	67.8 (29.71)	76.1 (29.97)	11.5 (3.51)*
Avanafil 100 mg	46.6 (38.24)	73.9 (32.26)	27.2 (2.32)*	32.5 (35.19)	54.0 (39.40)	21.5 (2.85)*	61.6 (34.68)	79.2 (26.51)	16.7 (3.37)*
Avanafil 200 mg	48.3 (38.22)	77.3 (31.44)	29.8 (2.33)*	41.5 (37.66)	63.5 (38.67)	25.9 (2.90)*	66.8 (31.02)	79.8 (27.90)	15.4 (3.50)*
Avanafil 300 mg	–	–	–	–	–	–	62.8 (32.59)	83.7 (20.52)	20.8 (3.46)*
IIEF Erectile Function Domain Score									
Placebo	12.4 (5.11)	15.3 (7.79)	2.9 (0.57)	11.4 (5.01)	13.2 (7.72)	1.8 (0.64)	15.8 (4.04)	16.9 (7.32)	0.9 (0.95)
Avanafil 50 mg	12.6 (5.20)	18.1 (7.94)	5.4 (0.57)*	–	–	–	16.1 (3.46)	19.4 (7.54)	3.2 (0.94)
Avanafil 100 mg	12.6 (5.39)	20.9 (7.90)	8.3 (0.56)*	11.2 (4.78)	15.8 (8.26)	4.5 (0.64)*	16.2 (4.08)	22.3 (7.00)	6.1 (0.90)*
Avanafil 200 mg	12.8 (5.00)	22.2 (7.73)	9.5 (0.56)*	12.0 (5.10)	17.3 (8.65)	5.4 (0.66)*	16.5 (3.82)	22.4 (7.41)	6.0 (0.94)*
Avanafil 300 mg	–	–	–	–	–	–	16.5 (3.83)	22.5 (7.17)	6.1 (0.94)*

1. Baseline values were calculated from all subject diary entries available for the non-treatment run-in period.
2. During treatment values were calculated from all subject diary entries beginning with the first dose of study drug and ending with the last study visit.
3. The LS mean and SE are from an analysis of covariance model with treatment and erectile dysfunction severity as factors and baseline response as the covariate for the change from baseline response. Statistically significant p-value for the treatment comparison between avanafil and placebo is indicated by an asterisk (*).

IIEF = International Index of Erectile Function; LS = least squares; SD = standard deviation; SE = standard error; SEP = Sexual Encounter Profile.

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6.1.5 Analysis of Secondary Endpoints(s)

Changes in other IIEF domain scores from baseline to end of treatment

The analysis of secondary endpoints was conducted with pivotal studies.

Table 6.1.5.1 Changes in IIEF Orgasmic Function, Sexual Desire, Intercourse Satisfaction, and Overall Satisfaction Domain Scores From Baseline to End of Treatment –Analysis of Studies TA-301 and TA-302 (ITT Population)

Change in IIEF Orgasmic Function Domain Score From Baseline to End of Treatment – ITT Population

TA-301

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	4.8 (2.55)	5.2 (3.00)	0.5 (2.62)	0.5 (0.21)	0.0271
Avanafil 50 mg	152	4.8 (2.61)	6.3 (2.98)	1.6 (2.84)	1.6 (0.21)	<0.0001
Avanafil 100 mg	156	4.8 (2.68)	7.4 (2.90)	2.6 (3.12)	2.6 (0.21)	<0.0001
Avanafil 200 mg	155	4.7 (2.63)	7.5 (2.80)	2.9 (3.18)	2.8 (0.21)	<0.0001

TA-302

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	5.0 (2.83)	5.2 (3.06)	0.2 (2.84)	0.4 (0.25)	0.1634
Avanafil 100 mg	125	4.9 (2.70)	6.2 (3.13)	1.3 (3.09)	1.4 (0.25)	<0.0001
Avanafil 200 mg	125	4.8 (2.63)	6.1 (3.36)	1.4 (3.04)	1.4 (0.25)	<0.0001

1. n is the number of subjects with values at both time points.
2. Baseline value was obtained at Visit 2 (Week 0).
3. End of treatment value is the last available value during the treatment period.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment and erectile dysfunction severity as factors and baseline response as the covariate for the change from baseline response

Change in IIEF Sexual Desire Domain Score From Baseline to End of Treatment – ITT Population

TA-301

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	6.4 (2.17)	6.6 (2.25)	0.2 (2.06)	0.1 (0.13)	0.2778
Avanafil 50 mg	152	6.2 (2.05)	6.9 (1.97)	0.7 (1.83)	0.5 (0.13)	<0.0001
Avanafil 100 mg	156	6.8 (2.16)	7.4 (1.87)	0.7 (1.90)	0.8 (0.13)	<0.0001
Avanafil 200 mg	155	6.7 (2.04)	7.6 (1.79)	0.9 (1.81)	1.0 (0.13)	<0.0001

TA-302

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	7.1 (1.89)	7.2 (1.96)	0.1 (1.90)	0.2 (0.16)	0.1413
Avanafil 100 mg	125	7.0 (1.90)	7.2 (1.96)	0.1 (1.91)	0.3 (0.16)	0.1061
Avanafil 200 mg	125	6.8 (2.00)	7.2 (2.09)	0.3 (2.09)	0.3 (0.16)	0.0373

1. n is the number of subjects with values at both time points.
2. Baseline value was obtained at Visit 2 (Week 0).
3. End of treatment value is the last available value during the treatment period.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment and erectile dysfunction severity as factors and baseline response as the covariate for the change from baseline response

Change in IIEF Intercourse Satisfaction Domain Score From Baseline to End of Treatment – ITT Population

TA-301

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	6.5 (1.96)	7.6 (2.83)	1.1 (2.74)	1.1 (0.23)	<0.0001
Avanafil 50 mg	152	6.5 (1.89)	8.7 (3.13)	2.3 (2.78)	2.3 (0.23)	<0.0001
Avanafil 100 mg	156	6.6 (1.96)	10.0 (3.25)	3.4 (3.06)	3.5 (0.22)	<0.0001
Avanafil 200 mg	155	6.3 (1.79)	9.9 (3.21)	3.7 (2.85)	3.6 (0.23)	<0.0001

TA-302

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	6.4 (2.01)	7.3 (3.19)	0.9 (2.70)	1.1 (0.27)	<0.0001
Avanafil 100 mg	125	6.2 (1.82)	8.0 (3.42)	1.8 (3.08)	2.0 (0.27)	<0.0001
Avanafil 200 mg	125	6.4 (1.98)	8.5 (3.38)	2.1 (3.11)	2.3 (0.27)	<0.0001

1. n is the number of subjects with values at both time points.
2. Baseline value was obtained at Visit 2 (Week 0).
3. End of treatment value is the last available value during the treatment period.
4. Least-squares mean, SE, 95% CI, and two-sided p-value are from an analysis of covariance model with treatment and erectile dysfunction severity as factors and baseline response as the covariate for the change from baseline response

Change in IIEF Overall Satisfaction Domain Score From Baseline to End of Treatment – ITT Population

TA-301

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	4.0 (1.98)	5.1 (2.60)	1.1 (2.40)	1.1 (0.19)	<0.0001
Avanafil 50 mg	152	3.9 (1.85)	5.7 (2.64)	1.8 (2.36)	1.7 (0.19)	<0.0001
Avanafil 100 mg	156	4.2 (2.03)	6.8 (2.68)	2.6 (2.83)	2.7 (0.19)	<0.0001
Avanafil 200 mg	155	3.9 (1.80)	6.9 (2.60)	3.0 (2.64)	2.9 (0.19)	<0.0001

TA-302

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	4.1 (2.07)	4.7 (2.49)	0.6 (2.04)	0.7 (0.21)	0.0008
Avanafil 100 mg	125	4.0 (1.91)	5.6 (2.61)	1.6 (2.47)	1.7 (0.21)	<0.0001
Avanafil 200 mg	125	4.2 (2.00)	5.8 (2.69)	1.6 (2.85)	1.8 (0.21)	<0.0001

Scores for the IIEF orgasmic function domain range from 0 to 10, with higher scores indicating better orgasmic function. The LS mean change in IIEF orgasmic function domain score from baseline to end of treatment was 0.4 for the placebo group, 1.2 for the avanafil 50 mg group, 2.0 for the avanafil 100 mg group, and 2.0 for the avanafil 200 mg group. For all treatment groups, the LS mean change in IIE orgasmic function domain score from baseline was statistically significant ($p \leq 0.0152$). The treatment comparisons of each avanafil dose with placebo were statistically significant ($p \leq 0.0007$).

Percentage of Subjects With an Improvement in IIEF Erectile Function Domain Score

- In total, 838 of 1216 subjects had an improvement in IIEF erectile function domain score from baseline to end of treatment: 176 (53.2%) subjects on placebo, 146 (70.2%) subjects on avanafil 50 mg, 256 (75.1%) subjects on avanafil 100 mg, and 260 (77.4%) subjects on avanafil 200 mg.

Percentage of Subjects With an IIEF Erectile Function Domain Score in the Normal Range

- In study TA-301, 189 of 622 subjects had an IIEF erectile function domain score in the normal range (defined as ≥26 points) at the end of treatment: 20 (12.9%) subjects on placebo, 34 (22.1%) subjects on avanafil 50 mg, 65 (41.4%) subjects on avanafil 100 mg, and 70 (44.9%) subjects on avanafil 200 mg.
- In study TA-302, 66 of 379 subjects had an IIEF erectile function domain score in the normal range (defined as ≥26 points) at the end of treatment: 15 (11.8%) subjects on placebo, 22 (17.5%) subjects on avanafil 100 mg, and 29 (23.0%) subjects on avanafil 200 mg.

Efficacy by Dosing Timing: Percentage of successful response to diary questions by time interval between dose administration and sexual attempt.

The Sponsor further analyzed the successful response vs. the time interval between dosing and sexual attempt. (b) (4) In the Sponsor's study reports ,instead of using pre-defined categories, time between dose administration and sexual attempts were re-catagorized into into the following intervals: less than or equal to 15 minutes; greater than 15 minutes and less or equal to 30 minutes; greater than 30 and less than or equal to 45 minutes; greater than 45 and less than or equal to 60 minutes; greater than 60 and less than or equal to 120

minutes; greater than 120 and less than or equal to 240 minutes; greater than 240 and less than or equal to 360 minutes; and greater than 360 minutes.

Table 6.1.5.2: Study TA-301 - Summary of Attempts in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse by Time Interval (SEP3) – Intent-to-Treat Population

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 defined as a YES response to the diary question "Did your erection last long enough for you to have successful intercourse?"
Source: Table 20 in the Applicant's TA-301 study report.
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 defined as a YES response to the diary question "Did your erection last long enough for you to have successful intercourse?"
2. The 95% CI of the difference between avanafil and placebo for the proportion of successes is based on normal approximation.

CI = confidence interval

Reviewer's comment: The majority of attempts occurred greater than 15 minutes after dosing. The Reviewer does not believe (b) (4) **In Phase 3 studies, patients were instructed to attempt intercourse at approximately 30 minutes after taking the product, and the efficacy demonstrated in Phase 3 support that same instruction in labeling.**

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Reviewer's comment: The majority of the attempts were within 2 hours of dosing, with fewer occurring in the third or fourth hour after dosing, and very few occurring in the fifth or sixth hour after dosing. Based on these data, it is only possible to conclude that efficacy is likely up to 2 hours after taking avanafil, but might be possible at later timpoints. Based on these data, no specific timeframe should be allowed in labeling.

Reviewer's comment: The efficacy results from the open-label, safety extension study TA-314 are not reviewed here, nor do they support labeling claims, due to the open-label nature of the study design.

6.1.6 Other Endpoints

6.1.6.1 Phase 2a Study TA-01

6.1.6.1.1 Study description

In study TA-01, 89 subjects were randomized. The doses studied were 50 mg, 100 mg, 200 mg and placebo. Six (6.7%) subjects discontinued prematurely from the study after randomization but before taking study drug. Eighty-three (93.3%) randomized subjects received at least 1 dose of study drug and were included in the All Treated Subjects Population for safety analyses. Eighty-two (92.1%) subjects completed the study. One (1.1%) subject requested to be withdrawn from the study. Eighty (89.9%) randomized subjects took all 3 doses of their scheduled treatments and were included in the Efficacy Analysis Population. The mean age of All Treated Subjects in study TA-01 was 51.5 years. The majority of subjects were White (67.5%). Overall, the subject assessment of the erectile dysfunction severity at baseline was moderate for 68 (81.9%) subjects, minimal for 14 (16.9%) subjects, and severe for 1 (1.2%) subject. The mean duration of erectile dysfunction was 58.1 months. No statistically significant differences in demographic and baseline characteristics between Groups 1, 2, and 3 were noted.

The efficacy of avanafil was assessed based on the time to and duration of ≥60% penile rigidity (tip and base) as measured by penile plethysmography (RigiScan) and evaluated by a central reader who was blinded to each subject's randomization. Subject responses to the 5-point Erection Assessment Scale (EAS) (1 = no response to 5 = rigid) were also evaluated.

Visual sexual stimulation (video) was presented to the subject during three 20-minute periods beginning at 20 minutes post dose and concluding at 120 minutes post dose. Response during early (20-40 minutes), mid (60-80 minutes), and late (100-120 minutes) windows of viewing were considered independently as well as cumulatively. The overall statistical significance of treatment differences (within each group) in this two-way (subject-by-treatment) layout was evaluated by the Friedman rank sum test. Separate tests were performed for each avanafil dose (50 mg, 100 mg, and 200 mg). Pairwise comparisons of the active treatments with placebo were performed by the Wilcoxon signed rank test if the preliminary Friedman rank sum test was significant.

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Differences among groups in the proportion of subjects achieving EAS score thresholds were evaluated using Chi-square tests.

6.1.6.1.2 Study Results

6.1.6.1.2.1 Duration of Penile Rigidity:

- Statistically significant differences between avanafil treatment and placebo treatment for the objective efficacy assessments were generally noted most frequently during the early (20- to 40-minute) interval from dosing. During the 20- to 40-minute interval, the majority of values for duration of ≥60% rigidity with avanafil 50 mg, 100 mg, and 200 mg treatments were statistically superior to placebo.
- While all avanafil treatments showed some degree of efficacy during the middle (60- to 80-minute) interval, avanafil 200 mg continued to show efficacy during the late (100- to 120-minute) interval.

6.1.6.1.2.2 Subject Responses on the 5-point Erection Assessment Scale

Statistically significant differences between avanafil treatment and placebo treatment for the subjective endpoint, EAS rating of ≥3 (full penile enlargement), were noted most frequently at the early (20- to 40-minute) interval from dosing. The percentages of subjects with EAS ≥4 (erection sufficient for intercourse) were significantly higher with avanafil 100 mg and 200 mg treatment than with placebo treatment at each post-dosing interval.

6.1.6.2 Phase 2a Study TA-03

6.1.6.2.1 Study description

In this exploratory, Phase 2a study, avanafil 200 mg was compared to sildenafil 100 mg. 51 subjects were randomized to one of the 2 treatment sequences: (1) Avanafil 200 mg (Treatment Period 1); sildenafil 100 mg (Treatment Period 2); avanafil 200 mg (Treatment Period 3), or (2) Sildenafil 100 mg (Treatment Period 1); avanafil 200 mg (Treatment Period 2); avanafil 200 mg (Treatment Period 3). Subjects were given a Subject Diary and 6 doses of their assigned study drug, and instructed to use ≥ 4 doses of study drug during each treatment period and to use the diary to record specific study-related information (e.g., the date and time of study drug dosing, details concerning the times and outcomes of sexual activity, and food and alcohol consumption from 2 hours before to 2 hours after study drug dosing). Subjects were instructed to initiate sexual activity 5 to 10 minutes post-dose during Treatment Periods 1 and 2, and 2 hours post-dose during Treatment Period 3. Forty-nine (96.1%) subjects took at least 1 dose of study drug and were included in the ITT Population for safety analyses. Forty-seven (92.2%) subjects completed the study. Four (7.8%) subjects discontinued from the study. Three (5.9%) subjects were discontinued from the study due to protocol non-compliance, and 1 (2.0%) subject requested to be withdrawn from the study. Forty-three (84.3%) subjects reported on at least 4 attempts at intercourse during each of the first two treatment periods and were included in the

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Efficacy Evaluable Population. The mean age of subjects in the ITT Population in study TA-03 was 55.9 years. The majority of subjects were White (75.5%). Overall, the subject assessment of the erectile dysfunction severity at baseline was moderate for 45 (91.8%) subjects, minimal for 3 (6.1%) subjects, and severe for 1 (2.0%) subject in the TA-03 ITT Population. The mean duration of erectile dysfunction was 87.8 months.

The efficacy of avanafil was assessed by the proportion of doses providing an erection sufficient for vaginal penetration, the proportion of doses providing an erection sufficient for successful intercourse, and the time following dosing at which an erection sufficient for intercourse was achieved.

Efficacy results were summarized using frequency counts and descriptive statistics. Binary efficacy endpoints in treatment groups 1 and 2 were compared using paired t-tests. Two median duration values were calculated. In one, results from attempts resulting in an erection sufficient to permit intercourse were reported. In the other, results of all attempts were employed. Descriptive statistics were calculated, and p-values were calculated using paired t-tests (mean values) and the Wilcoxon signed rank test (median values).

6.1.6.2.2 Study Results

6.1.6.2.2.1 Proportion of Doses Enabling Successful Intercourse

The mean intercourse success rates for avanafil and sildenafil 5- to 10-minute treatments were 56% and 69%, respectively. The comparison of avanafil and sildenafil 5- to 10-minute treatments was statistically significant (p=0.0172). The mean intercourse success rate for avanafil 2-hour treatment was 75%.

6.1.6.2.2.2 Proportion of Doses Enabling Successful Vaginal Penetration

The mean vaginal penetration success rates for avanafil and sildenafil 5- to 10-minute treatments were 79% and 85%, respectively. The comparison of avanafil and sildenafil 5- to 10-minute treatments was not statistically significant (p=0.2538). The mean vaginal penetration success rate for the avanafil 2-hour treatment was 88%.

6.1.6.2.2.3 Time Between Dosing and Erection Sufficient for Intercourse

The mean times from dosing to an erection sufficient for intercourse for avanafil and sildenafil 5- to 10-minute treatments were 27.2 and 24.8 minutes, respectively. The comparison of avanafil and sildenafil 5- to 10-minute treatments was not statistically significant (p=0.3770). The mean time to an erection sufficient for intercourse for the avanafil 2-hour treatment was 57.0 minutes, indicating that not all subjects followed instructions to wait for 2 hours before starting sexual activity.

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6.1.7 Subpopulations

6.1.7.1 By Age

Table 6.1.7.1.1 Change between run-in period and treatment period in SEP3 (%) – by age group – ITT Population – Age Subgroups

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Subjects <50 years of age						
Placebo	48	14.4 (18.04)	34.0 (30.55)	19.6 (28.72)		
Avanafil 50 mg	46	12.8 (17.44)	49.0 (36.58)	36.3 (36.62)	15.6(6.50)	0.0166
Avanafil 100 mg	46	12.5 (18.83)	66.9 (36.92)	54.4 (36.10)	35.3(6.51)	<0.0001
Avanafil 200 mg	40	13.8 (17.87)	67.6 (34.31)	53.8 (32.60)	35.3(6.76)	<0.0001
Subjects ≥50 and <65 years of age						
Placebo	72	13.5 (17.99)	30.8 (33.65)	17.4 (30.49)		
Avanafil 50 mg	80	16.9 (20.07)	43.9 (35.29)	27.0 (32.42)	10.8(5.12)	0.0346
Avanafil 100 mg	73	17.9 (20.18)	60.7 (34.22)	42.8 (31.60)	27.0(5.24)	<0.0001
Avanafil 200 mg	78	12.8 (19.85)	58.6 (38.11)	45.8 (37.50)	28.4(5.14)	<0.0001
Subjects ≥65 years of age						
Placebo	35	8.4 (16.97)	9.6 (20.11)	1.2 (11.85)		
Avanafil 50 mg	28	4.8 (12.51)	20.9 (29.82)	16.1 (30.35)	15.4(7.99)	0.0547
Avanafil 100 mg	38	7.9 (14.36)	38.1 (32.08)	30.2 (31.28)	27.2(7.38)	0.0002
Avanafil 200 mg	38	10.2 (16.51)	42.7 (37.15)	32.5 (32.23)	29.2 (7.39)	<0.0001
P-value for treatment by age group interaction term: 0.9617						

Source: Table 23 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Subjects <50 years of age						
Placebo	23	12.7 (17.37)	32.7 (36.19)	20.0 (34.59)		
Avanafil 100 mg	28	3.1 (8.07)	46.1 (39.98)	42.9 (38.18)	20.2 (8.45)	0.0171
Avanafil 200 mg	24	6.3 (11.33)	59.6 (34.08)	53.3 (33.42)	32.6 (8.72)	0.0002
Subjects ≥50 and <65 years of age						
Placebo	70	11.6 (17.37)	22.6 (29.23)	11.0 (28.33)		
Avanafil 100 mg	61	12.7 (21.02)	36.4 (36.07)	23.7 (32.09)	13.0 (5.22)	0.0129
Avanafil 200 mg	70	7.7 (14.98)	35.6 (35.25)	27.9 (30.52)	16.4 (5.06)	0.0013
Subjects ≥65 years of age						
Placebo	34	4.8 (12.56)	7.9 (17.21)	3.1 (18.43)		
Avanafil 100 mg	37	4.7 (14.24)	22.2 (30.99)	17.5 (28.80)	14.6 (7.08)	0.0394
Avanafil 200 mg	32	9.9 (17.20)	35.2 (36.52)	25.3 (32.21)	20.0 (7.41)	0.0073
P-value for treatment by age group interaction term: 0.6282						

Source: Table 23 in TA-302 study report and reviewer's analysis results

For all age subgroups, the results for SEP3 showed that dose-related increases in the percentage of attempts resulting in successful intercourse were observed. And also the dose response to

avanafil treatment was more pronounced in younger subjects (<50 years of age) than in older subjects (≥65 years of age).

Table 6.1.7.1.2: Change between run-in period and treatment period in SEP2 (%) – by age group

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Subjects <50 years of age						
Placebo	48	56.7 (35.29)	69.5 (32.66)	12.8 (31.54)		
Avanafil 50 mg	46	59.6 (36.53)	78.9 (30.34)	19.2 (38.04)	7.6 (5.85)	0.1964
Avanafil 100 mg	46	49.0 (39.30)	82.4 (29.31)	33.4 (40.72)	16.4 (5.87)	0.0053
Avanafil 200 mg	40	53.1 (33.82)	84.5 (24.69)	31.4 (34.14)	16.4 (6.09)	0.0071
Subjects ≥50 and <65 years of age						
Placebo	72	47.5 (36.07)	55.7 (36.52)	8.1 (34.97)		
Avanafil 50 mg	80	47.2 (34.59)	64.4 (35.82)	17.1 (32.10)	8.8 (4.61)	0.0554
Avanafil 100 mg	73	52.7 (38.96)	76.1 (29.04)	23.4 (30.47)	18.3 (4.72)	0.0001
Avanafil 200 mg	78	45.7 (40.29)	79.8 (28.71)	34.2 (38.34)	25.3 (4.64)	<0.0001
Subjects ≥65 years of age						
Placebo	35	31.3 (34.03)	28.6 (35.02)	-2.7 (24.13)		
Avanafil 50 mg	28	16.9 (26.75)	40.3 (39.98)	23.5 (41.07)	19.2 (7.21)	0.0081
Avanafil 100 mg	38	31.9 (32.06)	59.2 (37.15)	27.4 (36.26)	29.7 (6.65)	<0.0001
Avanafil 200 mg	38	48.6 (38.67)	64.4 (39.28)	15.9 (29.52)	27.4 (6.67)	<0.0001
P-value for treatment by age group interaction term: 0.5783						

Source: Table 24 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Subjects <50 years of age						
Placebo	23	47.6 (32.92)	61.9 (39.30)	14.4 (32.15)		
Avanafil 100 mg	28	39.5 (34.88)	71.5 (32.93)	32.0 (37.21)	13.9 (8.72)	0.1120
Avanafil 200 mg	24	50.6 (35.49)	77.0 (30.90)	26.4 (29.49)	15.0 (9.03)	0.0971
Subjects ≥50 and <65 years of age						
Placebo	70	39.4 (38.24)	45.8 (38.08)	6.4 (33.65)		
Avanafil 100 mg	61	37.3 (35.68)	53.0 (40.01)	15.7 (36.42)	8.3 (5.41)	0.1282
Avanafil 200 mg	70	38.0 (36.70)	60.9 (39.30)	22.9 (37.65)	16.4 (5.24)	0.0019
Subjects ≥65 years of age						
Placebo	34	21.3 (31.66)	20.6 (32.64)	-0.8 (23.54)		
Avanafil 100 mg	37	19.2 (31.72)	42.3 (39.09)	23.1 (37.50)	23.1 (7.35)	0.0018
Avanafil 200 mg	32	42.5 (41.15)	59.0 (41.29)	16.5 (33.00)	24.7 (7.70)	0.0015
P-value for treatment by age group interaction term: 0.5714						

Source: Table 24 in TA-302 study report and reviewer's analysis results

The results for SEP2 showed that for subjects <50 years of age and subjects ≥50 years and <65 years of age, dose-related increases in the percentage of attempts resulting in successful intercourse were observed. For all treatment groups including placebo, mean success rates at baseline and end of treatment were higher in younger subjects (<50 years of age) than in older

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subjects (≥65 years of age). The magnitude of the treatment effect of avanafil relative to placebo was greater in older subjects (≥65 years of age) than in younger subjects (<50 years of age) across all doses, which is likely reflective of the marked difference in the placebo response across the age subgroups.

Table 6.1.7.1.3 change between run-in period and treatment period in IIEF EF domain score – by age group

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Subjects <50 years of age						
Placebo	47	14.2 (4.88)	17.2 (7.02)	3.0 (5.85)		
Avanafil 50 mg	46	14.4 (4.82)	19.8 (6.64)	5.4 (7.40)	2.5 (1.41)	0.0799
Avanafil 100 mg	45	12.6 (5.33)	23.2 (7.26)	10.5 (7.64)	6.9 (1.42)	<.0001
Avanafil 200 mg	40	13.8 (4.70)	24.4 (5.78)	10.6 (7.01)	7.4 (1.47)	<.0001
Subjects ≥50 and <65 years of age						
Placebo	72	12.2 (5.16)	16.7 (7.91)	4.5 (6.90)		
Avanafil 50 mg	78	12.9 (5.18)	18.8 (8.07)	5.9 (7.45)	1.7 (1.11)	0.1197
Avanafil 100 mg	73	13.4 (5.64)	21.9 (7.25)	8.5 (7.28)	4.5 (1.13)	<.0001
Avanafil 200 mg	77	12.7 (5.05)	22.8 (7.43)	10.1 (6.87)	5.8 (1.12)	<.0001
Subjects ≥65 years of age						
Placebo	33	10.2 (4.51)	9.8 (6.04)	-0.4 (4.52)		
Avanafil 50 mg	28	9.1 (4.14)	13.1 (7.84)	4.0 (8.11)	4.1 (1.75)	0.0199
Avanafil 100 mg	38	11.1 (4.73)	16.6 (8.31)	5.5 (7.73)	6.2 (1.62)	0.0002
Avanafil 200 mg	38	12.0 (5.15)	19.0 (9.13)	7.0 (6.96)	8.0 (1.62)	<.0001
P-value for treatment by age group interaction term: 0.7669						

Source: Table 25 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Subjects <50 years of age						
Placebo	22	14.0 (5.06)	16.9 (8.65)	2.9 (7.24)		
Avanafil 100 mg	28	12.5 (4.32)	18.9 (7.28)	6.5 (6.80)	3.1 (1.96)	0.1112
Avanafil 200 mg	23	12.9 (4.34)	20.3 (7.21)	7.4 (8.17)	4.5 (2.04)	0.0274
Subjects ≥50 and <65 years of age						
Placebo	70	11.5 (5.06)	13.8 (7.76)	2.3 (6.25)		
Avanafil 100 mg	60	11.5 (4.89)	15.8 (8.52)	4.3 (7.73)	2.0 (1.21)	0.0946
Avanafil 200 mg	70	11.2 (4.67)	16.2 (8.92)	5.0 (7.51)	2.5 (1.17)	0.0314
Subjects ≥65 years of age						
Placebo	33	9.5 (4.09)	9.4 (5.13)	-0.1 (5.21)		
Avanafil 100 mg	37	9.8 (4.69)	13.3 (7.90)	3.5 (5.68)	3.8 (1.64)	0.0211
Avanafil 200 mg	32	13.1 (6.26)	17.6 (8.73)	4.5 (6.92)	5.3 (1.72)	0.0023
P-value for treatment by age group interaction term: 0.7185						

Source: Table 25 in TA-302 study report and reviewer's analysis results

The results for IIEF showed that for all age subgroups, dose-related increases in IIEF erectile function domain score were observed. For all treatment groups including placebo, mean IIEF erectile function domain scores at baseline and end of treatment were higher in younger subjects (<50 years of age) than in older subjects (≥65 years of age). The magnitude of the treatment effect of avanafil relative to placebo was greater in older subjects (≥65 years of age) than in younger subjects (<50 years of age) across all doses.

6.1.7.2 By Baseline ED Severity

Table 6.1.7.2.1 Change between run-in period and treatment period in SEP3 (%) – by ED severity
TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Mild						
Placebo	55	20.0 (18.83)	39.7 (33.49)	19.7 (32.04)		
Avanafil 50 mg	55	24.1 (20.52)	56.9 (34.73)	32.9 (36.86)	14.8 (6.13)	0.0162
Avanafil 100 mg	54	22.3 (22.80)	64.1 (36.01)	41.8 (32.74)	23.0 (6.15)	0.0002
Avanafil 200 mg	53	16.8 (21.14)	67.4 (37.01)	50.6 (36.75)	29.7 (6.18)	<.0001
Moderate						
Placebo	49	14.7 (19.74)	28.8 (30.96)	14.1 (27.10)		
Avanafil 50 mg	48	12.3 (17.28)	41.9 (32.75)	29.6 (30.57)	14.5 (6.52)	0.0261
Avanafil 100 mg	51	13.8 (16.50)	64.4 (33.96)	50.6 (34.72)	36.1 (6.42)	<0.0001
Avanafil 200 mg	52	15.6 (18.78)	58.8 (35.71)	43.3 (33.17)	29.5 (6.39)	<0.0001
Severe						
Placebo	51	2.6 (7.27)	11.6 (22.04)	9.0 (21.85)		
Avanafil 50 mg	51	3.2 (9.40)	23.8 (32.58)	20.7 (32.86)	11.9 (6.35)	0.0622
Avanafil 100 mg	52	5.3 (11.42)	42.5 (34.28)	37.3 (33.45)	29.3 (6.33)	<0.0001
Avanafil 200 mg	51	4.7 (12.17)	44.4 (37.70)	39.7 (36.77)	31.5 (6.36)	<0.0001
P-value for treatment by age group interaction term: 0.7103						

Source: Table 29 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Mild						
Placebo	28	24.2 (22.12)	40.4 (33.94)	16.2 (38.09)		
Avanafil 100 mg	26	17.8 (25.45)	43.9 (36.70)	26.1 (30.29)	7.4 (8.34)	0.3757
Avanafil 200 mg	28	14.9 (19.12)	57.9 (33.85)	43.0 (36.25)	23.2 (8.22)	0.0050
Moderate						
Placebo	39	9.7 (14.07)	25.6 (30.81)	15.9 (30.10)		
Avanafil 100 mg	39	12.1 (19.00)	49.0 (35.00)	36.9 (35.38)	21.9 (6.92)	0.0017
Avanafil 200 mg	41	11.5 (17.01)	46.0 (35.10)	34.5 (30.88)	19.3 (6.83)	0.0050
Severe						
Placebo	60	3.5 (9.22)	7.9 (17.41)	4.4 (17.93)		
Avanafil 100 mg	61	1.6 (6.30)	21.0 (32.52)	19.4 (32.71)	14.2 (5.55)	0.0107
Avanafil 200 mg	57	2.1 (6.73)	27.0 (34.03)	25.0 (31.49)	20.0 (5.65)	0.0004
P-value for treatment by age group interaction term: 0.5132						

Source: Table 29 in TA-302 study report and reviewer's analysis results

The results for SEP3 showed that for all baseline ED severity subgroups, treatment with avanafil resulted in a clinically relevant increase in the rate of successful intercourse. Although the end-of-treatment success rates generally decreased as severity of erectile dysfunction increased, no consistent differences in the magnitude of the response to avanafil treatment (placebo-subtracted values) by baseline ED severity were observed.

Table 6.1.7.2.2 Change between run-in period and treatment period in SEP2 (%) – by ED severity
TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Mild						
Placebo	55	62.8 (33.76)	66.8 (34.28)	4.0 (30.71)		
Avanafil 50 mg	55	66.7 (34.13)	79.8 (28.34)	13.1 (38.78)	11.3 (5.54)	0.0415
Avanafil 100 mg	54	63.0 (39.41)	82.6 (27.02)	19.6 (36.11)	15.7 (5.56)	0.0050
Avanafil 200 mg	53	62.0 (36.94)	81.3 (29.25)	19.3 (32.32)	14.8 (5.59)	0.0082
Moderate						
Placebo	49	57.5 (33.13)	63.6 (34.60)	6.2 (39.64)		
Avanafil 50 mg	48	50.4 (31.37)	69.9 (32.96)	19.5 (29.24)	9.3 (5.90)	0.1163
Avanafil 100 mg	51	58.5 (32.68)	80.8 (26.78)	22.3 (27.22)	16.7 (5.81)	0.0042
Avanafil 200 mg	52	59.1 (33.43)	87.6 (20.22)	28.4 (35.78)	23.2 (5.78)	<.0001
Severe						
Placebo	51	19.0 (24.47)	30.4 (34.07)	11.5 (24.70)		
Avanafil 50 mg	51	17.7 (25.26)	42.4 (39.52)	24.6 (36.88)	12.5 (5.75)	0.0302
Avanafil 100 mg	52	17.9 (23.39)	58.0 (36.57)	40.1 (38.05)	28.1 (5.72)	<0.0001
Avanafil 200 mg	51	23.0 (31.52)	62.6 (37.55)	39.7 (37.24)	30.5 (5.75)	<0.0001
P-value for treatment by age group interaction term: 0.3566						

Source: Table 30 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Mild						
Placebo	28	67.5 (29.27)	74.1 (33.47)	6.6 (27.73)		
Avanafil 100 mg	26	62.1 (37.66)	67.7 (37.33)	5.6 (17.99)	-3.6 (8.50)	0.6705
Avanafil 200 mg	28	77.8 (28.55)	85.6 (23.52)	7.8 (25.31)	6.1 (8.36)	0.4627
Moderate						
Placebo	39	45.4 (33.70)	54.6 (35.05)	9.2 (40.09)		
Avanafil 100 mg	39	47.7 (31.38)	68.3 (30.52)	20.7 (40.68)	12.5 (7.06)	0.0771
Avanafil 200 mg	41	48.4 (32.36)	73.8 (31.53)	25.4 (32.87)	17.6 (6.98)	0.0120
Severe						
Placebo	60	15.3 (27.88)	18.8 (29.28)	3.5 (25.94)		
Avanafil 100 mg	61	10.1 (18.07)	39.0 (40.25)	28.8 (39.14)	22.9 (5.68)	<.0001
Avanafil 200 mg	57	18.8 (28.38)	45.2 (41.20)	26.5 (39.04)	24.6 (5.77)	<.0001
P-value for treatment by age group interaction term: 0.1280						

Source: Table 30 in TA-302 study report and reviewer's analysis results

The results for SEP2 showed that as severity of ED increased, the end-of-treatment success rates generally decreased. However, the magnitude of the treatment effect of avanafil relative to placebo increased, particularly for the 100 mg and 200 mg doses.

Table 6.1.7.2.3 Change between run-in period and treatment period in IIEF EF domain score – by ED severity

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Mild						
Placebo	54	16.1 (5.43)	19.0 (7.70)	2.9 (6.67)		
Avanafil 50 mg	53	17.1 (4.63)	22.1 (6.59)	4.9 (7.71)	2.4 (1.35)	0.0711
Avanafil 100 mg	53	16.7 (5.90)	22.7 (7.46)	6.1 (7.34)	3.4 (1.35)	0.0126
Avanafil 200 mg	53	16.9 (4.87)	24.1 (7.07)	7.2 (5.97)	4.6 (1.35)	0.0007
Moderate						
Placebo	48	13.3 (2.62)	16.2 (7.21)	2.9 (6.77)		
Avanafil 50 mg	48	12.8 (3.16)	18.1 (6.99)	5.3 (7.14)	2.2 (1.43)	0.1289
Avanafil 100 mg	51	13.4 (2.75)	22.4 (6.34)	9.1 (6.31)	6.2 (1.40)	<0.0001
Avanafil 200 mg	52	13.2 (2.52)	23.5 (5.94)	10.3 (5.64)	7.3 (1.40)	<0.0001
Severe						
Placebo	50	7.6 (1.70)	10.6 (5.90)	3.0 (5.79)		
Avanafil 50 mg	51	7.9 (2.32)	13.9 (8.06)	6.0 (7.82)	3.2 (1.39)	0.0236
Avanafil 100 mg	52	7.8 (1.99)	17.7 (8.79)	9.9 (8.75)	7.0 (1.38)	<0.0001
Avanafil 200 mg	50	8.0 (2.14)	19.0 (9.06)	11.0 (8.68)	8.2 (1.40)	<0.0001
P-value for treatment by age group interaction term: 0.3161						

Source: Table 31 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
Mild						
Placebo	28	17.8 (4.74)	18.8 (7.77)	1.1 (7.07)		
Avanafil 100 mg	26	17.2 (5.38)	20.2 (7.25)	3.0 (5.01)	1.9 (1.89)	0.3131
Avanafil 200 mg	28	18.7 (3.92)	21.8 (6.68)	3.1 (6.74)	2.1 (1.85)	0.2569
Moderate						
Placebo	39	12.6 (2.49)	15.4 (8.01)	2.8 (7.48)		
Avanafil 100 mg	39	12.7 (1.99)	18.2 (7.39)	5.6 (7.25)	2.8 (1.57)	0.0779
Avanafil 200 mg	41	13.5 (2.33)	19.8 (8.26)	6.3 (8.14)	3.6 (1.55)	0.0213
Severe						
Placebo	58	7.6 (2.00)	9.0 (4.58)	1.4 (4.75)		
Avanafil 100 mg	60	7.7 (1.83)	12.3 (7.78)	4.6 (7.54)	3.2 (1.27)	0.0134
Avanafil 200 mg	56	7.6 (1.64)	13.3 (8.14)	5.8 (7.27)	4.3 (1.30)	0.0009
P-value for treatment by age group interaction term: 0.9125						

Source: Table 31 in TA-302 study report and reviewer's analysis results

Reference ID: 3117872

The results for IIEF showed that for all baseline ED severity subgroups, dose-related increases in IIEF erectile function domain score were observed. Although the end-of-treatment scores generally decreased as severity of erectile dysfunction increased, no consistent differences in the magnitude of the response to avanafil treatment by baseline ED severity were observed.

6.1.7.3 By Duration of Erectile Dysfunction

Table 6.1.7.3.1 Change between run-in period and treatment period in SEP3 (%) – by ED duration

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
< 24 months						
Placebo	29	15.6 (19.12)	38.7 (31.67)	23.1 (22.75)		
Avanafil 50 mg	23	10.1 (17.91)	54.3 (35.32)	44.2 (39.74)	17.1 (8.82)	0.0536
Avanafil 100 mg	22	14.5 (19.28)	53.2 (37.71)	38.7 (31.22)	14.2 (8.90)	0.1114
Avanafil 200 mg	18	13.3 (22.82)	55.3 (38.41)	41.9 (46.47)	16.9 (9.45)	0.0742
≥24 months and <60 months						
Placebo	50	11.2 (16.06)	33.7 (36.15)	22.5 (37.29)		
Avanafil 50 mg	52	15.8 (18.73)	53.6 (32.43)	37.8 (29.26)	18.3 (6.26)	0.0035
Avanafil 100 mg	59	14.8 (19.34)	64.3 (34.62)	49.6 (35.01)	30.1 (6.09)	<0.0001
Avanafil 200 mg	62	13.6 (18.08)	61.2 (35.90)	47.6 (34.51)	28.3 (6.02)	<0.0001
≥ 60 months						
Placebo	76	12.4 (18.49)	18.1 (25.20)	5.7 (17.78)		
Avanafil 50 mg	79	12.9 (18.72)	29.4 (34.62)	16.4 (31.09)	10.6 (5.06)	0.0370
Avanafil 100 mg	76	13.1 (18.59)	52.5 (36.21)	39.5 (33.35)	33.3 (5.11)	<0.0001
Avanafil 200 mg	76	11.2 (17.94)	54.0 (39.28)	42.8 (34.04)	35.3 (5.12)	<0.0001
P-value for treatment by age group interaction term: 0.1117						

Source: Table 32 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
< 24 months						
Placebo	19	22.3 (19.15)	37.9 (34.13)	15.6 (38.22)		
Avanafil 100 mg	16	11.1 (16.66)	47.9 (42.08)	36.8 (43.26)	17.2 (10.40)	0.1001
Avanafil 200 mg	19	11.0 (19.65)	50.1 (38.21)	39.1 (34.79)	18.7 (9.97)	0.0620
≥24 months and < 60 months						
Placebo	39	9.8 (17.04)	25.1 (30.88)	15.2 (27.21)		
Avanafil 100 mg	49	9.1 (19.43)	37.5 (38.29)	28.4 (33.46)	14.1 (6.54)	0.0316
Avanafil 200 mg	49	9.3 (14.40)	45.2 (34.16)	35.9 (30.95)	20.7 (6.54)	0.0017
≥60 months						
Placebo	69	6.7 (13.65)	13.1 (23.99)	6.4 (24.24)		
Avanafil 100 mg	61	6.7 (16.00)	28.3 (32.33)	21.6 (30.79)	14.6 (5.36)	0.0068
Avanafil 200 mg	58	5.9 (13.51)	32.4 (36.57)	26.5 (33.62)	19.5 (5.43)	0.0004
P-value for treatment by age group interaction term: 0.9958						

Source: Table 32 in TA-302 study report and reviewer's analysis results

Reference ID: 3117872

The results for SEP3 showed that for all ED duration subgroups, treatment with avanafil resulted in a clinically relevant increase in the rate of successful intercourse. For subjects with ED duration ≥24 months and <60 months and subjects with ED duration ≥60 months, dose-related increases in the percentage of attempts resulting in successful intercourse were observed. The magnitude of the treatment effect of avanafil relative to placebo increased with ED duration for the 100 mg and 200 mg doses.

Table 6.1.7.3.2 change between run-in period and treatment period in SEP2 (%) – by ED duration

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
<24 months						
Placebo	29	39.4 (32.56)	59.0 (37.30)	19.6 (22.60)		
Avanafil 50 mg	23	48.0 (34.51)	86.1 (21.33)	38.1 (29.73)	22.3 (7.88)	0.0047
Avanafil 100 mg	22	40.7 (44.04)	70.0 (37.84)	29.3 (33.93)	9.7 (7.97)	0.2237
Avanafil 200 mg	18	64.4 (30.43)	84.3 (27.96)	19.9 (41.51)	13.7 (8.50)	0.1082
≥24 months and < 60 months						
Placebo	50	58.6 (36.94)	66.3 (36.24)	7.8 (37.77)		
Avanafil 50 mg	52	55.6 (35.61)	78.9 (27.57)	23.2 (37.92)	14.4 (5.59)	0.0101
Avanafil 100 mg	59	50.5 (37.36)	82.1 (25.39)	31.5 (34.51)	19.7 (5.44)	0.0003
Avanafil 200 mg	62	47.1 (37.65)	81.7 (28.36)	34.6 (36.77)	21.4 (5.38)	<0.0001
≥60 months						
Placebo	76	41.7 (35.85)	43.7 (36.73)	2.0 (30.04)		
Avanafil 50 mg	79	37.9 (36.76)	48.4 (39.41)	10.5 (33.04)	6.3 (4.53)	0.1676
Avanafil 100 mg	76	45.2 (37.35)	68.6 (34.34)	23.4 (36.04)	23.2 (4.58)	<0.0001
Avanafil 200 mg	76	45.4 (39.79)	72.0 (33.97)	26.6 (33.50)	26.1 (4.58)	<0.0001
P-value for treatment by age group interaction term: 0.0384						

Source: Table 33 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
<24 months						
Placebo	19	68.0 (28.96)	72.8 (32.59)	4.8 (37.28)		
Avanafil 100 mg	16	49.8 (37.31)	64.0 (38.53)	14.2 (33.18)	0.6 (10.62)	0.9574
Avanafil 200 mg	19	59.3 (36.49)	80.3 (32.42)	21.0 (28.16)	11.8 (10.14)	0.2433
≥24 months and <60 months						
Placebo	39	38.8 (36.82)	51.3 (39.43)	12.5 (34.04)		
Avanafil 100 mg	49	31.7 (36.14)	54.6 (41.24)	22.9 (39.74)	7.8 (6.70)	0.2437
Avanafil 200 mg	49	45.2 (33.83)	68.8 (36.67)	23.6 (30.95)	14.6 (6.70)	0.0306
≥60 months						
Placebo	69	25.7 (33.29)	28.2 (34.78)	2.5 (27.32)		
Avanafil 100 mg	61	28.5 (33.02)	50.8 (38.29)	22.3 (36.41)	20.8 (5.48)	0.0002
Avanafil 200 mg	58	32.6 (39.11)	53.5 (39.95)	20.9 (40.31)	21.5 (5.57)	0.0001
P-value for treatment by age group interaction term: 0.4151						

Source: Table 33 in TA-302 study report and reviewer's analysis results

The results for SEP2 showed that for all ED duration subgroups, treatment with avanafil resulted in a clinically relevant increase in the rate of successful vaginal penetration. For subjects with erectile ED duration ≥24 months and <60 months and subjects with ED duration ≥60 months, dose-related increases in the percentage of attempts resulting in successful vaginal penetration were observed. The magnitude of the treatment effect of avanafil relative to placebo increased with ED duration for the 100 mg and 200 mg doses.

Table 6.1.7.3.3 Change between run-in period and treatment period in IIEF EF domain score – by ED duration

TA-301

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
< 24 months						
Placebo	29	13.4 (5.12)	17.6 (7.83)	4.2 (5.75)		
Avanafil 50 mg	22	13.5 (4.63)	21.7 (6.28)	8.2 (6.73)	4.0 (1.93)	0.0407
Avanafil 100 mg	21	13.1 (6.08)	19.4 (8.12)	6.3 (7.15)	1.9 (1.96)	0.3290
Avanafil 200 mg	18	14.2 (3.75)	23.3 (5.51)	9.1 (6.76)	5.1 (2.05)	0.0124
≥24 months and < 60 months						
Placebo	50	14.2 (5.46)	17.4 (7.37)	3.3 (7.10)		
Avanafil 50 mg	52	13.5 (4.80)	21.7 (6.67)	8.1 (7.71)	4.7 (1.35)	0.0006
Avanafil 100 mg	59	12.9 (4.93)	22.6 (6.68)	9.7 (6.91)	5.9 (1.32)	<0.0001
Avanafil 200 mg	62	13.3 (5.11)	22.9 (7.23)	9.6 (6.54)	6.1 (1.31)	<0.0001
≥60 months						
Placebo	73	10.8 (4.39)	13.0 (7.50)	2.2 (6.09)		
Avanafil 50 mg	78	11.8 (5.51)	14.6 (7.68)	2.8 (6.77)	1.0 (1.11)	0.3675
Avanafil 100 mg	76	12.3 (5.57)	20.1 (8.57)	7.8 (8.27)	6.2 (1.12)	<0.0001
Avanafil 200 mg	75	12.0 (5.09)	21.5 (8.54)	9.4 (7.55)	7.6 (1.13)	<0.0001
P-value for treatment by age group interaction term: 0.0085						

Source: Table 34 in TA-301 study report and reviewer's analysis results

TA-302

Treatment	n	Baseline Mean (SD)	End of Treatment Mean (SD)	Change From Baseline		
				Mean (SD)	LS Mean Diff trt vs. placebo (SE)	P-value trt vs. placebo
<24 months						
Placebo	19	15.6 (5.60)	19.0 (8.30)	3.3 (7.58)		
Avanafil 100 mg	16	13.7 (5.35)	17.8 (8.47)	4.1 (8.29)	0.5 (2.35)	0.8255
Avanafil 200 mg	19	16.1 (5.13)	18.9 (9.40)	2.8 (7.82)	-0.3 (2.24)	0.8838
≥24 months and <60 months						
Placebo	39	11.9 (4.76)	14.4 (7.37)	2.5 (6.16)		
Avanafil 100 mg	48	11.8 (5.00)	16.5 (8.67)	4.6 (6.69)	2.2 (1.49)	0.1435
Avanafil 200 mg	48	12.4 (4.95)	17.7 (8.67)	5.3 (7.46)	2.9 (1.49)	0.0544
≥60 months						
Placebo	67	9.9 (4.26)	10.9 (6.78)	0.9 (5.82)		
Avanafil 100 mg	61	10.1 (4.15)	14.7 (7.84)	4.6 (7.00)	3.7 (1.22)	0.0026
Avanafil 200 mg	58	10.3 (4.45)	16.5 (8.45)	6.2 (7.37)	5.2 (1.24)	<0.0001
P-value for treatment by age group interaction term: 0.2741						

Source: Table 34 in TA-302 study report and reviewer's analysis results

The results for IIEF showed that all ED duration subgroups, avanafil treatment resulted in a clinically relevant improvement in IIEF erectile function domain score. For subjects with ED duration ≥24 months and <60 months and subjects with ED duration ≥60 months, dose-related increases in the IIEF erectile function domain score were observed. The magnitude of the treatment effect of avanafil relative to placebo increased with ED duration for the 100 mg and 200 mg doses.

6.1.7.4 By Baseline Diabetic Status

ED subjects with type 1 or type 2 diabetes were only allowed to be enrolled in Study TA-302.

Table 6.1.7.4.1 Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which Subjects Were Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) – Individual Study TA-302 and Integrated Analysis of Studies TA-301, TA-302, and TA-05 – ITT Population – Diabetic Status Subgroups

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline Mean (SD)	Comparison [4] Avanafil vs. Placebo	
					LS Mean (SE)	P-value
Subjects with diabetes						
Placebo	127	10.0 (16.41)	20.5 (29.10)	10.5 (27.73)	–	–
Avanafil 100 mg	126	8.2 (17.42)	34.4 (36.37)	26.2 (33.71)	15.2 (3.84)	<0.0001
Avanafil 200 mg	126	8.0 (14.91)	40.0 (36.34)	32.1 (32.94)	20.4 (3.84)	<0.0001
Subjects without diabetes						
Placebo	210	13.7 (18.36)	27.5 (31.03)	13.8 (28.20)	–	–
Avanafil 100 mg	217	15.3 (19.39)	57.5 (35.32)	42.1 (34.06)	29.1 (3.08)	<0.0001
Avanafil 200 mg	212	14.5 (18.91)	58.3 (36.57)	43.8 (35.06)	30.4 (3.10)	<0.0001

The results for SEP3 showed that for both subgroups of subjects with diabetes and subjects without diabetes, treatment with avanafil resulted in a clinically relevant increase in the rate of successful intercourse. For both diabetic status subgroups, dose-related increases in the percentage of attempts resulting in successful intercourse were observed. Both the end-of-treatment success rates and the magnitude of the treatment effect of avanafil relative to placebo were greater in subjects without diabetes than in subjects with diabetes across both doses.

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Table 6.1.7.4.2 Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which Subjects Were Able to Achieve Successful Vaginal Penetration (SEP2) – Individual Study TA-302 and Integrated Analysis of Studies TA-301, TA-302, and TA-05 – ITT Population – Diabetic Status Subgroups

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline Mean (SD)	Comparison [4] Avanafil vs. Placebo	
					LS Mean (SE)	P-value
Subjects with diabetes						
Placebo	127	36.0 (36.63)	42.0 (39.34)	5.9 (31.16)	–	–
Avanafil 100 mg	126	32.5 (35.19)	54.0 (39.40)	21.5 (37.19)	14.0 (3.94)	0.0004
Avanafil 200 mg	126	41.5 (37.66)	63.5 (38.67)	22.0 (35.00)	18.4 (3.95)	<0.0001
Subjects without diabetes						
Placebo	210	49.3 (36.45)	55.6 (37.56)	6.3 (33.17)	–	–
Avanafil 100 mg	217	50.7 (37.82)	75.3 (30.81)	24.6 (34.16)	19.2 (2.76)	<0.0001
Avanafil 200 mg	212	53.2 (37.29)	77.9 (30.50)	24.8 (36.06)	20.7 (2.78)	<0.0001

The results for SEP2 showed that for both subgroups of subjects with diabetes and subjects without diabetes, treatment with avanafil resulted in a clinically relevant increase in the rate of successful vaginal penetration. For both diabetic status subgroups, dose-related increases in the percentage of attempts resulting in successful vaginal penetration were observed. Both the end-of-treatment success rates and the magnitude of the treatment effect of avanafil relative to placebo were greater in subjects without diabetes than in subjects with diabetes across both doses.

Table 6.1.7.4.3 Change in IIEF Erectile Function Domain Score From Baseline to End of Treatment – Individual Study TA-302 and Integrated Analysis of Studies TA-301, TA-302, and TA-05 – ITT Population – Diabetic Status Subgroups

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline Mean (SD)	Comparison [4] Avanafil vs. Placebo	
					LS Mean (SE)	P-value
Subjects with diabetes						
Placebo	125	11.4 (5.01)	13.2 (7.72)	1.8 (6.24)	–	–
Avanafil 100 mg	125	11.2 (4.78)	15.8 (8.26)	4.6 (7.00)	2.8 (0.87)	0.0017
Avanafil 200 mg	125	12.0 (5.10)	17.3 (8.65)	5.3 (7.50)	3.6 (0.87)	<0.0001
Subjects without diabetes						
Placebo	206	13.3 (5.07)	15.8 (7.68)	2.5 (6.43)	–	–
Avanafil 100 mg	216	13.6 (5.30)	21.3 (7.67)	7.7 (7.46)	5.4 (0.68)	<0.0001
Avanafil 200 mg	211	13.8 (4.98)	22.3 (7.63)	8.5 (7.19)	6.2 (0.68)	<0.0001

1. n is the number of subjects with values at both time points.
2. Baseline value was obtained at Visit 2 (Week 0).
3. End of treatment value is the last available value during the treatment period.
4. Least-squares mean, SE, and p-value are from an analysis of covariance model with treatment, erectile dysfunctionseverity category, and study as factors and baseline response as the covariate for the change from baseline response.

LS = least squares; SD = standard deviation; SE = standard error; vs. = versus.

The results for IIEF showed that for both subgroups of subjects with diabetes and subjects without diabetes, treatment with avanafil resulted in a clinically relevant improvement in IIEF erectile function domain score. For both diabetic status subgroups, dose-related increases in the

IIEF erectile function domain score were observed. Both the end-of-treatment scores and the magnitude of the treatment effect of avanafil relative to placebo were greater in subjects without diabetes than in subjects with diabetes across both doses.

Reviewer's comment: As observed, the magnitude of the treatment effect of avanafil on erectile function was numerically greater in subjects without diabetes than in subjects with diabetes, it is speculated whether or not these may be related to a function of the greater degree of ED severity at baseline in men with diabetes. However, in the enrolled diabetic subjects, avanafil at both 100 mg and 200mg resulted in clinically and statistically significant improvement in the three co-primary endpoints relative to placebo. Avanafil treatment at doses of either 100 mg or 200 mg in diabetic subjects with ED improved their ability to have successful intercourse 3-fold and 4-fold, respectively, from the start of treatment. In both diabetics and non-diabetics, there was a dose-response relationship, with 200 mg being numerically better than 100 mg. The 200 mg dose provided clear numeric improvements in ED compared to the 100 mg dose in diabetics, as well as in older, non-diabetic men, and in non-diabetic men with more severe or prolonged baseline ED. The improvement observed for the 200 mg dose over the 100 mg dose in other non-diabetic populations was numerically smaller.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The effects of avanafil treatment on erectile function were substantial, clinically relevant, and dose related. Subjects treated with avanafil achieved erections sufficient for the successful completion of intercourse (SEP3) on 44.5% of attempts with the 50 mg dose, 49.0% of attempts with the 100 mg dose, and 51.5% of attempts with the 200 mg dose, versus 24.9% of attempts for placebo-treated subjects. Subjects treated with avanafil achieved erections sufficient for successful vaginal penetration (SEP2) on 67.5% of attempts with the 50 mg dose, 67.5% of attempts with the 100 mg dose, and 72.6% of attempts with the 200 mg dose, versus 50.5% of attempts for placebo-treated subjects. For avanafil treated subjects, the IIEF erectile function domain score improved to 18.4 with the 50 mg dose, 19.3 with the 100 mg dose, and 20.4 with the 200 mg dose, versus 14.8 for placebo-treated subjects.

The Sponsor believes that the evidence 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 studied in the double-blind studies and open-label study: 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 improved efficacy or reduced to 50 mg for tolerability reasons. This treatment algorithm follows that used in the open-label extension study.

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In Division's 74-day letter on September 1, 2011, DRUP asked Sponsor to provide further support for the benefit of using 200 mg dose in the general ED population. The specific DRUP comment was:

> "*While there may be a need for the 200 mg dose in the diabetic population, the clinical benefit of treatment with 200 mg over 100 mg is not clear in the general ED population. Provide additional justification for the need for the 200 mg dose in the general ED population.*"

The Sponsor responded on October 27, 2011. In general, the Sponsor still believes that the integrated analysis of the Phase 2 and 3 double-blind studies (TA-301, TA-302, and Phase 2b study TA-05), in conjunction with the open-labeled Phase 3 long term safety study TA-314, supports approval of the 100 mg and 200mg doses for all patients. The Sponsor stated

> "*Avanafil provided consistently greater mean point estimates for the 200 mg dose compared to the 100 mg, and the integrated analyses of the double-blind studies in conjunction with the data from the TA-314 study support conclusions of a dose response from 50 mg through 200 mg.*"

The Sponsor provided evidence to support the need for the higher 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).

Table 6.1.8.1 Change from Baseline SEP 3 and IIEF-EF Domain 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 concluded that the effects of avanafil treatment on erectile function were substantial, clinically relevant, and dose related (even if without statistical significance when comparing 200 mg vs. 100 mg).

In addition, the Sponsor had the following additional justifications:

- During the final month of the qualifying 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 get as much benefit from

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100 mg, do not find 100 mg to be completely satisfactory, and 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 qualifying 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.

Reviewer's comment: The data from Studies TA-05, TA-301, TA-302 and TA-314 supports the conclusion that the effects of avanafil treatment on ED at both 100 mg and 200 mg are substantial, clinical relevant, and dose related. There appears to be sufficient justification for the need for the 200 mg dose in diabetics, as well as in the non-diabetic (general) ED population.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

(b) (4)

Reviewer's comment: (b) (4)

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues/analyses to be reviewed except the Sponsor's [redacted] (b) (4)

Reviewer's comment: [redacted] (b) (4)

Medical Officer's Overall Assessment of Efficacy

The efficacy results for avanafil for the treatment of ED come from two Phase 3 studies and one Phase 2 study, and are supported by two, small, Phase 2a studies.

1. Avanafil met all three co-primary endpoints at all three doses (50, 100, and 200 mg) studied in the general ED population, and at both doses (100, and 200 mg) studied in diabetic men with ED. The primary efficacy data come from the Phase 3 studies TA-301 and TA-302, as well as the Phase 2 study TA-05. The two Phase 2a studies provide supportive evidence of benefit.
2. [redacted] (b) (4) .
3. The Sponsor's claim [redacted] (b) (4)
4. The benefit of avanafil is observed in all relevant subgroups.
5. The clinical efficacy of avanafil is dose-related. The benefit of the 100 mg dose over the 50 mg dose is clear. The benefit of the 200 mg dose over the 100 mg dose is less clear compared to the 100 mg over the 50 mg. Nonetheless, in diabetics, the benefit of the 200 mg over the 100 mg is evident, and for non-diabetics the benefit of the 200 mg over the 100 mg is evident in the elderly (> 65 years), as well as in men with severe ED or a longer history of ED at baseline.

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7 Review of Safety

Safety Summary

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.

7.1 Methods

The focus of this safety review was the Phase 3 pivotal studies TA-301 and TA-302, the Phase 1 and Phase 2 studies, including Phase 2 study TA-05, the long term exposure study TA-314, and several special studies (e.g., for cardiovascular and male reproductive safety).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 7.1.1 lists some of the important safety studies. The Integrated Summary of Safety (ISS) and individual studies TA-05, TA-301, TA-302, TA-314 were reviewed first. Subsequently, the alcohol study, the sperm study, and QT study were reviewed. All safety-related submissions were taken into consideration during the review of safety.

Study Type		Studies
Pivotal Studies		**TA-301, TA-302, TA-05**
Supportive Studies		**TA-314, TA-01, TA-03**
Phase 1 Clinical Pharmacology Studies	**Single and multiple-dose PK Studies**	**HP-01, TA-02, TA-07, TA-010**
	Alcohol and food effect Studies	**TA-015, TA-020**
	Sperm function Studies	**TA-014, TA-021**
	Drug-drug interaction Studies	**TA-04, TA-011, TA-016, TA-017, TA-018, TA-019**
	QT/QTc Study	**TA-140**
	Special population Studies	**TA-012, TA-013**

7.1.2 Categorization of Adverse Events

Adverse events were categorized using standard defined MedDRA terminology.

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7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from pivotal studies were pooled for analysis. The trials were similarly designed so that pooling of safety data is appropriate and brings additional power to the analysis.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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.

7.2.1.1 Overall Exposure at Appropriate Doses/Durations

7.2.1.1.1 Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

Table 7.2.1.1 Summary of Exposure – Double-Blind Studies (TA-05 and TA-301 and TA-302)

	Placebo (N=349)	Avanafil 50 mg (N=217)	Avanafil 100 mg (N=349)	Avanafil 200 mg (N=352)	Total (N=1267)
Duration of exposure (weeks) [1]					
n	349	217	349	352	1267
Mean (SD)	11.8 (2.69)	11.9 (2.56)	12.3 (3.44)	12.3 (2.68)	12.1 (2.90)
Median	12.1	12.3	12.3	12.3	12.3
Number (%) in specified exposure range					
<4 weeks	5 (1.4)	3 (1.4)	4 (1.1)	6 (1.7)	18 (1.4)
≥4 weeks and <8 weeks	24 (6.9)	14 (6.5)	13 (3.7)	11 (3.1)	62 (4.9)
≥8 weeks and <12 weeks	65 (18.6)	40 (18.4)	60 (17.2)	55 (15.6)	220 (17.4)
≥12 weeks	255 (73.1)	160 (73.7)	272 (77.9)	280 (79.5)	967 (76.3)
Number of doses taken					
n	337	210	343	338	1228
Mean (SD)	16.7 (7.47)	17.5 (8.51)	18.5 (8.64)	18.4 (7.80)	17.8 (8.11)
Median	16.0	17.0	17.0	18.0	17.0
Number of times study drug taken within 24 hrs of previous dose					
n	171	113	179	166	629
Mean (SD)	3.0 (3.46)	3.6 (4.06)	3.4 (4.43)	2.8 (3.11)	3.2 (3.79)
Number (%) who took 2 doses within 24 hours					
1 time to ≤5 times	148 (42.4)	92 (42.4)	155 (44.4)	146 (41.5)	541 (42.7)
5 times to ≤10 times	15 (4.3)	11 (5.1)	11 (3.2)	14 (4.0)	51 (4.0)
10 times to ≤20 times	7 (2.0)	9 (4.1)	11 (3.2)	6 (1.7)	33 (2.6)
20 times to ≤30 times	1 (0.3)	1 (0.5)	1 (0.3)	0 (0.0)	3 (0.2)
≥30 times	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Data from studies TA-05, TA-301, and TA-302 are included.
1. Duration of exposure is the number of weeks between the first drug dispense date and the study termination or completion date.
SD = standard deviation.

For the double-blind cohort, the mean duration of exposure was 12.1 weeks. For the majority of subjects in each treatment group, the duration of exposure was ≥12 weeks. Overall mean time on treatment, or the time between the first and last dose of study drug, was 10.6 weeks, and overall median time on treatment was 11.3 weeks. In general, exposure to treatment was similar across all treatment groups.

Overall, the mean total number of doses taken was 17.8 across the treatment groups: 16.7 doses for the placebo group, 17.5 doses for the avanafil 50 mg group, 18.5 doses for the avanafil 100 mg group, and 18.4 doses for the avanafil 200 mg group.

In total, 629 of the 1267 (49.6%) subjects in the double-blind cohort took two doses of study drug within 24 hours: 171 of the 349 (49.0%) subjects in the placebo group, 113 of the 217 (52.1%) subjects in the avanafil 50 mg group, 179 of the 349 (51.3%) subjects in the avanafil 100 mg group, and 166 of the 352 (47.2%) subjects in the avanafil 200 mg group. For these 629 subjects, the mean number of times during the study that two doses were taken within 24 hours was 3.2. Overall, 541 (42.7%) subjects took two doses of study drug within 24 hours >1 and ≤5 times during the study; 51 (4.0%) subjects took two doses of study drug within 24 hours >5 and ≤10 times during the study; 33 (2.6%) subjects took two doses of study drug within 24 hours >10 and ≤20 times during the study; 3 (0.2%) subjects took two doses of study drug within 24 hours >20 and ≤30 times during the study; and 1 (0.1%) subject took two doses of study drug within 24 hours ≥30 times during the study.

Reviewer's Comment: (b) (4)

For the two Phase 3 studies alone, the total exposure is showing as Table 7.2.1.2.

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Table 7.2.1.2 Summary of Duration of Exposure – Phase 3 Double-Blind Cohort – (TA-301+TA-302)

	Placebo (N=291)	Avanafil 50 mg (N=160)	Avanafil 100 mg (N=288)	Avanafil 200 mg (N=293)	Total (N=1032)
Duration of exposure (weeks) [1]					
n	291 (100.0)	160 (100.0)	288 (100.0)	293 (100.0)	1032 (100.0)
Mean (SD)	12.1 (2.37)	12.0 (2.43)	12.1 (2.57)	12.4 (2.42)	12.2 (2.45)
Median	12.1	12.2	12.1	12.3	12.3
Number (%) in specified exposure range					
<4 weeks	3 (1.0)	2 (1.3)	4 (1.4)	2 (0.7)	11 (1.1)
≥4 weeks and <8 weeks	14 (4.8)	10 (6.3)	12 (4.2)	10 (3.4)	46 (4.5)
≥8 weeks and <12 weeks	57 (19.6)	31 (19.4)	49 (17.0)	51 (17.4)	188 (18.2)
≥12 weeks	217 (74.6)	117 (73.1)	223 (77.4)	230 (78.5)	787 (76.3)
Number of doses taken					
n	282	154	283	282	1001
Mean (SD)	17.5 (7.64)	18.6 (9.35)	19.3 (9.22)	19.2 (8.12)	18.6 (8.53)
Median	16.0	17.0	17.0	18.0	17.0
Number of times study drug taken within 24 hrs of previous dose					
n	158	88	151	152	549
Mean (SD)	3.1 (3.56)	4.1 (4.41)	3.7 (4.74)	2.9 (3.21)	3.4 (3.99)
Number (%) who took 2 doses within 24 hours					
1 time to ≤5 times	135 (46.4)	67 (41.9)	127 (44.1)	132 (45.1)	461 (44.7)
5 times to ≤10 times	15 (5.2)	11 (6.9)	11 (3.8)	14 (4.8)	51 (4.9)
10 times to ≤20 times	7 (2.4)	9 (5.6)	11 (3.8)	6 (2.0)	33 (3.2)
20 times to ≤30 times	1 (0.3)	1 (0.6)	1 (0.3)	0 (0.0)	3 (0.3)
≥30 times	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Data from studies TA-301 and TA-302 are included.

1. Duration of exposure is the number of weeks between the first drug dispense date and the study termination or completion date.

SD = standard deviation.

Overall, with two Phase 3 studies, the mean total number of doses taken was 18.6: 17.5 doses for the placebo group, 18.6 doses for the avanafil 50 mg group, 19.3 doses for the avanafil 100 mg group, and 19.2 doses for the avanafil 200 mg group.

In total, 549 of the 1032 (53.2%) subjects in the Phase 3 double-blind cohort took two doses of study drug within 24 hours: 158 of the 291 (54.3%) subjects in the placebo group, 88 of the 160 (55.0%) subjects in the avanafil 50 mg group, 151 of the 288 (52.4%) subjects in the avanafil 100 mg group, and 152 of the 293 (51.9%) subjects in the avanafil 200 mg group. For these 549 subjects, the mean number of times during the study that two doses were taken within 24 hours was 3.4. Overall, 461 (44.7%) subjects took two doses of study drug within 24 hours >1 and ≤5 times during the study; 51 (4.9%) subjects took two doses of study drug within 24 hours >5 and ≤10 times during the study; 33 (3.2%) subjects took two doses of study drug within 24 hours >10 and ≤20 times during the study; 3 (0.3%) subjects took two doses of study drug within 24 hours >20 and ≤30 times during the study; and 1 (0.1%) subject took two doses of study drug within 24 hours ≥30 times during the study.

Reviewer's Comment: (b) (4)

7.2.1.2.2 Individual Phase 3, Open-label, Long term Study TA-314

Table 7.2.1.2 summarizes the duration of exposure for the Safety Population in study TA-314 by TA-314 titration dose. The mean duration of exposure to avanafil was 35.3 weeks, and the median duration of exposure was 38.1 weeks. 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). Mean and median duration of exposure were longer for subjects who received avanafil 100 mg and 200 mg (as part of a titration regimen) than for subjects who received avanafil 100 mg only.

Table 7.2.1.3 Summary of Duration of Exposure by TA-314 Titration Dose – TA-314 Safety Population

	TA-314 100 mg only (N=171)	TA-314 100 & 200 mg (N=536)	TA-314 Other (N=5)	Total (N=712)
Duration of exposure (weeks) [1]				
n	171	536	5	712
Mean (SD)	28.6 (17.19)	37.4 (14.01)	34.4 (22.04)	35.3 (15.33)
Median	24.3	39.0	40.7	38.1
Number (%) in specified exposure range				
<3 months (12 weeks)	27 (15.8)	27 (5.0)	1 (20.0)	55 (7.7)
≥3 months (12 weeks) and <6 months (26 weeks)	62 (36.3)	101 (18.8)	1 (20.0)	164 (23.0)
≥6 months (26 weeks) and <9 months (38 weeks)	22 (12.9)	94 (17.5)	0 (0.0)	116 (16.3)
≥9 months (38 weeks) and <12 months (52 weeks)	28 (16.4)	195 (36.4)	1 (20.0)	224 (31.5)
≥12 months (52 weeks)	32 (18.7)	119 (22.2)	2 (40.0)	153 (21.5)

1. Duration of exposure is the number of weeks between the first drug dispense date and the study termination or completion date. The summary includes treatment in the qualifying period. For subjects who received placebo in the qualifying study, the first drug dispense date is the first drug dispense date in TA-314.

SD = standard deviation.

Overall, the mean total number of doses taken was 68.6: 47.5 doses for subjects who received avanafil 100 mg only during this study; 75.4 doses for subjects who received avanafil 100 mg and 200 mg during this study; and 58.2 doses for other subjects (i.e., subjects who received avanafil 100 mg and 50 mg and subjects who received all three doses of avanafil).

In total, 536 (75.3%) subjects were dispensed avanafil 100 mg and 200 mg during study TA-314; 171 (24.0%) subjects were dispensed avanafil 100 mg only; 3 (0.4%) subjects were dispensed avanafil 100 mg and 50 mg; 1 (0.1%) subject was dispensed all three doses of avanafil; and 1 (0.1%) subject was not dispensed study drug during this study.

7.2.1.1.3 Additional Phase 3 Double-blind Study – Study TA-303 (submitted with the 120-Day Safety Update)

TA-303 was a Phase 3, randomized, double-blind, placebo-controlled, parallel study in men with ED status post radical prostatectomy for prostate cancer. Table 7.2.1.4 summarizes the duration of exposure for the TA-303 safety population. The mean duration of exposure was 13.0 weeks, and the median duration of exposure was 12.6 weeks. The duration of exposure to study drug was similar across treatment groups. For the majority of subjects in each treatment group, the duration of exposure was ≥12 weeks.

Table 7.2.1.4 Summary of Duration of Exposure – TA-303 – Safety Population

	Placebo (n = 100)	Avanafil 100 mg (n = 99)	Avanafil 200 mg (n = 99)	Total (n = 298)
Duration of exposure (weeks) [1]				
n	100	99	99	298
Mean (SD)	12.7 (3.56)	13.2 (5.19)	13.2 (2.49)	13.0 (3.90)
Median	12.3	12.4	12.9	12.6
Number (%) in specified exposure range				
< 4 weeks	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
≥ 4 weeks and < 8 weeks	5 (5.0)	7 (7.1)	1 (1.0)	13 (4.4)
≥ 8 weeks and < 12 weeks	28 (28.0)	11 (11.1)	10 (10.1)	49 (16.4)
≥ 12 weeks and < 16 weeks	60 (60.0)	70 (70.7)	76 (76.8)	206 (69.1)
≥ 16 weeks	7 (7.0)	10 (10.1)	11 (11.1)	28 (9.4)

1. uration of exposure (weeks) = (study termination or completion date – first drug dispense date + 1)/7.
SD = standard deviation.

The mean number of doses of study drug was 16.2, and the median number of doses was 14.0. Overall mean time on treatment, or the time between the first dose and last dose, was 10.8 weeks; and overall median time on treatment was 11.3 weeks. The time on treatment was similar across treatment groups.

7.2.1.1.4 Phase 1 Studies

In total, in all Phase 1 studies combined, 621 subjects were exposed to avanafil: 83 subjects received a dose of avanafil ≤50 mg, 73 subjects received avanafil 100 mg, 462 subjects received avanafil 200 mg, and 80 subjects received a dose of avanafil >200 mg.

Table 7.2.1.5 Number of Subjects Exposed to Study Drug During the Phase 1 Program

	Placebo	Avanafil ≤50 mg	Avanafil 100 mg	Avanafil 200 mg	Avanafil >200 mg	Total Avanafil
HP-01	16	18	7	6	18	49
TA-02	12	12	12	12	–	36
TA-04	97	–	–	102	–	102
TA-07	–	–	–	15	–	15
TA-010	–	–	–	–	6	6
TA-011	–	29	–	15	–	44
TA-012	–	–	–	24	–	24
TA-013	–	–	–	24	–	24
TA-014	–	–	–	32	–	32
TA-015	15	–	–	14	–	14
TA-016	24	–	–	23	–	23
TA-017	48	–	–	48	–	48
TA-018	–	–	–	59	–	59
TA-019	47	–	–	48	–	48
TA-020	–	24	–	23	–	24
TA-021	17	–	–	17	–	17
TA-140	54	–	54	–	56	56
Total	330	83	73	462	80	621

Sources: HP-01 CSR, TA-02 CSR, TA-04 CSR, TA-07 CSR, TA-010 CSR, TA-011 CSR, TA-012 CSR, TA-013 CSR, TA-014 CSR, TA-015 CSR, TA-016 CSR, TA-017 CSR, TA-018 CSR, TA-019 CSR, TA-020 CSR, TA-021 CSR, TA-140 CSR

7.2.1.1.5 Exposure during the Clinical Development Program

Table 7.2.1.6 Summary of Avanafil Exposure During the Clinical Development Program (excludes the Phase 1 studies and Phase 3 study TA-303)

		Total Exposure	Avanafil Exposure					Placebo
			Total	≤ 50 mg [1]	100 mg	200 mg	300-800 mg [2]	
Phase 1 Studies								
Total	17 Phase 1 Studies	**657**	**621**	**83**	**73**	**462**	**80**	**330**
Phase 2 Studies								
TA-01	Visual stimulation (cross-over study)	83	82	27	27	28	NA	82
TA-03	Home administration (crossover)	49	49	NA	NA	49	NA	NA
TA-05	Safety and efficacy	284	229	56	60	56	57	55
Total		**416**	**360**	**83**	**87**	**133**	**57**	**137**
Phase 3 Studies								
TA-301	Generalized ED	644	483	160	161	162	NA	161
TA-302	Subjects with diabetes	388	258	NA	127	131	NA	130
TA-314	Open-label, long-term roll over from TA-301 & TA-302		201 [3]	–	–	–	NA	NA
Total		**1032**	**942**	**160**	**288**	**293**	**0**	**291**
Program TOTAL		**2105**	**1923**	**326**	**448**	**888**	**137**	**758**

1. Column includes subjects who received avanafil 50 mg in Phase 2 and Phase 3 studies and subjects who received avanafil doses ≤50 mg in Phase 1 studies.
2. Column includes subjects who received avanafil 300 mg in Phase 2 and Phase 3 studies and subjects who received avanafil 300 mg to 800 mg in Phase 1 studies.
3. Subjects who received placebo in studies TA-301 and TA-302 received avanafil in study TA-314.

Reviewer's Comment: This reviewer believes that for NDA 202276, the total population exposure requirement is sufficient, including the long term exposure.

7.2.1.2 Subject Disposition, Demographics and Other Characteristics of Study Populations

7.2.1.2.1 Integrated Double-Blind Cohort (TA-301, TA-302, TA-05)

Table 7.2.1.7 Subject Disposition – Double-Blind Cohort (TA-301. TA-302, TA-05)

	Placebo n (%)	Avanafil 50 mg n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Randomized	349	217 (100.0)	349 (100.0)	352 (100.0)	1267 (100.0)
Completed study	290 (83.1)	179 (82.5)	305 (87.4)	307 (87.2)	1081 (85.3)
Discontinued from study	59 (16.9)	38 (17.5)	44 (12.6)	45 (12.8)	186 (14.7)
Protocol non-compliance [1]	30 (8.6)	16 (7.4)	23 (6.6)	18 (5.1)	87 (6.9)
Subject lost to follow-up	11 (3.2)	11 (5.1)	8 (2.3)	15 (4.3)	45 (3.6)
Adverse event	6 (1.7)	3 (1.4)	7 (2.0)	7 (2.0)	23 (1.8)
Subject or partner request	9 (2.6)	6 (2.8)	4 (1.1)	4 (1.1)	23 (1.8)
Requirement for restricted medication	1 (0.3)	2 (0.9)	1 (0.3)	0 (0.0)	4 (0.3)
Death [3]	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Improper enrollment [2]	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lack of efficacy [2]	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Data from studies TA-05, TA-301, and TA-302 are included.
Percentages are based on the number of randomized subjects in a treatment group.
1. The category of protocol non-compliance includes subjects who withdrew consent or discontinued due to improper enrollment or due to lack of efficacy in studies TA-301 and TA-302.
2. The categories of subject or partner request, improper enrollment, and lack of efficacy apply only to study TA-05.
3. A subject who discontinued from the study due to a fatal adverse event is summarized under the category of death.

Table 7.2.1.6 summarizes subject disposition for the double-blind cohort in Studies TA-05, TA-301 and TA-302. In total, 1267 subjects were assigned randomly to treatment in the double-blind cohort. Of these 1267 subjects, 1081 (85.3%) subjects completed the study and 186 (14.7%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was slightly higher in the placebo group (16.9%) and avanafil 50 mg group (17.5%) than the avanafil 100 mg group (12.6%) and avanafil 200 mg group (12.8%). The most common reasons for discontinuation were protocol non-compliance (which also includes subjects who withdrew consent or were discontinued due to improper enrollment or lack of efficacy in studies TA-301 and TA-302) (6.9%), loss to follow-up (3.6%), adverse event (1.8%), and subject or partner request (1.8%).

Reviewer's comment: The Sponsor included patients who discontinued due to "lack of efficacy" in the category of "non-compliance". This is suboptimal, but only applies to very few patients and only Study TA-05.

Table 7.2.1.7 summarizes demographic and baseline characteristics for the double-blind cohort in Studies TA-05, TA-301 and TA-302. The majority of subjects were White (83.9%). The mean age of subjects was 56.4 years. Overall, the erectile dysfunction severity was mild for 32.5% of subjects, moderate for 36.5% of subjects, and severe for 31.0% of subjects. The mean baseline IIEF erectile function domain score was 13.0. The proportion of subjects with a duration of erectile dysfunction < 24 months was lower than the proportions of subjects with a duration of erectile dysfunction ≥ 24 months and < 60 months and subjects with a duration of erectile dysfunction ≥ 60 months. Overall, 30.6% of subjects had diabetes at baseline; no subject in the

avanafil 50 mg group had diabetes as this treatment was used in study TA-301 which excluded subjects with diabetes. In general, the treatment groups were comparable with respect to demographic and baseline characteristics.

Table 7.2.1.8 Demographic and Baseline Characteristics – Double-Blind Cohort (Safety Population)

	Placebo (N=349)	Avanafil 50 mg (N=217)	Avanafil 100 mg (N=349)	Avanafil 200 mg (N=352)	Total (N=1267)
Age (years) [1]					
n	349	217	349	352	1267
Mean (SD)	56.6 (9.90)	55.0 (10.37)	57.0 (9.72)	56.6 (10.00)	56.4 (9.97)
Minimum - Maximum	23 - 78	29 - 83	23 - 88	24 - 80	23 - 88
Age category n (%)					
<50 years	88 (25.2)	66 (30.4)	94 (26.9)	83 (23.6)	331 (26.1)
≥50 years and <65 years	178 (51.0)	116 (53.5)	169 (48.4)	186 (52.8)	649 (51.2)
≥65 years	83 (23.8)	35 (16.1)	86 (24.6)	83 (23.6)	287 (22.7)
Race n (%)					
White	288 (82.5)	181 (83.4)	300 (86.0)	294 (83.5)	1063 (83.9)
Black	54 (15.5)	30 (13.8)	44 (12.6)	47 (13.4)	175 (13.8)
Asian	3 (0.9)	3 (1.4)	4 (1.1)	5 (1.4)	15 (1.2)
Hispanic	1 (0.3)	3 (1.4)	0 (0.0)	4 (1.1)	8 (0.6)
Multiple	2 (0.6)	0 (0.0)	1 (0.3)	1 (0.3)	4 (0.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Ethnicity n (%) [2]					
Hispanic or Latino	46 (13.2)	28 (12.9)	53 (15.2)	55 (15.6)	182 (14.4)
Not Hispanic or Latino	245 (70.2)	132 (60.8)	235 (67.3)	238 (67.6)	850 (67.1)
Weight (kg)					
n	349	217	349	351	1266
Mean (SD)	94.6 (18.76)	92.5 (18.91)	94.6 (16.98)	94.2 (17.69)	94.1 (18.01)
Height (cm)					
n	349	217	349	352	1267
Mean (SD)	178.3 (7.29)	178.5 (7.41)	177.9 (7.39)	177.9 (7.58)	178.1 (7.41)
Body mass index (kg/m^2)					
n	349	217	349	351	1266
Mean (SD)	29.7 (5.42)	29.0 (5.24)	29.9 (4.94)	29.8 (5.16)	29.7 (5.19)
Erectile dysfunction severity n (%)					
Mild	111 (31.8)	81 (37.3)	110 (31.5)	110 (31.3)	412 (32.5)
Moderate	125 (35.8)	84 (38.7)	125 (35.8)	128 (36.4)	462 (36.5)
Severe	113 (32.4)	52 (24.0)	114 (32.7)	114 (32.4)	393 (31.0)
Erectile dysfunction duration (months) [3]					
n	349	217	349	352	1267
Mean (SD)	75.2 (65.00)	75.6 (66.76)	78.8 (74.54)	67.7 (51.33)	74.2 (64.79)
Erectile dysfunction duration					
<24 months	54 (15.5)	29 (13.4)	49 (14.0)	44 (12.5)	176 (13.9)
≥24 months and <60 months	118 (33.8)	78 (35.9)	129 (37.0)	138 (39.2)	463 (36.5)
≥60 months	177 (50.7)	110 (50.7)	171 (49.0)	170 (48.3)	628 (49.6)
Baseline IIEF erectile function					
n	349	217	349	352	1267
Mean (SD)	12.6 (5.18)	13.7 (5.03)	12.7 (5.22)	13.0 (5.10)	13.0 (5.15)

Diabetic status n (%)					
Subjects with diabetes	130 (37.2)	0 (0.0)	127 (36.4)	131 (37.2)	388 (30.6)
Subjects without diabetes	219 (62.8)	217 (100.0)	222 (63.6)	221 (62.8)	879 (69.4)
Type of diabetes n (%)					
Type 1	14 (4.0)	0 (0.0)	15 (4.3)	12 (3.4)	41 (3.2)
Type 2	116 (33.2)	0 (0.0)	112 (32.1)	119 (33.8)	347 (27.4)
Smoking status n (%) [2]					
Current	64 (18.3)	30 (13.8)	45 (12.9)	52 (14.8)	191 (15.1)
History	88 (25.2)	46 (21.2)	110 (31.5)	86 (24.4)	330 (26.0)
Never	139 (39.8)	84 (38.7)	133 (38.1)	155 (44.0)	511 (40.3)

Data from studies TA-05, TA-301, and TA-302 are included. Baseline was defined as the observation at Visit 2 (end of run-in).

1. Age was calculated according to the date of informed consent.
2. Only includes data from studies TA-301 and TA-302.
3. For studies TA-301 and TA-302, the duration of erectile dysfunction was calculated according to the date of informed consent. For study TA-05, the duration of erectile dysfunction was calculated as (the number of reported years of erectile dysfunction × 12) + the number of reported months of erectile dysfunction.

IIEF = International Index of Erectile Function; SD = standard deviation.

Table 7.2.1.7 presents the numbers and percentages of subjects in the double-blind cohort who a history of medical conditions in categories of special interest. In total, 543 (42.9%) subjects reported a history of hypertension, 157 (12.4%) subjects reported a history of other cardiovascular disease, 145 (11.4%) subjects reported a history of coronary artery disease, and 130 (10.3%) subjects reported a history of depression. A higher proportion of subjects in the avanafil 50 mg group reported a history of depression than in the other treatment groups. A lower proportion of subjects in the avanafil 50 mg group reported a history of hypertension and a history of coronary artery disease than in the other treatment groups, which is likely due to the fact that study TA-302, which evaluated subjects with diabetes who have a higher risk for these co-morbidities, did not include an avanafil 50 mg dose group.

Table 7.2.1.9 Summary of Medical History of Special Interest – Double-Blind Cohort

Medical History Category	Placebo (N=349) n (%)	Avanafil 50 mg (N=217) n (%)	Avanafil 100 mg (N=349) n (%)	Avanafil 200 mg (N=352) n (%)	Total (N=1267) n (%)
Hypertension	156 (44.7)	62 (28.6)	164 (47.0)	161 (45.7)	543 (42.9)
Other cardiovascular disease	36 (10.3)	21 (9.7)	53 (15.2)	47 (13.4)	157 (12.4)
Coronary artery disease	41 (11.7)	14 (6.5)	40 (11.5)	50 (14.2)	145 (11.4)
Depression	35 (10.0)	31 (14.3)	33 (9.5)	31 (8.8)	130 (10.3)
Anxiety	14 (4.0)	19 (8.8)	23 (6.6)	16 (4.5)	72 (5.7)
Transurethral resection of the prostate	5 (1.4)	1 (0.5)	8 (2.3)	4 (1.1)	18 (1.4)

Table 7.2.1.8 presents the numbers and percentages of subjects in the double-blind cohort who took concomitant medications in categories of special interest. In total, 499 (39.4%) subjects took antihypertensives, 96 (7.6%) subjects took antidepressants, and 74 (5.8%) subjects took α-blockers. Consistent with proportions of subjects with a medical history of hypertension, a lower proportion of subjects in the avanafil 50 mg group took antihypertensives than in the other treatment groups. Consistent with the proportions of subjects with a medical history of depression, a higher proportion of subjects in the avanafil 50 mg group took antidepressants than

in the other treatment groups. The proportion of subjects who took α-blockers was similar in each treatment group.

Table 7.2.1.10 Number (%) of Subjects Who Took Concomitant Medications in Categories of Special Interest – Double-Blind Cohort (TA-301, TA-302, TA-05)

Category	Placebo (N=349) n (%)	Avanafil 50 mg (N=217) n (%)	Avanafil 100 mg (N=349) n (%)	Avanafil 200 mg (N=352) n (%)	Total (N=1267) n (%)
Antihypertensives	134 (38.4)	52 (24.0)	162 (46.4)	151 (42.9)	499 (39.4)
Antidepressants	25 (7.2)	27 (12.4)	25 (7.2)	19 (5.4)	96 (7.6)
α-blockers	18 (5.2)	10 (4.6)	25 (7.2)	21 (6.0)	74 (5.8)

7.2.1.2.2 Integrated Phase 3 Double-Blind Cohort Only (TA-301 and TA-302)

Table 7.2.1.9 summarizes subject disposition for the Phase 3 double-blind cohort. In total, 1032 subjects were assigned randomly to treatment in the Phase 3 double-blind cohort. Of these 1032 subjects, 883 (85.6%) subjects completed the study and 149 (14.4%) 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 were protocol non-compliance (which also includes subjects who withdrew consent) (8.2%), loss to follow-up (3.6%), and adverse event (2.0%).

Table 7.2.1.11 Subject Disposition – Phase 3 Double-Blind Cohort Only (TA-301+TA-302)

	Placebo n (%)	Avanafil 50 mg n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Randomized	291 (100.0)	160 (100.0)	288 (100.0)	293 (100.0)	1032 (100.0)
Completed study	247 (84.9)	131 (81.9)	250 (86.8)	255 (87.0)	883 (85.6)
Discontinued from study	44 (15.1)	29 (18.1)	38 (13.2)	38 (13.0)	149 (14.4)
Protocol non-compliance [1]	30 (10.3)	15 (9.4)	23 (8.0)	17 (5.8)	85 (8.2)
Subject lost to follow-up	8 (2.7)	9 (5.6)	6 (2.1)	14 (4.8)	37 (3.6)
Adverse event	5 (1.7)	3 (1.9)	7 (2.4)	6 (2.0)	21 (2.0)
Requirement for restricted medication	1 (0.3)	2 (1.3)	1 (0.3)	0 (0.0)	4 (0.4)
Death	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)

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

The Sponsor reported that the following three aspects were similar between the Phase 3 double blind cohort (TA–301 + TA–302) and the double blind cohort (TA– 301 + TA– 02+ TA–05): demographic and baseline characteristics; the numbers and percentages of subjects who reported a history of medical conditions in categories of special interest; and the numbers and percentages of subjects who took concomitant medications in categories of special interest.

7.2.1.2.3 Individual Phase 3, Open-label, Long-term Study TA-314

Reference ID: 3117872

Table 7.2.1.10 summarizes subject disposition by TA-314 titration dose. In total, 712 subjects enrolled in the study. All 712 enrolled subjects came from the qualifying study TA-301 or study TA-302. Of the 712 enrolled subjects, 492 (69.1%) subjects completed the study and 220 (30.9%) subjects discontinued from the study. After enrolling a sufficient number of subjects to ensure that at least 300 subjects would be exposed to avanafil for 6 months and at least 100 subjects would be exposed to avanafil for at least 12 months, the Sponsor made the decision to close enrollment in December 2009. Subjects who were discontinued at the Sponsor's request were considered to have completed the study and an end-of-study visit was performed. The primary reasons for discontinuation from the study were subject withdrawal of consent (13.8%), subject lost to follow-up (9.4%), protocol non-compliance (4.2%), and adverse event (2.8%). The percentage of subjects who discontinued from the study was lower among those who received avanafil 100 mg and 200 mg (25.9%) than among those who received avanafil 100 mg only (46.2%). Discontinuations due to adverse events were also lower among those who received avanafil 100 mg and 200 mg (1.5%) than among those who received avanafil 100 mg only (6.4%).

Table 7.2.1.12 Subject Disposition by TA-314 Titration Dose – TA-314 – All Enrolled Subjects

	TA-314 100 mg only n (%)	TA-314 100 & 200 mg n (%)	TA-314 Other n (%)	Total n (%)
Enrolled [1]	171	536	5	712
Completed study	92 (53.8)	397 (74.1)	3 (60.0)	492 (69.1)
Discontinued from study	79 (46.2)	139 (25.9)	2 (40.0)	220 (30.9)
Subject withdrew consent	23 (13.5)	75 (14.0)	0 (0.0)	98 (13.8)
Subject lost to follow-up	31 (18.1)	36 (6.7)	0 (0.0)	67 (9.4)
Protocol non-compliance	12 (7.0)	18 (3.4)	0 (0.0)	30 (4.2)
Adverse event	11 (6.4)	8 (1.5)	1 (20.0)	20 (2.8)
Investigator decision	2 (1.2)	1 (0.2)	0 (0.0)	3 (0.4)
Enrollment failure	0 (0.0)	0 (0.0)	1 (20.0)	1 (0.1)
Other	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
Safety Population [2]	171 (100.0)	536 (100.0)	5 (100.0)	712 (100.0)

1. Subjects who enrolled in the study include all subjects who signed the informed consent form.
2. The Safety Population includes all roll-over subjects who signed the informed consent form. Subjects were assumed to have dosed if they returned fewer tablets of study drug than were dispensed. Four subjects (Subjects 103-008, 136-025, 215-054, and 236-024) did not take study drug in TA-314 but are included in the Safety Population.

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Table 7.2.1.13 Demographic & Baseline Characteristics by TA-314 Titration Dose – All Enrolled Subjects

	TA-314 100 mg only (N=171)	TA-314 100 &200 mg (N=536)	TA-314 Other (N=5)	Total (N=712)
Age (years)				
n	171	536	5	712
Mean (SD)	54.2 (10.87)	57.1 (9.87)	55.8 (11.65)	56.4 (10.19)
Minimum, maximum	23 , 88	28 , 83	37 , 68	23, 88
Age category n (%)				
<50 years	61 (35.7)	123 (22.9)	1 (20.0)	185 (26.0)
≥50 years and <65 years	79 (46.2)	282 (52.6)	3 (60.0)	364 (51.1)
≥65 years	31 (18.1)	131 (24.4)	1 (20.0)	163 (22.9)
Race n (%)				
White	147 (86.0)	459 (85.6)	4 (80.0)	610 (85.7)
Black, of African heritage, or African American	20 (11.7)	73 (13.6)	1 (20.0)	94 (13.2)
Asian	3 (1.8)	4 (0.7)	0 (0.0)	7 (1.0)
Multiple	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.1)
Ethnicity n (%)				
Hispanic or Latino	47 (27.5)	67 (12.5)	0 (0.0)	114 (16.0)
Not Hispanic or Latino	124 (72.5)	469 (87.5)	5 (100.0)	598 (84.0)
Weight (kg)				
n	171	536	5	712
Mean (SD)	93.0 (19.47)	95.3 (18.57)	79.3 (13.42)	94.6 (18.81)
Height (cm)				
n	171	536	5	712
Mean (SD)	177.5 (7.80)	178.6 (7.36)	174.9 (3.24)	178.3 (7.46)
Body mass index (kg/m^2)				
n	171	536	5	712
Mean (SD)	29.5 (5.95)	29.8 (5.34)	25.9 (3.69)	29.7 (5.49)
Erectile dysfunction severity n (%)				
Mild	64 (37.4)	142 (26.5)	1 (20.0)	207 (29.1)
Moderate	59 (34.5)	177 (33.0)	2 (40.0)	238 (33.4)
Severe	48 (28.1)	217 (40.5)	2 (40.0)	267 (37.5)
Erectile dysfunction duration (months)				
n	171	536	5	712
Mean (SD)	63.7 (58.61)	79.8 (72.34)	78.4 (39.09)	75.9 (69.39)
ED duration category n (%)				
<24 months	38 (22.2)	65 (12.1)	0 (0.0)	103 (14.5)
≥24 months and <60 months	65 (38.0)	186 (34.7)	2 (40.0)	253 (35.5)
≥60 months	68 (39.8)	285 (53.2)	3 (60.0)	356 (50.0)
Baseline IIEF ED domain score				
n	171	536	5	712
Mean (SD)	13.5 (5.16)	11.9 (5.01)	9.8 (3.42)	12.2 (5.09)
Type of diabetes n (%)				

Type 1	6 (3.5)	14 (2.6)	0 (0.0)	20 (2.8)
Type 2	57 (33.3)	148 (27.6)	1 (20.0)	206 (28.9)
Diabetes duration (years)				
n	63	162	1	226
Mean (SD)	11.9 (9.17)	10.9 (9.19)	4.6	11.1 (9.17)
Smoking status n (%)				
Current	33 (19.3)	105 (19.6)	0 (0.0)	138 (19.4)
History	43 (25.1)	181 (33.8)	1 (20.0)	225 (31.6)
Never	95 (55.6)	250 (46.6)	4 (80.0)	349 (49.0)

Baseline was defined as the last available measurement prior to the first dose of study drug in the qualifying study.
Age and duration of erectile dysfunction and diabetes were calculated from informed consent for the qualifying study.
IIEF = International Index of Erectile Function; SD = standard deviation.

7.2.1.2.4 Supportive Phase 2 Studies

Phase 2 Study TA-01: In total, 89 subjects were randomly assigned to treatment: 83 subjects received study drug and were included in the safety analyses and 6 subjects discontinued from the study prior to receiving study drug. Of the 83 subjects who received study drug, 82 subjects completed the study and 1 subject requested to be withdrawn from the study. The majority of subjects in study TA-01 were Caucasian (67.5%). The mean age of subjects was 51.5 years. The proportion of subjects who assessed their ED as moderate (81.9%) was higher than the proportions of subjects who assessed their ED as minimal (16.9%) or complete (1.2%). At baseline, mean duration of ED was 58.1 months.

Phase 2 Study TA-03: In total, 51 subjects were randomly assigned to treatment. Of the 51 randomized subjects, 47 (92.2%) subjects completed the study and 4 (7.8%) subjects discontinued from the study. The reasons for discontinuation from the study were protocol non-compliance (5.9%) and withdrawal by subject (2.0%). In total, 49 (96.1%) subjects received at least one dose of study drug and were included in the safety analyses. The majority of subjects in study TA-03 were Caucasian (75.5%). The mean age of subjects was 55.9 years. The proportion of subjects who assessed their ED as moderate (91.8%) was higher than the proportions of subjects who assessed their ED as minimal (6.1%) or complete (2.0%). At baseline, mean duration of ED was 87.8 months.

7.2.1.2.5 Individual Phase 3 Double-blind Study TA-303 (120-Day Safety Update)

For Study TA-303, conducted in men who had undergone radical prostatectomy, and submitted with the 120-day safety update, the mean age of subjects was 58.4 years. The majority of subjects were White (81.5%). Across all treatment groups, the erectile dysfunction severity at baseline was mild for 9.1% of subjects, moderate for 19.5% of subjects, and severe for 71.5% of subjects. At baseline, the mean duration of post-surgery erectile dysfunction for all subjects was 18.7 months. The mean duration of erectile dysfunction was similar between the treatment groups. The majority of subjects had robotic surgical technique for their radical prostatectomy (80.5%). Overall, the treatment groups were comparable with respect to demographic and baseline characteristics.

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Table 7.2.1.14 Demographic and Baseline Characteristics – TA-303 – Randomized Population

	Placebo (N=100)	Avanafil 100 mg (N=99)	Avanafil 200 mg (N=99)	Total (N=298)
Age (years) [1]				
n	100	99	99	298
Mean (SD)	58.6 (5.87)	58.9 (5.88)	57.7 (6.60)	58.4 (6.13)
Minimum, maximum	40, 70	46, 69	42, 69	40, 70
Race n (%)				
White	84 (84.0)	83 (83.8)	76 (76.8)	243 (81.5)
Black	16 (16.0)	16 (16.2)	22 (22.2)	54 (18.1)
Unknown	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Ethnicity n (%)				
Hispanic or Latino	4 (4.0)	4 (4.0)	6 (6.1)	14 (4.7)
Not Hispanic or Latino	96 (96.0)	95 (96.0)	93 (93.9)	284 (95.3)
Weight (kg)				
n	100	99	99	298
Mean (SD)	88.4 (13.91)	89.7 (13.00)	91.1 (14.50)	89.7 (13.82)
Height (cm)				
n	100	99	99	298
Mean (SD)	178.6 (7.28)	178.7 (7.50)	179.0 (7.73)	178.7 (7.48)
Body mass index (kg/m^2)				
n	100	99	99	298
Mean (SD)	27.7 (3.42)	28.1 (3.93)	28.4 (3.94)	28.1 (3.77)
Erectile dysfunction severity n (%)				
Mild	8 (8.0)	7 (7.1)	12 (12.1)	27 (9.1)
Moderate	22 (22.0)	17 (17.2)	19 (19.2)	58 (19.5)
Severe	70 (70.0)	75 (75.8)	68 (68.7)	213 (71.5)
Erectile dysfunction duration (months) [1]				
n	100	99	99	298
Mean (SD)	18.0 (10.89)	19.8 (15.36)	18.4 (13.03)	18.7 (13.19)
Type of radical prostatectomy surgical technique				
Open	14 (14.0)	19 (19.2)	9 (9.1)	42 (14.1)
Robotic	83 (83.0)	76 (76.8)	81 (81.8)	240 (80.5)
Laparoscopic	3 (3.0)	4 (4.0)	9 (9.1)	16 (5.4)

Reviewer's comments: In this study compared to the others, more patients had severe ED, and the mean weight was lower.

According to the 120-day safety update, in total 528 subjects were enrolled in the study TA-303, and 298 subjects were assigned randomly to treatment. Of the 298 randomized subjects, 252 (84.6%) subjects completed the study and 46 (15.4%) subjects discontinued from the study. A higher percentage of subjects in the placebo group discontinued from the study compared to either of the avanafil 100 mg or 200 mg treatment groups. The reasons for discontinuation from the study were withdrew consent (7.7%), subject lost to follow-up (3.4%), protocol non-compliance (2.3%), adverse event (1.7%), and other reason (0.3%).

Table 7.2.1.15 Subject Disposition – TA-303 – All Enrolled Subjects

	Placebo n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Enrolled [1]				528
Randomized	100 (100.0)	99 (100.0)	99 (100.0)	298 (100.0)
Completed study	76 (76.0)	85 (85.9)	91 (91.9)	252 (84.6)
Discontinued from study	24 (24.0)	14 (14.1)	8 (8.1)	46 (15.4)
Withdrew consent	14 (14.0)	7 (7.1)	2 (2.0)	23 (7.7)
Subject lost to follow-up	5 (5.0)	4 (4.0)	1 (1.0)	10 (3.4)
Protocol non-compliance	3 (3.0)	1 (1.0)	3 (3.0)	7 (2.3)
Adverse event	1 (1.0)	2 (2.0)	2 (2.0)	5 (1.7)
Other	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Safety Population [2]	100 (100.0)	99 (100.0)	99 (100.0)	298 (100.0)

1. Subjects who enrolled in the study include all subjects who signed the informed consent form.
2. The Safety Population includes all subjects who received at least 1 dose of study drug and had any safety data available. Subjects were assumed to have dosed if they returned fewer tablets of study drug than were dispensed. Subjects were included in the treatment group reflective of the treatment they actually received, if different from the randomized treatment. A subject was summarized by the first active treatment group received if that subject received study drug from more than one treatment group.

7.2.1.2.6 Phase 1 Studies

Subject disposition and demographic and baseline characteristics in various phase 1 studies were reviewed and were found to be acceptable. The reader is referred to the Clinical Pharmacologist's review, as details are not included in this review.

Reviewer's comment: The demographic and other characteristics of the study populations are acceptable.

7.2.2 Explorations for Dose Response

No special pre-designed explorations for dose-response were planned and conducted, however, details of dose response on both of efficacy and safety have been reviewed and analyzed in this clinical review.

7.2.3 Special Animal and/or In Vitro Testing

No special animal as well as in vitro testing were planned and conducted during the clinical development.

7.2.4 Routine Clinical Testing

Details of outine clinical testing incluing various clinical laboratory tests are reviewed in the related sections, are adequate.

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7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacologist's review for details concerning avanafil metabolism and clearance, as well as for the drug-drug interaction workup. These issues are reviewed in great detail by the primary clinical pharmacologist in the separate review. In later sections of this primary medical officer's review, information is provided on the clinical impact of the pharmacodynamic drug interactions, such as with nitroglycerin, alpha blockers and alcohol.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse reactions for similar drugs in the class of PDE5 inhibitor were evaluated and no exceptions are determined. The adverse reaction profile for avanafil is consistent with all marketed PDE5 inhibitors.

7.3 Major Safety Results

Table 7.3.1 Overview of Adverse Events – Double-Blind Cohort (TA-05+TA-301+TA-302)

	Placebo (N=349) n (%)	Avanafil				Total (N=1267) n (%)
		50 mg (N=217 n (%)	100 mg (N=349) n (%)	200 mg (N=352) n (%)	Total (N=918) n (%)	
Subjects with TEAEs						
Any TEAE	89 (25.5)	68 (31.3)	140 (40.1)	128 (36.4)	336 (36.6)	425 (33.5)
Any drug-related TEAE	15 (4.3)	23 (10.6)	50 (14.3)	61 (17.3)	134 (14.6)	149 (11.8)
Maximum severity of TEAEs						
Mild	51 (14.6)	41 (18.9)	77 (22.1)	75 (21.3)	193 (21.0)	244 (19.3)
Moderate	34 (9.7)	25 (11.5)	54 (15.5)	49 (13.9)	128 (13.9)	162 (12.8)
Severe	4 (1.1)	2 (0.9)	9 (2.6)	4 (1.1)	15 (1.6)	19 (1.5)
Maximum severity of drug-related TEAEs						
Mild	12 (3.4)	17 (7.8)	37 (10.6)	45 (12.8)	99 (10.8)	111 (8.8)
Moderate	3 (0.9)	6 (2.8)	11 (3.2)	16 (4.5)	33 (3.6)	36 (2.8)
Severe	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)	2 (0.2)
Deaths	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Subjects with SAEs						
Any SAE	3 (0.9)	2 (0.9)	6 (1.7)	7 (2.0)	15 (1.6)	18 (1.4)
Any treatment-emergent SAE	2 (0.6)	2 (0.9)	6 (1.7)	7 (2.0)	15 (1.6)	17 (1.3)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study drug discontinuations due to adverse events						
Any adverse event	5 (1.4)	3 (1.4)	8 (2.3)	6 (1.7)	17 (1.9)	22 (1.7)
Any TEAE	5 (1.4)	3 (1.4)	7 (2.0)	6 (1.7)	16 (1.7)	21 (1.7)
Any drug-related TEAE	0 (0.0)	1 (0.5)	2 (0.6)	3 (0.9)	6 (0.7)	6 (0.5)
Any SAE	1 (0.3)	1 (0.5)	3 (0.9)	2 (0.6)	6 (0.7)	7 (0.6)

An overview of adverse events for the double-blind cohort (TA-05+TA-301+TA-302):

- In total, 425 (33.5%) subjects reported at least one TEAE during the study. The incidence of TEAEs was higher in the avanafil groups (31.3% to 40.1%) than in the placebo group (25.5%).
- In total, 149 (11.8%) subjects had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (10.6% to 17.3%) than in the placebo group (4.3%).
- Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups.
- One subject (in the avanafil 100 mg group) died during study TA-301 from a self-inflicted gunshot wound; the event was considered by the investigator to be not related to study drug. In total, 18 (1.4%) subjects had an SAE. The incidence of SAEs was similar across all treatment groups. No subject had an SAE that was considered by the investigators to be related to study drug.
- In total, 22 (1.7%) subjects discontinued study drug due to an adverse event. The percentage of subjects who discontinued study drug due to an adverse event was similar across all treatment groups. In total, 6 (0.5%) subjects discontinued study drug due to a drug-related TEAE.

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Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

Table 7.3.2 Summary of Treatment-Emergent Adverse Events (TEAEs) (≥1% of Subjects in Any Treatment Group) by System Organ Class and PT – Double-Blind Cohort (TA-05+TA-301+TA-302)

System Organ Class Preferred Term (PT)	Placebo (N=349) n (%)	Avanafil				Total (N=1267) n (%)
		50 mg (N=217) n (%)	100 mg (N=349) n (%)	200 mg (N=352) n (%)	Total (N=918) n (%)	
Infections and infestations	25 (7.2)	16 (7.4)	39 (11.2)	36 (10.2)	91 (9.9)	116 (9.2)
Nasopharyngitis	10 (2.9)	2 (0.9)	9 (2.6)	12 (3.4)	23 (2.5)	33 (2.6)
Upper respiratory tract infection	1 (0.3)	4 (1.8)	4 (1.1)	5 (1.4)	13 (1.4)	14 (1.1)
Bronchitis	1 (0.3)	3 (1.4)	1 (0.3)	4 (1.1)	8 (0.9)	9 (0.7)
Influenza	0 (0.0)	1 (0.5)	6 (1.7)	1 (0.3)	8 (0.9)	8 (0.6)
Sinusitis	4 (1.1)	0 (0.0)	5 (1.4)	3 (0.9)	8 (0.9)	12 (0.9)
Nervous system disorders	12 (3.4)	15 (6.9)	31 (8.9)	41 (11.6)	87 (9.5)	99 (7.8)
Headache	6 (1.7)	11 (5.1)	24 (6.9)	37 (10.5)	72 (7.8)	78 (6.2)
Musculoskeletal & connective tissue disorders	15 (4.3)	15 (6.9)	21 (6.0)	13 (3.7)	49 (5.3)	64 (5.1)
Back pain	4 (1.1)	7 (3.2)	7 (2.0)	4 (1.1)	18 (2.0)	22 (1.7)
Respiratory, thoracic, and mediastinal disorders	7 (2.0)	7 (3.2)	18 (5.2)	20 (5.7)	45 (4.9)	52 (4.1)
Nasal congestion	4 (1.1)	4 (1.8)	10 (2.9)	7 (2.0)	21 (2.3)	25 (2.0)
Sinus congestion	1 (0.3)	1 (0.5)	3 (0.9)	6 (1.7)	10 (1.1)	11 (0.9)
Vascular disorders	2 (0.6)	8 (3.7)	22 (6.3)	14 (4.0)	44 (4.8)	46 (3.6)
Flushing	0 (0.0)	7 (3.2)	15 (4.3)	14 (4.0)	36 (3.9)	36 (2.8)
Hypertension	1 (0.3)	1 (0.5)	5 (1.4)	0 (0.0)	6 (0.7)	7 (0.6)
Gastrointestinal disorders	9 (2.6)	9 (4.1)	15 (4.3)	19 (5.4)	43 (4.7)	52 (4.1)
Dyspepsia	0 (0.0)	1 (0.5)	2 (0.6)	5 (1.4)	8 (0.9)	8 (0.6)
Nausea	0 (0.0)	0 (0.0)	2 (0.6)	4 (1.1)	6 (0.7)	6 (0.5)
Constipation	1 (0.3)	3 (1.4)	0 (0.0)	0 (0.0)	3 (0.3)	4 (0.3)
Skin & subcutaneous tissue disorders	5 (1.4)	5 (2.3)	3 (0.9)	5 (1.4)	13 (1.4)	18 (1.4)
Rash	1 (0.3)	3 (1.4)	0 (0.0)	1 (0.3)	4 (0.4)	5 (0.4)

Treatment-emergent adverse events were defined as adverse events occurring after the first dose of study drug or after the first drug dispense date (if the first dose date was missing) and up to 28 days after the last dose of study drug.

In total, 425 (33.5%) subjects in the double-blind cohort reported at least one TEAE. The incidence of TEAEs was higher in the avanafil groups (31.3% to 40.1%) than in the placebo group (25.5%). The TEAEs that occurred more frequently in the avanafil groups than in the placebo group were upper respiratory tract infection, influenza, headache, nasal congestion, sinus congestion, flushing, and dyspepsia.

In total, 149 (11.8%) subjects in the double-blind cohort had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (10.6% to 17.3%) than in the placebo group (4.3%). The incidences of the following drug-related TEAEs were higher in the avanafil groups than in the placebo group:

- Headache (placebo, 1.1%; avanafil 50 mg, 4.6%; avanafil 100 mg, 5.7%; and avanafil 200 mg, 8.8%);

- Flushing (placebo, 0.0%; avanafil 50 mg, 2.8%; avanafil 100 mg, 4.3%; and avanafil 200 mg, 4.0%); and
- Nasal congestion (placebo, 0.9%; avanafil 50 mg, 1.8%; avanafil 100 mg, 2.0%; and avanafil 200 mg, 1.7%).

Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups. In total, 19 (1.5%) subjects in the double-blind cohort had a severe TEAE: 4 (1.1%) subjects in the placebo group, 2 (0.9%) subjects in the avanafil 50 mg group, 9 (2.6%) subjects in the avanafil 100 mg group, and 4 (1.1%) subjects in the avanafil 200 mg group. The most frequently reported severe TEAE was headache (2 subjects); no other specific severe TEAEs were reported by more than 1 subject.

Reviewer's comment: Headache itself is an expected adverse reaction. Severe headache appears to pose a potential but infrequent risk. This is not unexpected for this class of drugs.

7.3.1 Deaths

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

Subject # 108-020: Self-inflicted gunshot wound
Subject 108-020, a 53-year-old White male with a history of ED and depression, signed informed consent on 12-Mar-2009. The subject was randomized to avanafil 100 mg on 09-Apr-2009. The last dose of study drug was taken on 02-Jun-2009. On (b) (6) the subject experienced a fatal self-inflicted gunshot wound. On (b) (6), an autopsy revealed findings of gunshot wound of head with associated subarachnoid hemorrhage and coronary atherosclerosis. Toxicology results revealed positive blood ethanol. Cause of death was noted as gunshot wound of head with manner of death noted as suicide. The subject had been arrested in (b) (6) and charged with grand theft, accused of stealing from the commercial real estate company where he previously worked. A pretrial hearing had been set for (b) (6). The subject's medical history also includes current tobacco use, hypertension, rapid ejaculation, left inguinal hernia, migraine headaches, anxiety, seasonal allergies, and asthma. Concomitant medications include Xanax, ibuprofen, lisinopril, and Tylenol Sinus. The investigator considered the event of self-inflicted gunshot wound as severe in severity and not related to study drug.

Reviewer's comment: The death of this subject has nothing to do with study drug avanafil.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Integrated Double-Blind Cohort (TA-301, TA-302, and TA-05)

The incidence of SAE's in the double-blind cohort was reported as: 3 (0.9%) subjects in the placebo group, 2 (0.9%) subjects in the avanafil 50 mg group, 6 (1.7%) subjects in the avanafil 100 mg group, and 7 (2.0%) subjects in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group.

7.3.2.1.1 Study TA-05:
1 subject in the avanafil 300 mg group had 2 SAE's (abdominal injury and head injury) due to a motor vehicle accident.

7.3.2.1.2 Phase 3 double-blind cohort (TA-301 and TA-302)
The incidence of SAEs in Phase 3 pivotal studies was: 3 (1.0%) subjects in the placebo group, 1 (0.6%) subject in the avanafil 50 mg group, 6 (2.1%) subjects in the avanafil 100 mg group, and 7 (2.4%) subjects in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group. Narratives for each of these SAEs are provided in Section 7.3.2.6 below.

7.3.2.2 Individual Phase 3, Open-label, Long-Term Study TA-314
Eleven subjects had an SAE during study TA-314. No subject had an SAE that was considered by the investigators to be related to study drug. The SAE resulted in discontinuation of study drug for 6 subjects: 1 subject with acute psychosis, 1 subject with femoral artery occlusion, 1 subject with coronary artery disease, 1 subject with aortic valve stenosis, 1 subject with cervical vertebral fracture, and 1 subject with congestive cardiac failure.

7.3.2.3 Individual Phase 3 Study TA-303 (120-Day Safety Update)

For TA-303, no subject died or had an SAE during the study.

7.3.2.4 Supportive Studies
No subject had an SAE in the Phase 2 Studies TA-01 and TA-03.

7.3.2.5 Phase 1 Studies
One subject had an SAE during the Phase 1 program. In study TA-02, Subject #16 had an SAE of pharyngolaryngeal pain, which the investigator considered to be unlikely related to study drug. This SAE resulted in discontinuation of study drug.

7.3.2.6 Review of the Narratives of Serious Adverse Events

7.3.2.6.1 Serious Adverse Events: TA-301

Non-randomized group
Subject 129-033: acute inferior non-ST elevation myocardial infarction
Subject 129-033, a 72-year-old White male with a history of ED, signed informed consent on 19-Feb-2009. The subject had not yet been randomized to study drug at the time of the event. On 19-Feb-2009, the subject experienced chest pain, shortness of breath with exertion, and mild

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nausea. On [redacted] (b) (6) the subject presented to the emergency room with continued complaints of chest pain. Initial laboratory results revealed a creatine kinase of 222 and troponin of 2.9 (normal ranges [NR] and units not provided). The subject was subsequently admitted to the hospital with a diagnosis of acute inferior non-ST elevation myocardial infarction. On (b) (6) [redacted], an echocardiogram revealed mild mitral and tricuspid regurgitation, inferolateral hypokinesis, and an ejection fraction of 50%. On that same date, a cardiac catheterization revealed significant two-vessel coronary disease involving total occlusion of the right coronary artery and the subject underwent successful thrombectomy, percutaneous coronary angioplasty and drug-eluting stent placement. A second percutaneous coronary intervention of the proximal left anterior descending artery was planned for a future date after discharge. During the cardiac catheterization and on [redacted] (b) (6) the subject experienced bradycardia that was treated with Neo-Synephrine, atropine, and Nipride. During the hospitalization, troponin levels ranged from 3 to 1.46 (NR and units not provided). An electrocardiogram revealed a significant inferolateral T inversion and questionable evolution of myocardial infarction. Treatment of the event included heparin, Integrillin, Plavix, aspirin, carvedilol, and nitroglycerin. The subject was discharged from the hospital on [redacted] (b) (6) and recovered from the event on [redacted] (b) (6) The subject was subsequently withdrawn from the study prior to receiving any study drug. The subject's medical history also includes obesity, hypercholesterolemia, increased blood pressure without diagnosis of hypertension, sleep disorder, gastroesophageal reflux disease, and depression. Concomitant medications included Sleep Ease, Zegerid, Wellbutrin XL, aspirin, red yeast rice, Xanax, Sonata, and doxazosin mesylate. The investigator considered the event of acute inferior non-ST elevation myocardial infarction as severe in severity and not related to study drug.

Reviewer's comment: The SAE of acute inferior non-ST elevation myocardial infarction in this particular patient is not related to study drug.

Subject 142-018: chronic wound of left lower leg
Subject 142-018, a 71-year-old White male with a history of erectile dysfunction, signed informed consent on 21-Apr-2009. The subject had not yet been randomized to study drug at the time of the event. On 02-May-2009, the subject experienced a traumatic injury to his left leg and developed a hematoma. Despite treatment with doxycycline, the wound did not improve. On (b) (6) [redacted] (b) (6) the subject was admitted to hospital for surgical debridement. Physical examination revealed a large eschar on the left lower extremity with an open wound measuring about 5 cm in diameter. Laboratory results revealed a white blood cell count of 9.3 (normal range and units not provided). The subject underwent wound debridement involving the skin and subcutaneous tissue and evacuation of the hematoma. Wound cultures revealed moderate probable enterococcus. Treatment medications included intravenous Zosyn and vancomycin. On [redacted] (b) (6) the subject was discharged from the hospital. On [redacted] (b) (6), the subject underwent a split-thickness skin graft to the left leg and placement of a wound Vacuum Assisted Closure device. The subject recovered from the event on [redacted] (b) (6). The subject was subsequently withdrawn from the study prior to receiving any study drug. The subject's medical history includes anxiety, depression, insomnia, past tobacco use, alcohol abuse, inguinal hernia repair, decreased sodium levels, hypertension, and appendectomy. Concomitant medications included

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Lexapro, trazodone, Antabuse, Dyazide, and benazepril HCl. The investigator considered the event of chronic wound of left lower leg as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of chronic wound of the subject's lower left leg is not related to study drug.

Placebo group
Subject 129-046: non-cardiac chest pain
Subject 129-046, a 56-year-old Black male with a history of ED, signed informed consent on 27-Mar-2009. The subject had not yet been randomized at the time of the event. On 28-Mar-2009, the subject experienced palpitations and was subsequently hospitalized for evaluation and treatment on (b) (6) An echocardiogram revealed mild left ventricular hypertrophy with mild diastolic dysfunction and an estimated ejection fraction of 65-75%. Laboratory testing revealed a creatine phosphokinase of 396 u/L (normal range [NR] 45-225 u/L), creatine phosphokinase-MB of 4.8 ng/mL (NR 0.0-3.6 ng/mL), MB ratio of 1.2% (NR 4.5-14.0%), and troponin I of 0.08 ng/mL (NR 0.0-0.05 ng/mL). The subject was subsequently diagnosed with non-cardiac chest pain. The event was treated with enteric coated aspirin and Zetia. The subject recovered from the event on (b) (6). The subject continued in the study and was randomized to placebo on 24-Apr-2009. The last dose of study drug was taken on 20-Jul-2009 and the subject completed the study on 28-Jul-2009. The subject's medical history includes previous tobacco use, elevated cholesterol, colonoscopy, endoscopy, decreased libido, hyperopia, general pain, and common cold. Concomitant medications include Comtrex, Welchol, and Advil. The investigator considered the event as mild in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE in this subject is not related to study drug.

Subject 140-024: acute depression with suicidality
Subject 140-024, a 43-year-old White male with a history of ED, signed informed consent on 11-Dec-2008. The subject was randomized to placebo on 22-Jan-2009. The last dose of study drug was taken on 14-Feb-2009. On (b) (6) the subject was transported to the emergency room by emergency medical services with toxic symptoms of drug overdose and intoxication exhibited by drowsiness and confusion. The subject's girlfriend reported that the subject had been drinking the night prior and found unspecified sleeping pills scattered on the floor. Physical examination upon admission revealed lethargy, confusion, and restlessness with slurred speech, hypertension (blood pressure unknown), tachycardia (heart rate unknown), with normal respiratory rate, oxygen saturation, and temperature. The subject appeared intoxicated, depressed, and uncooperative with no signs of apparent trauma. The subject was subsequently admitted to the hospital for evaluation and treatment of acute depression with suicidality. Further examination revealed the subject had a moderately altered mental status, was confused and disoriented to place and time with slow and incoherent responses to simple questions and commands. Cranial nerve testing was normal with no motor deficit. A CT scan of the brain revealed no acute abnormalities. A urine drug screen was positive for tricyclic antidepressants. Laboratory testing revealed an ethanol level of 15 (not legally intoxicated). On (b) (6), an electrocardiogram

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showed tachycardia with non-specific ST/T wave abnormalities. Psychiatric evaluation revealed somewhat incoherent and illogical speech, confused and depressed mood, inappropriate and labile affect, and poor insight and judgment. The subject was unable to continue with mental status examination due to confusion. Treatment of the events included oral charcoal with sorbitol and psychiatric therapy. The subject recovered from the event of acute depression with suicidality on (b) (6). The subject was withdrawn from the study due to the event on 10-Mar-2009. The subject's medical history includes current tobacco use, hypercholesterolemia and right elbow pain and swelling. It was also noted that the subject had a history of depression with a previous suicide attempt and that recent life changes had increased his depression. No concomitant medications were taken at the time of the event. The investigator considered the event of acute depression with suicidality as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of acute depression with suicidality in this subject is not related to study drug.

Avanafil 50 mg group
Subject 104-043: ST elevation myocardial infarction
Subject 104-043, a 58-year-old White male with a history of ED, signed informed consent on 04-Mar-2009. The subject was randomized to avanafil 50 mg on 08-Apr-2009. The last dose of study drug was taken on 13-May-2009. On (b) (6), the subject presented to the emergency department with complaints of substernal crushing chest pain radiating to the bilateral arms, neck and jaw with associated nausea, shortness of breath, and diaphoresis. The subject reported feeling short of breath after moving heavy objects earlier in the day and developed an acute onset of substernal chest pain rated as 10 out of 10 on a pain scale. Physical examination revealed a blood pressure of 145/96 mmHg, heart rate of 77 beats per minute, respirations 18, and oxygen saturation 96% on 2 liters per nasal cannula. An electrocardiogram confirmed ST-elevation in V1 and AVL along with V2 through V6. A chest x-ray revealed bibasilar areas of atelectasis/infiltrate. Laboratory testing revealed a troponin of 0.52 (normal range and units not provided). The subject was subsequently diagnosed with an ST-elevation myocardial infarction and underwent left heart catheterization, left ventriculogram, and coronary angiography which revealed two-vessel coronary artery disease involving a co-dominant right and proximal left anterior descending, ischemic cardiomyopathy, and an ejection fraction of 30-35%. Successful complex intervention of a 100% occluded left anterior descending and mid left anterior descending lesion utilizing two drug-eluting stents was performed. Treatment of the event also included heparin, lisinopril, Lopressor, Zocor, Lasix, Reopro, aspirin, and Plavix. The subject recovered from the event of ST elevation myocardial infarction on (b) (6) and was withdrawn from the study due to the event on 03-Jun-2009. The subject's medical history includes previous tobacco use, heartburn, hypertension, astigmatism, headaches, obesity, nocturia, frequent urination, knee surgery, and oral surgery. Additionally, the investigator noted the subject had a greater than five-year history of non-compliance with hypertension treatment and severe multi-vessel coronary artery disease. Concomitant medications include multivitamins and aspirin. The investigator considered the event of ST elevation myocardial infarction severe in severity and not related to study drug.

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Reviewer's comment: Based on the lack of temporal relationship to drug (event occurred 4 days after last dose), and considering the patient's underlying severe coronary artery disease (e.g., 100% LAD occlusion), the Reviewer agrees with the Sponsor that the SAE of ST elevation myocardial infarction in this subject is not related to study drug.

Avanafil 100 mg group
Subject 102-041: stage 1 prostate cancer
Subject 102-041, a 69-year-old White male with a history of ED, signed informed consent on 22-Apr-2009, with a prostate specific antigen (PSA) of 0.1 ng/dL (normal range [NR] not provided). On 15-May-2009, laboratory testing revealed a PSA of 4.31 ng/dL (NR 0-4.0 ng/dL) and PSA, free of 9% (NR negative). The subject was randomized to avanafil 100 mg on 20-May-2009. On [redacted] (b) (6) the subject underwent punch needle biopsy. The histology report revealed a Gleason score of 3+4=7, with 7 out of 12 cores mostly positive on the left and prostate size of 26 grams. The subject was subsequently diagnosed with stage T1c prostate cancer on 06-Jul-2009. The last dose of study drug was taken on 14-Jul-2009. The subject was withdrawn from the study due to the event on 20-Jul-2009. This non-serious adverse event was considered resolved on 10-Aug-2009. On [redacted] (b) (6) the subject was admitted to the hospital and underwent prostatectomy. The subject recovered from the serious adverse event of stage 1 prostate cancer on [redacted] (b) (6) and was discharged from the hospital on [redacted] (b) (6) The subject's medical history includes benign prostatic hypertrophy, current tobacco use, hyperlipidemia, atherosclerotic calcification, mild hypertension, peripheral artery disease, migraines, herpes simplex, skin lesions, colon polyps, diverticulosis, gastroesophageal reflux disease, internal hemorrhoids, right inguinal hernia, peptic ulcer, 1.2 centimeter cyst in right kidney, right hepatic hemangioma, right shoulder pain, neck fusion C3 and C4, dislocated posterior intraocular lens of the left eye, and chronic obstructive pulmonary disease. Concomitant medications include Lipitor, Nexium, Imitrex, and Topamax. The investigator considered both events of stage 1 prostate cancer and subsequent prostatectomy as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of stage 1 prostate cancer, occurring approximately 1 month after starting drug in this subject with a baseline serum PSA of 4.3 ng/dL, is not related to study drug.

Subject 108-020: self-inflicted gunshot wound See the narrative for this event in "Death" subsection.

Subject 142-008: papillary transitional cell carcinoma, bladder
Subject 142-008, a 59-year-old White male with a history of ED, signed informed consent on 03-Apr-2009. The subject was randomized to avanafil 100 mg on 12-May-2009. The last dose taken prior to the event was on 26-Jun-2009. On [redacted] (b) (6) the subject was admitted to the hospital after an episode of heavy bleeding with voiding every 30 minutes in small amounts the night prior. The subject reported a 4-week history of intermittent hematuria. The subject underwent cystoscopy and clot evacuation. A 2-3 cm diameter papillary lesion was identified on the left lateral wall of the bladder during the procedure. A Foley catheter was inserted for continuous bladder irrigation. On [redacted] (b) (6) the subject underwent transurethral resection of the bladder

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mass. On (b) (6), biopsy revealed surface low-grade papillary transitional cell carcinoma, no invasion identified. The subject was subsequently diagnosed with papillary transitional cell carcinoma of the bladder. Treatment of the event included cephalexin, hydrocodone /acetaminophen, ciprofloxacin, lidocaine, phisohex and clobetasol. The subject recovered from the event and was discharged from the hospital on (b) (6) with plans to undergo follow-up cystoscopy examinations. The last dose of study drug was taken on 19-Jul-2009, and the subject was withdrawn from the study due to the event on 18-Aug-2009. The subject's medical history includes a history of tobacco use, occasional headaches, seborrheic keratosis, stomach hernia with repair, gallbladder removal, gastric bypass surgery, kidney stones, knee cartilage surgeries, lateral epicondylitis surgery, and seasonal allergies. Concomitant medications include aspirin, vitamin C, cetirizine, fish oil, fluticasone, ibuprofen, iron, multivitamins, acetaminophen, and vitamin B-50. The investigator considered the event of papillary transitional cell carcinoma, bladder as mild in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of bladder papillary transitional cell carcinoma, occurring 6 weeks after starting drug in this subject with a 4-week history of intermittent hematuria, is not related to study drug.

Avanafil 200 mg group
Subject 124-008: left arm numbness
Subject 124-008, a 57-year-old White male with a history of ED, signed informed consent on 12-Jan-2009. The subject was randomized to avanafil 200 mg on 10-Feb-2009. On (b) (6) the subject experienced left arm numbness which occurred suddenly and abated approximately 2 hours later. The subject drove to a local fire station where an electrocardiogram was performed. The subject was transported to the hospital and admitted for evaluation and treatment of left arm numbness. Physical examination revealed a blood pressure of 120/72 mmHg, heart rate 74 beats per minute, and respirations of 14. Lungs were clear to auscultation and percussion with equal bilateral breath sounds and the heart was without murmurs, rubs or gallops. Neurological evaluations were grossly nonfocal. An electrocardiogram revealed no acute changes and troponin levels were normal. A chest x-ray showed minimal linear infiltrates of the left costophrenic angle. Magnetic resonance imaging of the brain was normal and magnetic resonance angiogram of the brain and neck was normal. On 22-Mar-2009, an echocardiogram revealed normal size left ventricle with an estimated ejection fraction of >50%, normal right ventricular size and function, normal left and right atrial size, sclerosis of the aortic valve without stenosis or aortic deficiency, mildly thickened mitral valve with trace mitral regurgitation and mild mitral annular calcification, trace tricuspid valve regurgitation, no intracardiac mass or thrombus, and small pericardial effusion without evidence of pericardial tamponade. Bilateral venous duplex showed no evidence of deep venous thrombosis in the lower extremities. A computed tomography pulmonary angiogram revealed no evidence of pulmonary emboli, minimal infiltrates in both lung bases, evidence for passive congestion with reflux of contrast into the inferior vena cava, and prominent nodes in the mediastinum and both hilar regions. The etiology of the event of left arm numbness was reported as gastroesophageal reflux. Treatment of the event was not reported. The subject recovered with sequelae from the event of left arm numbness on (b) (6). The study drug was continued and the subject continued in the study. The subject's medical history

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includes current tobacco use, gastroesophageal reflux disease (GERD), frequent urination, left shoulder pain, bilateral carpal tunnel surgery, depression, sinusitis, and dry cough. Concomitant medications include Pepcid Complete and Claritin. The investigator considered the event of left arm numbness as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of left arm numbness, which was ultimately attributed to an exacerbation of underlying GERD in this subject, is not related to study drug.

Subject 130-012: moderate non obstructive coronary artery disease
Subject 130-012, an 80-year-old White male with a history of ED, signed informed consent on 17-Mar-2009. The subject was randomized to avanafil 200 mg dose on 21-Apr-2009. The last dose of study drug was taken on [redacted] (b) (6). On [redacted] (b) (6) the subject presented to the emergency department with complaints of bitemporal headache and retrosternal and left-sided chest discomfort that radiated 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, non-specific ST-T changes, and poor wave progression. 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 acute pulmonary disease, with 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, 30-60% stenosis of the circumflex artery, normal left ventricular systolic function, and left ventricular end-diastolic pressure of 19 mmHg. A follow-up electrocardiogram revealed sinus bradycardia with first degree AV block. The subject was subsequently 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 [redacted] (b) (6). On 09-Jun-2009, the subject experienced sinusitis. The event did not require any additional diagnostic testing but was treated with cephalexin. The subject was withdrawn from the study due to the SAE on 16-Jun-2009. The sinusitis was still ongoing at the time of study exit. The subject's medical history includes previous tobacco use, hyperlipidemia, right and left coronary angioplasty, atherosclerotic heart disease, hypertension, peripheral artery disease, basal cell skin cancer of the head/face, hypothyroidism, hemochromatosis, renal artery stenosis stent placement, degenerative joint disease, spinal stenosis with decompression discectomy, right knee replacement, bilateral rotator cuff surgery, mild sleep disorder, and seasonal allergies. Concomitant medications include Lipitor, Atacand, hydrochlorothiazide, Synthroid, loratadine, lisinopril, and multivitamin. The investigator considered the events of moderate non obstructive coronary artery disease and headache as

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severe in severity and not related to study drug. The sinusitis was considered moderate in severity and not related to study drug.

Reviewer's comment: Based on a positive temporal relationship (event occurring 1 days after last dose), the relationship between the SAE of non obstructive coronary artery disease (angina) and study drug cannot be ruled out in this case; this is a different judgment from the Sponsor's.

Subject 137-014: infection of right arm secondary to dog bite
Subject 137-014, a 62-year-old White male with a history of ED, signed informed consent on 19-Feb-2009. The subject was randomized to avanafil 200 mg on 19-Mar-2009. On 26-May-2009, the subject developed an infection of the right arm secondary to a dog bite. The subject's right hand was noted to be red and swollen. Treatment with Keflex and Rocephin was unsuccessful and the subject was subsequently admitted to the hospital for further treatment on (b) (6) Laboratory testing revealed a white blood cell count of 12.2 x 10^3/L (normal range 4.0-10.0 x 10^3/L). Blood cultures were negative. An x-ray of the right wrist revealed no sign of bone infection. Treatment of the event included clindamycin, Motrin, and Ultram. The subject recovered from the event of infection of right arm secondary to dog bite on (b) (6). The subject continued on study drug and the last dose of study drug was taken on 09-Jun-2009. The subject completed the study on 11-Jun-2009. The subject's medical history includes atrial arrhythmia, bulging lumbar disc, mild irritable bowel, vasectomy, hiatal hernia, osteoarthritis of the knees, seasonal allergies, hyperopia, sinus infection, and allergies to grass, tomatoes, and pollen. Concomitant medications include aspirin, ibuprofen, and Claritin. The investigator considered the event of infection of right arm secondary to dog bite as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of infection of right arm secondary to dog bite in this subject is not related to study drug.

7.3.2.6.2 Serious Adverse Events: TA-302

Non-randomized subjects
Subject 219-004: melanoma right cheek
Subject 219-004, a 42-year-old White male with a history of ED and diabetes, signed informed consent on 26-Jan-2009. The subject was not randomized at the time of the event. On (b) (6) the subject underwent a biopsy and excision of a mole on the right cheek, present since birth, after his primary care physician noticed a change in the mole. The pathology revealed melanoma. On (b) (6) the subject had additional flesh from his cheek excised and lymph nodes removed from below the jaw. A biopsy of the right sentinel lymph node submandibular triangle contained metastatic malignant melanoma. On (b) (6) the subject underwent a right modified neck dissection with removal of lymph nodes. The pathology of the lymph nodes was negative with no malignancy identified. The subject recovered from the event on (b) (6). Concomitant medications included betamethasone, fish oil, multivitamin, and Levoxyl.

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The subject's medical history includes current cigarette use, hypothyroidism, mole right cheek, and psoriasis. The investigator considered the event of melanoma right cheek as severe in severity and not related to study drug.

Reviewer's comment: The SAE of melanoma right cheek in this non-randomized subject has nothing to do with study drug.

Placebo group
Subject 222-006: L1 burst fracture of the lumbar spine
Subject 222-006, a 52-year-old Hispanic male with a history of ED and diabetes, signed informed consent on 06-Jan-2009. The subject was randomized to placebo on 02-Feb-2009. The last dose of study drug was taken on 22-Apr-2009. On (b) (6), the subject was struck by a car while riding his bicycle and was subsequently admitted through the emergency room with back pain. A CT scan of the brain and cervical spine revealed no evidence of intracranial hemorrhage or mass and mild degenerative changes of the cervical spine without evidence of fracture or subluxation. An X-ray and CT scan of the thoracic and lumbar spine revealed an L1 burst fracture. Treatment of the event included a Jewett brace and Percocet. On (b) (6) the subject was discharged from the hospital. On 04-May-2009, the subject completed the study. The subject recovered from the event on (b) (6). The subject's medical history includes current tobacco use, cholecystitis, and cholecystectomy. No concomitant medications were taken at the time of the event. The investigator considered the event of L1 burst fracture of lumbar spine as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of L1 burst fracture of lumbar spine in this subject is not related to study drug.

Avanafil 100 mg group
Subject 203-033: deep vein thrombosis in right leg
Subject 203-033, a 56-year-old White male with a history of ED, diabetes, blood clotting problems, and deep vein thrombosis (4 episodes), signed informed consent on 17-Jul-2009. The subject was randomized to avanafil 100 mg on 14-Aug-2009. The last dose of study drug prior to onset of the event was taken on 24-Aug-2009. On 25-Aug-2009, the subject developed sudden onset pain in right calf associated with swelling. The subject had reportedly run out of warfarin 3 weeks prior to the event. On (b) (6) the subject was admitted to the hospital for evaluation and treatment of a deep vein thrombosis of the right leg. Physical examination revealed right calf edema without redness. Treatment of the event included enoxaparin and warfarin. The subject was discharged from the hospital and recovered from the event on (b) (6) The subject continued on study drug, and the last dose was taken on 05-Nov-2009. The subject's medical history includes current tobacco use, hypertension, gastrointestinal reflux disease, vasectomy, bilateral hip replacement, hyperopia, colonoscopy, endoscopy, and depression. Concomitant therapy taken within 30 days before onset of the event included insulin and warfarin. The investigator considered the event of deep vein thrombosis in right leg as severe in severity and not related to study drug.

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Reviewer's comment: Although a temporal relationship to drug exists (event occurring 1 day after most recent dose), the Reviewer believes that the SAE of deep vein thrombosis in right leg in this subject is a consequence of pre-existing DVT and not taking warfarin in 3 weeks, and is not related to study drug.

Subject 215-050: urinary tract infection
Subject 215-050, a 67-year-old Hispanic male with a history of erectile dysfunction and diabetes, signed informed consent on 23-Jul-2009. The subject was randomized to avanafil 100 mg on 04-Sep-2009. The last dose of study drug was taken on 29-Oct-2009. On (b) (6) the subject was hospitalized with complaints of generalized weakness, headache, increased urination, and dysuria. A urinalysis revealed 10 mg/dL of ketones, trace protein, positive nitrate, and large leukocytes, 70 white blood cells, and 11 red blood cells with many bacteria. Urine cultures isolated >100,000 CFU/mL lactose fermenting gram-negative rods and Escherichia coli. Laboratory results revealed a white blood cell (WBC) count of 23 K/µL (normal range 3.4-11.0 K/µL). Blood cultures were negative. The subject was hospitalized for evaluation and treatment of a urinary tract infection. On (b) (6), the subject's WBC count was 13.4 K/µL (normal range 3.4-11.0 K/µL) and prostate specific antigen was 33.95 ng/mL (normal range 0.00-4.00 ng/mL). Treatment of the event included intravenous ceftriaxone, Levaquin, finasteride, tamsulosin, acetaminophen, enoxaparin, insulin, bisacodyl, pneumovax, and intravenous fluids. The subject was discharged from the hospital on (b) (6). The subject recovered from the event and the subject was withdrawn from the study due to the event on (b) (6). The subject's medical history includes past tobacco use, hypertension, enlarged prostate, kidney stones, neck pain, insomnia, and asthma. Concomitant medications included cyclobenzaprine, benazepril, glipizide, ibuprofen, and lorazepam. The investigator considered the event of urinary tract infection as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer believes that the SAE of UTI in this subject was probably related to his BPH, or to a concurrent prostatitis, but not related to study drug.

Subject 234-052: right foot infection
Subject 234-052, a 48-year-old Hispanic male with a history of erectile dysfunction and diabetes, signed informed consent on 17-Sep-2009. The subject was randomized to avanafil 100 mg on 14-Oct-2009. The last dose of study drug was taken on 02-Jan-2010. On (b) (6) the subject was hospitalized for evaluation and treatment of a right foot infection. Treatment of the event is unknown. The subject was discharged from the hospital and recovered from the event on (b) (6) The subject withdrew consent and refused to return for an end-of-treatment visit. Study drug and diaries were returned by mail. Final contact with the subject was documented on 25-Jan-2010. The subject's medical history includes past tobacco use, high cholesterol, hypertension, diabetic neuropathy, hemorrhoids, benign prostatic hyperplasia, hematuria, urinary tract infections, bilateral joint pain in knees, chronic back pain, swelling of extremities, restless leg syndrome, 1st and 3rd toe right foot amputations, left cataract repair, abdominal obesity, hyperopia, myopia, and shortness of breath. Concomitant medications included amlodipine, enalapril, gabapentin, glipizide, hydrochlorothiazide, metformin, metoprolol, Actos, simvastatin,

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and terazosin. The investigator considered the event of right foot infection as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of right foot infection in this subject, with pre-existing peripheral vascular disease and history of toe amputations, was not related to study drug.

Avanafil 200 mg group

Subject 201-012: left arm pain and left arm weakness

Subject 201-012, a 64-year-old Black male with a history of ED and diabetes, signed informed consent on 01-Jul-2009. The subject was randomized to avanafil 200 mg on 10-Aug-2009. The last dose of study drug prior to onset of the event was taken on 18-Sep-2009. On (b) (6) the subject was hospitalized due to left arm pain and weakness. Neurologic examination revealed left elbow pain radiating toward the forearm and fingers, decreased grip strength, and inability to raise his arm toward his head. During the hospitalization, the subject refused a magnetic resonance imaging (MRI). An echocardiogram revealed a normal left ventricular systolic function, mild left hypertrophy, and an estimated ejection fraction of 60-65%. Carotid Doppler results unchanged from 13-Dec-2006 revealed moderate bilateral internal carotid artery stenosis (16-49%) and antegrade flow bilateral vertebral arteries. Treatment of the event included an unspecified pain medication and Aggrenox. The subject was discharged from the hospital and recovered from the events on (b) (6) On (b) (6), an outpatient MRI revealed mild diffuse atrophy, chronic microvascular ischemic changes with areas of old ischemia within the basal ganglia and brainstem, as well as cerebellar hemisphere that was noted previously on 23-Jan-2007. The study drug was continued. The last dose was taken on 25-Oct-2009, and the subject completed the study on 03-Nov-2009. The subject's medical history includes current tobacco use, hyperlipidemia, hypertension, benign prostatic hypertrophy, osteoarthritis, mild diabetic neuropathy, and sleep apnea. Concomitant medications included aspirin, glyburide, lisinopril, metformin, simvastatin, and terazosin. The investigator considered the events of left arm pain and left arm weakness as severe in severity and not related to study drug.

Reviewer's Comment: The reason for the left arm pain and weakness remains obscure, but could be musculoskeletal in origin. The Reviewer agrees with the Sponsor that the SAE of left arm pain and left arm weakness was not related to study drug.

Subject 203-031: unstable angina

Subject 203-031, a 54-year-old White male with a history of ED, diabetes, and coronary arterial stent insertion, coronary artery disease, and heart attack, signed informed consent on 15-Jul-2009. 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

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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 [redacted] (b) (6) The subject was withdrawn from the study due to the event on 03-Sep-2009. The subject's medical history includes hypertension, neuropathy in feet, hypothyroidism, and back surgery. Concomitant medications included Neurontin, Lantus, Apidra, lisinopril, levothyroxine, and metoprolol. The investigator considered the event of unstable angina as severe in severity and not related to study drug.

Reviewer's comment: Due to the temporal relationship (event occurring 1 day after last dose of study drug), in this case, it is not possible to exclude a potential relationship of the SAE of unstable angina in this subject with a history of coronary artery disease and a stent in the right coronary artery, to study drug; this is a different judgment from the Sponsor's.

Subject 221-031: pneumonia
Subject 221-031, a 65-year-old White male with a history of ED and diabetes, signed informed consent on 12-May-2009. The subject was randomized to avanafil 200 mg on 01-Jun-2009. On [redacted] (b) (6) the subject was hospitalized with a 1-week history of a non-productive cough, headache, and fever. The last dose of study drug prior to onset of the event was taken on 25-Jun-2009. Physical examination revealed clear lungs on auscultation bilaterally. Laboratory results revealed a white blood cell count of 21.3 K/mm^3 (normal range 4.0-11.5 K/mm^3) and lymphocyte of 4.7% (normal range 15-48%). Chest X-ray showed a right upper lobe infiltrate. The subject was subsequently diagnosed with pneumonia. On [redacted] (b) (6), laboratory results revealed a white blood cell count of 12.2 K/mm^3 (normal range 4.0-11.5 K/mm^3) and lymphocyte of 13.4% (normal range 15-48%). Blood cultures revealed no growth. Treatment of the event included nebulizer treatments, intravenous Levaquin, and amoxicillin. The subject was discharged and recovered from the event on [redacted] (b) (6) The study drug was continued. The last dose was taken on 22-Aug-2009, and the subject completed the study on 25-Aug-2009. The subject's medical history includes hyperlipidemia, hypertension, vertigo, diabetic neuropathy, gastrointestinal reflux disease, kidney stones, lumbar pain, mild calcaneal spur formation right foot, herniated L4-5, osteomyelitis, and spinal osteoarthritis. Concomitant medications included atenolol, Lantus, Humulin, Lotrel, Glucophage, Protonix, and Urocit-K. The investigator considered the event of pneumonia as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of pneumonia in this subject was not related to study drug.

Subject 221-072: poorly differentiated transitional cell and papillary carcinoma of bladder, grade 3
Subject 221-072, a 50-year-old White male with a history of ED, diabetes, and hematuria, signed informed consent on 06-Aug-2009. During investigation of hematuria on 17-Aug-2009, a computed tomogram scan of the abdomen and pelvis revealed a 2 cm enhancing nodule in the left posterolateral urinary bladder, concerning for bladder neoplasm. The subject was randomized to avanafil 200 mg on 03-Sep-2009. On [redacted] (b) (6) a cystoscopy revealed a

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suspicious pedunculated bladder lesion. A fluorescent in situ hybridization on voided urine showed atypical urothelial cells and voided urine was positive for aneuploid cells. On (b) (6) a cystoscopy revealed poorly differentiated transitional cell and papillary carcinoma of bladder, grade 3. A transurethral resection of the bladder tumor with instillation of intravesical mitomycin was performed. The study drug was continued. The last dose of study drug was taken on 30-Nov-2009, and the subject completed the study on 02-Dec-2009. The event was ongoing at the time of study completion. On (b) (6) the subject underwent a cystoscopy and transurethral resection of the bladder tumor. On (b) (6), a re-resection of the tumor site revealed no evidence of residual cancer. The subject's medical history includes current tobacco use, atrial fibrillation, cardiac catheterization, hyperlipidemia, hypertension, hematuria, nephrolithiasis, bilateral cataracts, sleep apnea, and upper respiratory infection. Concomitant medications included glipizide, lisinopril, Actos, simvastatin, and warfarin. The investigator considered the event of poorly differentiated transitional cell and papillary carcinoma of bladder, grade 3 as moderate in severity and not related to study drug.

Reviewer's Comment: The Reviewer agrees with the Sponsor that the SAE of poorly differentiated transitional cell and papillary carcinoma of bladder, grade 3, in this subject was pre-existing, and not related to study drug.

7.3.2.6.3 Serious Adverse Events: TA-314

Subject 103-010: acute psychosis
Subject 103-010, a 46-year-old White male with a history of ED, was randomized to avanafil 50 mg in the TA-301 study on 10-Mar-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 12-Jun-2009. The last dose of study drug was taken on 21-Jun-2009. On (b) (6) the subject was admitted to the hospital voluntarily with complaints of auditory hallucinations described as multiple voices telling him to hurt other people. The hallucinations reportedly started after his second closed head injury in July 2008. Upon examination, the subject did was able to hold a conversation without thought-blocking. The subject denied suicidal ideations, homicidal ideations, visual hallucinations, or personal injury. On admission, a global assessment function score was 30. A urine drug screen for alcohol, barbiturates, amphetamine, benzodiazepine, cocaine, tetrahydrocannabinol, methadone, phencyclidine, and opiate was negative. The subject was subsequently diagnosed with acute psychosis. The subject complained of a severe temporal headache and was noted to have a blood pressure of 156/99 mmHg. Laboratory results revealed a blood alcohol of <10 mg/dL (normal range 0-10 mg/dL). Treatment of the event included maghydrox/alhydrox/simeth suspension, Abilify, bismuth subsalicylate, Benadryl, Lexapro, Haldol, Ativan, magnesium hydroxide, acetaminophen, Paxil, promethazine, and zolpidemtartrate. The subject recovered from the event of acute psychosis and was discharged from the hospital on (b) (6) The subject was withdrawn from the study due to the event on 07-Jul-2009. The subject's medical history includes hypertension, headaches, anxiety attack, and two closed head injuries. Concomitant medication included Altace. The investigator considered the event of acute psychosis as severe in severity and not related to study drug.

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Reviewer's comment: The Reviewer considers that the SAE of acute psychosis was probably not related to study drug but more likely related to his previous closed head injuries.

Subject 110-040: acute pancreatitis and occlusion of the left femoral artery
Subject 110-040, a 69-year-old White male with a history of ED, was randomized to avanafil 50 mg in the TA-301 study on 16-Apr-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 10-Jul-2009 and was escalated to a dose of 200 mg on 24-Aug-2009. On (b) (6), the subject was admitted to the hospital with complaints of epigastric discomfort, diaphoresis, chills, and weakness. The last dose of avanafil 100 mg prior to the onset of the event was taken 22-Aug-2009. Laboratory testing revealed a white blood cell count of 11,900, alanine aminotransferase (ALT) of 70, aspartate aminotransferase (AST) of 174, lipase of 30811, creatine kinase of 32, creatine kinase-MB of < 0.5, and troponin I of < 0.015 (normal ranges and units not provided). A magnetic resonance cholangiopancreatograph was negative. A magnetic resonance imaging of the abdomen and pancreas revealed mild biliary ductal ectasia (common bile duct up to 10 mm), and mild inflammatory changes surrounding the pancreas consistent with pancreatitis. On (b) (6), the subject experienced pneumonia. On (b) (6), blood cultures were negative. An esophago-gastro-duodenoscopy showed a normal esophagus, anastomotic changes in the fundus, normal duodenum, no anastomotic ulcers, and no outlet obstruction. The subject was subsequently diagnosed with acute pancreatitis. On (b) (6), laboratory testing revealed an ALT of 106, AST of 38, and lipase of 230.Treatment of the pancreatitis included nothing by mouth and doripenem. Treatment of the pneumonia included Oxygen and Levaquin. The subject recovered from the event of acute pancreatitis and was discharged from the hospital on (b) (6) The study drug was continued, and the subject continued in the study. The event of pneumonia resolved without sequelae on 11-Sep-2009. On an unknown date, the subject reportedly developed activity-induced claudication to both legs prior to the hospitalization. Non-invasive peripheral vascular studies of the lower extremities on (b) (6) revealed an ankle brachial index of 0.86 on the right side and 0.62 on the left side at rest. Post-exercise ankle brachial index tests were 0.54 on the right side and 0.17 on the left side. On (b) (6) the subject developed worsening discomfort of the left foot associated with numbness of the toes. On (b) (6), a magnetic resonance angiography of the left leg revealed an occluded left superficial femoral artery without definite reconstitution of the popliteal, patent distal left popliteal, continuous run-off across the ankle, and continuous run-off of the right lower extremity. The subject was subsequently diagnosed with occlusion of the left femoral artery. On (b) (6) the subject underwent a left common femoral endarterectomy, femoral-popliteal bypass with gore-tex graft, and Miller vein cuff. Additional treatment of the event included Pletal and heparin. The subject recovered from the event of occlusion of the left femoral artery and was discharged from the hospital on (b) (6) The last dose of study drug (200 mg) was taken on 31-Oct-2009. The subject was instructed on 11-Nov-2009 not to continue dosing and was withdrawn from the study on that same day due to the event of occlusion of the left femoral artery. The subject's medical history includes right and left femoral artery bypass, cardiac bypass surgery, coronary artery disease, hypertension, peripheral vascular disease, post herpetic

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neuralgia, hypercholesterolemia, appendectomy, appendicitis, cholecystectomy, cholecystitis, colon polyps, partial gastrectomy, stomach ulcer, gastric ulcer, gastroesophageal reflux disease, kidney stones, nocturia, vasectomy, left and right knee replacement, degenerative joint disease, osteoarthritis of hips and legs, left eye cataract, left eye cataract surgery, right carotid endarterectomy, constipation, and cigaretteuse (1 pack per week). Concomitant medications included Plavix, gabapentin, Avapro, MiraLax, and Lovaza. The investigator considered the events of acute pancreatitis, occlusion of the left femoral artery, and pneumonia as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of acute pancreatitis, occlusion of the left femoral artery, and pneumonia in this subject was probably not related to study drug.

Subject 116-028: bilateral inguinal hernia
Subject 116-028, a 53-year-old White male with a history of ED, signed informed consent and was enrolled in study TA-314 on 02-Jun-2009. Prior to enrollment into TA-314, the subject completed a 3-month course of blinded avanafil 50 mg in TA-301, which started 04-Mar-2009. The subject was initially dispensed open-label avanafil 100 mg in TA-314 and was escalated to 200 mg at his next scheduled visit on 30-Jun-2009. On 03-Aug-2009, the subject experienced feeling lightheaded. The last dose of study drug prior to the onset of the event was taken on 30-Jul-2009. No additional diagnostic testing was performed and no treatment was required. The event resolved without sequelae on the same day as onset (03-Aug-2009). On 13-Oct-2009, the subject experienced a common cold. The last dose of study drug prior to the onset of the event was taken on 10-Oct-2009. No additional diagnostic testing was performed for the cold. Treatment for the event included Nyquil and Theraflu Daytime Severe Cold & Cough Caplets. The event resolved without sequelae on 20-Oct-2009. On [redacted] (b) (6) the subject experienced a penile lesion–squamous cell. The last dose of study drug prior to the onset of the event was taken on 01-Nov-2009. Treatment of the event included hydrocortisone butyrate. The event resolved without sequelae on [redacted] (b) (6). On [redacted] (b) (6), the subject was diagnosed with squamous cell carcinoma–penis. The last dose of study drug prior to the onset of the event was taken on 26-Dec-2009. Treatment of the event included excisional biopsy on [redacted] (b) (6), hydrocortisone butyrate, lidocaine, Valium, Bacitracin, and Keflex. The event resolved without sequelae on [redacted] During physical examination on an unknown date, the subject was noted to have bilateral inguinal hernias. On [redacted] (b) (6) the subject was admitted to the hospital and underwent a laparoscopic bilateral inguinal hernia repair with mesh. The subject recovered from the event of bilateral inguinal hernia and was discharged from the hospital on [redacted] (b) (6) The study drug was continued and the subject continued in the study. The last dose of study drug was taken on 11-Jan-2010. The subject completed the study on 09-Mar-2010. The subject's medical history includes presbyopia, hyperopia, seasonal allergic rhinitis, gastroesophageal reflux, colonoscopy, decreased libido, vasectomy, osteoarthritis bilateral hip and knee, recurrent back pain, cigarette use (1 pack per day), left knee surgery for torn meniscus, right knee surgery for ACL tear, kidney stones, and benign cyst left kidney. Concomitant medications included Neosporin (stopped 07-Jul-2009) and Protonix. The investigator considered the events of lightheaded and common cold as moderate in severity, the events of penile lesion–squamous cell,

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squamous cell carcinoma–penis, and bilateral inguinal hernia as severe in severity, and all events as not related to study drug.

Reviewer's Comment: The Reviewer agrees with the Sponsor that the SAE of bilateral inguinal hernia resulting in hospitalization and undergoing surgery, and squamous cell carcinoma of the penis, was not related to study drug.

Subject 117-028: syncope vasovagal post mepivacaine
Subject 117-028, a 40-year-old White male with a history of ED, was randomized to avanafil 50 mg in the TA-301 study on 01-May-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 21-Jul-2009. The subject's dose was up titrated to a 200 mg dose on 18-Aug-2009. On [redacted] (b) (6) the subject presented to the dentist and was administered mepivacaine local anesthesia. The last dose of study drug prior to the onset of the event was taken on [redacted] (b) (6). After the injection, the subject became nauseated and lightheaded, vomited, and lost consciousness for approximately 1-2 minutes. The subject was transported to the emergency room for evaluation and treatment. The subject initially was unable to talk or use his hands and complained of generalized numbness. The subject's symptoms resolved within 1 hour. Physical examination on admission revealed pupils reactive to light, extra-ocular movements intact, speech intact, no nystagmus or facial droop, power of 5/5 in all limbs, reflexes symmetrical, and gait unremarkable. The subject reported complaints of retrosternal chest pain the day prior to the event lasting 3-4 hours. An electrocardiogram revealed sinus bradycardia at 58 bpm. An echocardiogram revealed normal left ventricular size and function. The subject was subsequently diagnosed with syncope vasovagal post mepivacaine. The subject recovered from the event of syncope vasovagal post mepivacaine and was discharged from the hospital on [redacted] (b) (6) The study drug was continued and the subject continued in the study. The subject's medical history includes insomnia, kidney stone, prostatitis, removal of foreign body right eye, anxiety, pneumonia, depression, hypertension, laceration to the right hand, abscess incision and drainage, allergic rhinitis, and an allergy to sulfa. Concomitant medication included Ambien. The investigator considered the event of syncope vasovagal post mepivacaine as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer believes that the SAE of syncope vasovagal post mepivacaine was not related to study drug because the last dose of study drug was 3 days before the event and the event occurred immediately after injection of local anesthetic.

Subject 121-025: worsening of coronary artery disease
Subject 121-025, a 67-year-old White male with a history of ED, was randomized to placebo in the TA-301 study on 14-Aug-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 09-Jul-2009. The last dose of study drug was taken on 30-Jul-2009. On [redacted] (b) (6) a routine cardiac stress test revealed "irregularities." On the same date, the subject was admitted to the hospital and underwent a follow-up cardiac catheterization, left ventriculography, and selective coronary arteriography which revealed normal ventricular systolic function with inferior hypokinesis,

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mildly elevated left ventricular and diastolic pressure, patent site of intervention in the mid-left anterior descending artery with moderate left anterior descending disease distally, and significant proximal and mid-right coronary artery stenosis. A successful percutaneous transluminal coronary angioplasty and drug eluting stent placement (x3) of the proximal and mid right coronary artery were performed. The subject was subsequently diagnosed with worsening coronary artery disease. Additional treatment of the event included Plavix. The subject recovered from the event of worsening of coronary artery disease on (b) (6) and was discharged from the hospital on (b) (6) The subject was withdrawn from the study due to the event on 14-Aug-2009. The subject's medical history includes cardiac chest pain, elevated cholesterol, coronary artery disease, hypertension, heart palpitations, stent placement, psoriasis, gastroesophageal reflux disease, benign prostatic hypertrophy, surgery to correct facial spasm, osteoarthritis, surgery to correct compressed spinal cord, mild cataract in left eye, myopia, seasonal allergies, and allergies to Duragesic patch, methotrexate, Orudis, Zonegran, and Celebrex. Concomitant medications included aspirin, Zyrtec, Plavix, Voltaren, fish oil, gabapentin, Nitroquick, niacin/simvastatin (1000/20), Toprol XL, niacin, ramipril, Flomax, hydrocodone-acetaminophen (10/500), Altace, and vitamin D. The investigator considered the event of worsening of coronary artery disease as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsot that the SAE of worsening of coronary artery disease in this subject was not related to study drug as the worsened coronary artery disease was picked up on routine stress test conducted 4 days after the last dose of study drug.

Subject 122-013: cervical spinal stenosis
Subject 122-013, a 62-year-old White male with a history of erectile dysfunction, was randomized to avanafil 50 mg in the TA-301 study on 11-Feb-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 21-May-2009. The subject's dose was up titrated to a 200 mg dose on 18-Jun-2009. On (b) (6) the subject was hospitalized and underwent a right-sided facetectomy of C5-C6, C6-C7, C7-T1, and microscopic foraminotomy of C6, C7, C8 nerve roots for the treatment of cervical spinal stenosis. The last dose of study drug prior to the onset of the event was taken on 10-Oct-2009. The subject recovered from the event of cervical spinal stenosis and was discharged from the hospital on (b) (6). Additional treatment of the event included Zanaflex and Lortab 7.5. The study drug was continued and the subject continued in the study. The subject's medical history includes bilateral feet neuropathy, hypercholesterolemia, gastroesophageal reflux disease, vasectomy, bone spurs removed from neck, two occurrences of torn cartilage right knee, left knee repair due to torn cartilage, right knee surgery, right knee repaired, osteoarthritis, L4/L5 fused, T1-C5 and L4/L5 rod placement, scar tissue removed from uvula area, sleep apnea, and uvula removed. Concomitant medications included Celebrex. Nexium, Lyrica, pravastatin, and aspirin. The investigator considered the event of cervical spinal stenosis as moderate in severity and not related to study drug.

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Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of cervical spinal stenosis was not related to study drug.

Subject 129-011: subdural hematoma
Subject 129-011, a 61-year-old White male with a history of ED, was randomized to avanafil 50 mg in the TA-301 study on 15-Jan-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 15-Apr-2009. On [redacted] (b) (6) the subject was hospitalized with a 7-day history of a severe headache after hitting his head on his pickup truck. The last dose of study drug prior to the onset of the event was taken on [redacted] (b) (6). Additional complaints included "feeling abnormally sleepy," unsteady gait, and confusion. On physical examination, the subject was alert and oriented, slow to respond, and had word finding difficulties. A computerized tomogram (CT) scan revealed a subdural hematoma, approximately 3 cm, with compression of the left lateral ventricle as well as a midline shift. The subject was subsequently diagnosed with a subdural hematoma. On [redacted] (b) (6) the subject underwent a left frontoparietal bur hole and drainage. On [redacted] (b) (6), a CT scan performed postoperatively revealed marked reduction in midline shift and otherwise appropriate postoperative changes with excellent evacuation of the subdural hematoma. The subject's headache and confusion resolved and level of consciousness improved. The subject recovered from the event and was discharged from the hospital on [redacted] (b) (6) The study drug was interrupted from 26-Sep-2009 to 19-Nov-2009. The subject continued in the study. The subject's medical history includes hypercholesterolemia, tension headaches, actinic keratosis, psoriasis, diverticulitis, gastroesophageal reflux disease, genital herpes, calculus of kidney, enlarged prostate, hepatitis A antibody positive, recurrent back pain, osteoarthritis, alcohol use (10 glasses/week of wine), presbyopia, cigarette use (1 pack/day), recurrent bronchitis, chronic obstructive pulmonary disease, frequent cough, herpes simplex, and shortness of breath. Concomitant medications included aspirin, Lipitor, Dovonex 0.005%, clobetasol 0.05%, desonide 0.05%, Nexium, ibuprofen, nystatin/triamcinolone, Elidel 1%, Spiriva, and Halobetasol propionate 0.05%. The investigator considered the event of subdural hematoma as moderate in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of subdual hematoma in this subject was not related to study drug because the event began after hitting his head on a pickup truck and 14 days after the last dose.

Subject 135-064: paroxysmal atrial fibrillation, worsening aortic valve stenosis, and left pneumothorax
Subject 135-064, an 88-year-old White male with a history of ED, was randomized to avanafil 100 mg in the TA-301 study on 12-Mar-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 11-Jun-2009. The last dose of study drug was taken on 14-Jul-2009. The subject was withdrawn from the study due to the event on 16-Jul-2009. On an unknown date, the subject underwent a coronary angiography and hemodynamic study. The hemodynamic study revealed significant aortic stenosis with an aortic valve estimated area of 0.8 cm^2. The left ventricular angiogram was normal, and wedge was unremarkable. The subject's coronary angiogram revealed noncritical

disease with an intact and unremarkable circumflex stent. On [redacted] (b) (6) the subject was admitted to the hospital for evaluation and treatment of worsening aortic valve stenosis. On the same date, the subject underwent an aortic valve replacement, replacement of the ascending aorta, and single vessel bypass grafting. Postoperatively, the subject developed paroxysmal atrial fibrillation and a left pneumothorax. Treatment of the event of atrial fibrillation included amiodarone, and treatment of the event of left pneumothorax included a chest tube. The subject recovered from the events of paroxysmal atrial fibrillation and worsening aortic valve stenosis on [redacted] (b) (6), and the event of left pneumothorax on [redacted] (b) (6) The subject was discharged from the hospital on [redacted] (b) (6) The subject's medical history includes mild valve disease, bilateral carotid endarterectomy, coronary artery disease, hypertension, insomnia, restless leg syndrome, eczema, hyperlipidemia, benign prostatic hypertrophy, hip replacement, asthma, right coronary stent, hypertension, congestive heart failure, allergy to horse serum, and hay fever. Concomitant medications included aspirin, q-var, furosemide, lisinopril, lovastatin, Bystolic, niacin, Klor Con, albuterol, Flomax, temazepam, Centrum Silver, and Ambien. The investigator considered the events of paroxysmal atrial fibrillation and left pneumothorax as moderate in severity, the event of worsening aortic valve stenosis as severe in severity, and all events as not related to study drug.

The Reviewer agrees with the Sponsor that the SAE's of paroxysmal atrial fibrillation and left pneumothorax, as well as worsening aortic valve stenosis were not related to study drug in this 88 year old man.

Subject 137-007: small bowel obstruction
Subject 137-007, a 62-year-old White male with a history of ED, was randomized to avanafil 50 mg in the TA-301 study on 24-Feb-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 21-May-2009. The subject's dose was utitrated to a 200 mg dose on 18-Jun-2009. On [redacted] (b) (6) the subject experienced severe abdominal pain, diaphoresis, and nausea. The last dose of study drug prior to the onset of the event was taken on 20-Sep-2009. On admission, laboratory testing revealed a white blood cell count of 11.4 and absolute neutrophil count of 8.7 (normal ranges and units not provided). On [redacted] (b) (6), abdominal X-rays and a computerized tomography of the abdomen and pelvis with contrast revealed a small bowel obstruction at the level of the ileum. Treatment of the event included Zofran and morphine. The abdominal pain persisted. On [redacted] (b) (6), an abdominal X-ray revealed findings consistent with small bowel obstruction. On [redacted] (b) (6), a laparoscopic exploration revealed adhesions from prior laparoscopic gallbladder surgery, and lysis of adhesions and small bowel resection were performed. Postoperatively, the subject had a bowel movement and did not experience abdominal pain, nausea, or vomiting. Additional treatment of the event included fentanyl, lidocaine, Reglan, Versed, Phenergan, propofol, succinylcholine, and vecuronium. The subject recovered from the event and was discharged from the hospital on [redacted] (b) (6) The study drug was continued and the subject continued in the study. The subject's medical history includes hypertension, tropical ulcer, cholecystectomy, gallstones, diverticuli sigmoid colon, fractured left humerus, osteoarthritis of fingers bilateral, history of malaria, hearing loss, myopia, tonsillectomy, tonsillitis, and vasectomy. Concomitant

medications included baby aspirin and glucosamine chondroitin. The investigator considered the event of small bowel obstruction as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of small bowel obstruction in this subject was not related to study drug but rather to adhesions from a previous gallbladder surgery.

Subject 203-013: fractured neck
Subject 203-013, a 52-year-old White male with a history of ED and diabetes, was randomized to placebo in the TA-302 study on 24-Mar-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 23-Jun-2009. The subject's dose was up titrated to a 200 mg dose on 18-Aug-2009. The last dose of study drug was taken on 01-Sep-2009. On (b) (6) the subject was involved in a motorcycle accident while traveling 45-55 miles/hour. The subject was wearing a helmet at the time of the accident. Upon arrival at the emergency room, the subject was neurologically intact, awake, alert, oriented x3, and was in no acute distress. Physical examination revealed a motor examination of 5/5 throughout, bilaterally. A computed tomography (CT) scan revealed a hangman-type fracture at C2 with a minimally displaced fracture through the left pedicle of C2 and through the pedicle body juncture on the right at C2. A CT angiogram of the neck revealed no evidence of vertebral dissection. The subject was subsequently admitted to the hospital for treatment of a fractured neck. Treatment of the event included placement of a rigid cervical collar. The subject also experienced a scapula fracture and rib fracture (non-serious adverse events). The subject was discharged from the hospital on (b) (6) and was withdrawn from the study due to the events on 10-Sep-2009. The event of fractured neck was considered ongoing at the time of discontinuation. The subject's medical history includes high cholesterol, hypertension, headaches, night sweats, nocturia, joint and back pain, fatigue, vision problems (wears reading glasses), and surgery on bottom of left foot and shoulder. Concomitant medications included Tricor, metformin, Actos, and Altace. The investigator considered the event of fractured neck as severe in severity, rib and scapula fracture as moderate in severity, and all events as not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of fractured neck in this subject was not related to study drug.

Subject 222-004: congestive heart failure exacerbation
Subject 222-004, a 63-year-old White male with a history of ED and diabetes, was randomized to avanafil 100 mg in the TA-302 study on 23-Jan-2009. The subject signed informed consent for the TA-314 open-label extension study and was assigned to a 100 mg dose of avanafil on 15-Apr-2009. The last dose of study drug was on (b) (6). On (b) (6) the subject presented to his primary care physician with complaints of shortness of breath, and a chest X-ray revealed congestive heart failure and pulmonary edema. On that same date, the subject was admitted to the hospital for evaluation and treatment of exacerbation of congestive heart failure. A cardiac catheterization showed non-occlusive coronary artery disease (no greater than 20-35%), with an ejection fraction of 30-35%. An electrocardiogram revealed a new left bundle

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branch block. A duplex ultrasound of the lower extremities showed no evidence of deep vein thrombosis. Cardiac enzymes were negative. Treatment of the event included furosemide, nitroglycerine, and heparin. The subject recovered from the event of exacerbation of congestive heart failure, and was discharged from the hospital on (b) (6) The subject was withdrawn from the study due to the event on 17-Dec-2009. The subject's medical history includes hypertension, peripheral artery disease, mild cellulitis, skin allergies, plantar fasciitis, dyslipidemia, obesity, cholecystectomy, cholecystitis, dyspepsia, benign prostatic hyperplasia, acute right knee pain, chronic lower back pain, lumbar spine osteoarthritis, anxiety, diabetes, tobacco use, and depression. Concomitant medications included aspirin, Xanax, and Actos. The investigator considered the event of congestive heart failure exacerbation as severe in severity and not related to study drug.

Reviewer's comment: The Reviewer agrees with the Sponsor that the SAE of congestive heart failure exacerbation in this diabetic subject was not related to study drug because the last dose of study drug was taken more than 2 months before the event occurred.

7.3.2.6.4 Individual Phase 1 Study TA-02

Subject #16 reported moderate pharyngolaryngeal pain with onset on 21 October 2002, approximately 1 day following administration of avanafil 100 mg. Two days following onset of the pain, 23 October 2002, the Investigator noted the following findings upon physical examination: swollen glands, temperature 101°F, mild erythema of pharynx, bilateral anterior cervical nodes enlarged, clear mucous. The Investigator considered the pharyngolaryngeal pain to be probably due to a viral infection and unlikely related to avanafil. The pharyngolaryngeal pain for Subject #16 was considered an SAE as the subject was admitted to a local hospital on (b) (6) and was diagnosed with tonsillar abscess. Drainage of the abscess was performed and the subject remained hospitalized for 6 days. On (b) (6), Subject #16 was discharged from the hospital, the SAE was resolved, and early termination assessments were completed.

Reviewer's comment: The Reviewer agrees with the investigator that the SAE of pharyngo-laryngeal pain with tonsillar abscess was not related to study drug.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Integrated Double-Blind Cohort (TA-301, TA-302, and TA-05)

7.3.3.1.1 Integrated Phase 3 Double-blind Cohort (TA-301 and TA-302)

In total, 22 (2.1%) subjects in the Phase 3 double-blind cohort had an adverse event that resulted in study drug discontinuation: 5 (1.7%) subjects in the placebo group, 3 (1.9%) subjects in the avanafil 50 mg group, 8 (2.8%) subjects in the avanafil 100 mg group, and 6 (2.0%) subjects in

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the avanafil 200 mg group. No specific adverse event led to study drug discontinuation for more than 3 subjects in any treatment group.

7.3.3.1.2 Study TA-05

3 subjects in the avanafil 300 mg group discontinued from Study TA-05 due to adverse events. For 1 of the 3 subjects, the adverse event that led to discontinuation was experienced by the subject's partner.

7.3.3.2 Individual Phase 3, Open-Label, Long-Term Study TA-314

For 10 subjects, the adverse events that led to discontinuation in the long-term, open-label extension Study TA-314 were considered by the investigators to be related to study drug: 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 pruritus and eye swelling. The subject with pruritus and eye swelling (Subject 238-010) had previously completed the TA-302 study during which he received avanafil 100 mg; the subject did not have any adverse events during study TA-302. The events of pruritus and eye swelling were reported as itching in the neck area and swelling around the eyes. The subject recovered from the event after 6 days.

Table 7.3.3.1 Listing of subjects with AEs that resulted in study drug discontinuation Safety Population (TA-314)

Subject No.	Treatment at Onset	Adverse Event Preferred Term	Related to Study Drug?	Serious?
118-001	avanafil 50 mg	palpitations heart rate increased dizziness	yes yes yes	no no no
103-010	avanafil 100 mg	acute psychosis	no	yes
110-040	avanafil 100 mg	femoral artery occlusion	no	yes
113-039	avanafil 100 mg	dizziness	yes	no
114-029	avanafil 100 mg	pigmentation disorder	yes	no
115-050	avanafil 100 mg	chest discomfort	yes	no
121-025	avanafil 100 mg	coronary artery disease	no	yes
123-030	avanafil 100 mg	dyspepsia headache diarrhea	yes yes yes	no no no
135-064	avanafil 100 mg	aortic valve stenosis	no	yes
140-008	avanafil 100 mg	dizziness	yes	no
221-006	avanafil 100 mg	hyperkalemia	no	no
222-004	avanafil 100 mg	cardiac failure congestive	no	yes
224-017	avanafil 100 mg	diabetes mellitus inadequate control	no	no
238-010	avanafil 100 mg	pruritus eye swelling	yes yes	no no
113-032	avanafil 200 mg	back pain headache	yes yes	no no
130-010	avanafil 200 mg	headache	yes	no

135-021	avanafil 200 mg	hypogonadism	no	no
203-013	avanafil 200 mg	cervical vertebral fracture rib fracture scapula fracture	no no no	yes no no
209-011	avanafil 200 mg	back pain	no	no
236-003	avanafil 200 mg	erection increased	yes	no

7.3.3.3 Individual Phase 3 Study TA-303 (120-Day Safety Update)

Six (2.0%) subjects discontinued study drug due to an adverse event: 1 (1.0%) subject in the placebo group, 3 (3.0%) subjects in the avanafil 100 mg group, and 2 (2.0%) subjects in the avanafil 200 mg group. All adverse events leading to discontinuation were treatment emergent. For 2 (2.0%) subjects in the avanafil 100 mg group (Subjects 329-008 and 337-010), the adverse event that led to discontinuation was considered by the investigator to be related to study drug. For 1 (1.0%) subject in the avanafil 200 mg group (Subject 339-022), the adverse events that led to discontinuation were considered by the investigator to be related to study drug.

Table 7.3.3.2 Listing of Subjects with AEs Led to Study Drug Discontinuation – TA-303 – Safety Population

Treatment Subject No.	Adverse Event Preferred Term	Relationship to Study Drug	Serious
Placebo			
337-008	lumbar spinal stenosis	not related	no
Avanafil 100 mg			
326-015	abdominal pain upper	not related	no
329-008	vision blurred headache nausea	related related related	no no no
337-010	vomiting dyspepsia	related related	no no
Avanafil 200 mg			
337-005	hypertension	not related	no
339-022	psychomotor hyperactivity inappropriate affect headache	related related related	no no no

Subject 329-008: blurred vision, headache, and nausea
Subject 329-008, a 60-year-old Black male with a history of erectile dysfunction, signed informed consent for study TA-303 on 04-Feb-2010. The subject was randomized to avanafil 100 mg on 11-Mar-2010. The first and last dose of study drug was taken on 08-Apr-2010. On the same date, the subject experienced blurred vision, headache, and nausea. Treatment of the events is unknown. The subject recovered from the events on the same date. The study drug was discontinued and the subject was withdrawn from the study due to the events on 29-Apr-2010. The subject's medical history includes hypersensitivity to aspirin, hypercholesterolemia, hypertension, left dislocated shoulder, sterilization, and previous tobacco use. Concomitant medication included Caduet. The investigator considered the events of blurred vision, headache, and nausea as moderate in severity and related to study drug.

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Subject 337-010: indigestion and vomiting
Subject 337-010, a 52-year-old White male with a history of erectile dysfunction and esophageal reflux, signed informed consent for study TA-303 on 21-Oct-2010. The subject was randomized to avanafil 100 mg on 24-Nov-2010. The first dose of study drug was taken on 28-Nov-2010. On the same date, the subject experienced indigestion, which resolved on 29-Nov-2010. On 04-Dec-2010, the subject administered the study drug two more times and again experienced indigestion, which resolved on 05-Dec-2010. The subject took the final dose of study drug on 17-Dec-2010 and experienced vomiting and a third episode of indigestion. Treatment of the events is unknown. The event of vomiting resolved on 17-Dec-2010 and the third episode of indigestion resolved on 18-Dec-2010. The study drug was discontinued and the subject was withdrawn from the study due to the events on 29-Dec-2010. The subject's medical history includes dissection of the right carotid artery, allergies to amoxicillin, codeine, erythromycin, and sulfonamides, hypercholesterolemia, hypertension, pain due to injury of the right knee, seasonal allergies, and current tobacco use. Concomitant medications included Lipitor, Flonase, ibuprofen, Prevacid, Walatrin (loratadine), and verapamil hydrochloride CR. The investigator considered the event of vomiting as mild in severity, the event of indigestion as severe in severity, and both events as related to study drug.

Subject 339-022: hyperactivity, uncontrolled laughter, and headache
Subject 339-022, a 49-year-old White male with a history of erectile dysfunction, signed informed consent for study TA-303 on 20-Aug-2010. The subject was randomized to avanafil 200 mg on 10-Sep-2010. The first dose of study drug was taken on 12-Sep-2010. On 13-Sep-2010, the subject took the last dose of study drug and developed hyperactivity, uncontrolled laughter, and headache. Treatment of the event of headache included Tylenol PM. Treatment of the events of hyperactivity and uncontrolled laughter is unknown. The events of hyperactivity and uncontrolled laughter resolved on the same day. The event of headache resolved on 14-Sep-2010. The study drug was discontinued and the subject was withdrawn from the study due to the events on 23-Sep-2010. The subject's medical history includes hemangioma, hypertension, hypothyroidism, and previous tobacco use. Concomitant medications included Synthroid and Toprol. The investigator considered the events of hyperactivity, uncontrolled laughter, and headache as mild in severity and related to study drug.

7.3.3.4 Supportive Studies TA-01 and TA-03

Study TA-01: No subject discontinued study drug due to an adverse event.

Study TA-03: The partner of 1 subject became pregnant during the study and it was noted that the subject discontinued study drug due to this adverse event; however, "non-compliance with study requirements" was recorded as the reason the subject was discontinued from the study. No subject discontinued study drug due to an adverse event.

7.3.3.5 Phase 1 Studies:

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One subject discontinued from the study due to an adverse event during the Phase 1 program. In study TA-02, Subject #16 discontinued due to an SAE of pharyngolaryngeal pain; the investigator considered the event to be unlikely related to study drug. No other subjects discontinued study drug due to an adverse event during the Phase 1 program.

7.3.4 Common Adverse Events

7.3.4.1 An overview of adverse events for Phase 3 double-blind cohort (TA-301+TA-302)

Table 7.3.4.1 Overview of Adverse Events – Double-Blind Cohort (TA-301+TA-302)

	Placebo (N=291) n (%)	Avanafil				Total (N=1032) n (%)
		50 mg (N=160) n (%)	100 mg (N=288) n (%)	200 mg (N=293) n (%)	Total (N=741) n (%)	
Subjects with TEAEs						
Any TEAE	73 (25.1)	52 (32.5)	113 (39.2)	105 (35.8)	270 (36.4)	343 (33.2)
Any drug-related TEAE	9 (3.1)	14 (8.8)	34 (11.8)	46 (15.7)	94 (12.7)	103 (10.0)
Maximum severity of TEAEs						
Mild	43 (14.8)	31 (19.4)	63 (21.9)	58 (19.8)	152 (20.5)	195 (18.9)
Moderate	28 (9.6)	19 (11.9)	41 (14.2)	43 (14.7)	103 (13.9)	131 (12.7)
Severe	2 (0.7)	2 (1.3)	9 (3.1)	4 (1.4)	15 (2.0)	17 (1.6)
Maximum severity of drug-related TEAEs						
Mild	8 (2.7)	11 (6.9)	27 (9.4)	32 (10.9)	70 (9.4)	78 (7.6)
Moderate	1 (0.3)	3 (1.9)	5 (1.7)	14 (4.8)	22 (3.0)	23 (2.2)
Severe	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.3)	2 (0.2)
Deaths	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Subjects with SAEs						
Any SAE	3 (1.0)	1 (0.6)	6 (2.1)	7 (2.4)	14 (1.9)	17 (1.6)
Any treatment-emergent SAE	2 (0.7)	1 (0.6)	6 (2.1)	7 (2.4)	14 (1.9)	16 (1.6)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study drug discontinuations due to adverse events						
Any adverse event	5 (1.7)	3 (1.9)	8 (2.8)	6 (2.0)	17 (2.3)	22 (2.1)
Any TEAE	5 (1.7)	3 (1.9)	7 (2.4)	6 (2.0)	16 (2.2)	21 (2.0)
Any drug-related TEAE	0 (0.0)	1 (0.6)	2 (0.7)	3 (1.0)	6 (0.8)	6 (0.6)
Any SAE	1 (0.3)	1 (0.6)	3 (1.0)	2 (0.7)	6 (0.8)	7 (0.7)

In total, 343 (33.2%) subjects had a TEAE. The incidence of TEAEs was higher in the avanafil groups (32.5% to 39.2%) than in the placebo group (25.1%). In total, 103 (10.0%) subjects had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (8.8% to 15.7%) than in the placebo group (3.1%). Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups. One subject (in the avanafil 100 mg

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group) died during study TA-301 from a self-inflicted gunshot wound; the event was considered by the investigator to be not related to study drug. In total, 17 (1.6%) subjects had an SAE. The incidence of SAEs was similar for the treatment groups. No subject had an SAE that was considered by the investigators to be related to study drug. In total, 22 (2.1%) subjects discontinued study drug due to an adverse event. The percentage of subjects who discontinued study drug was similar for the treatment groups. In total, 6 (0.6%) subjects discontinued study drug due to a TEAE that was considered by the investigators to be related to study drug.

Treatment-Emergent Adverse Events (TEAEs) in Phase 3 Double-Blind Cohort (TA-301, and TA-302)

Table 7.3.4.2 Summary of Treatment-Emergent Adverse Events (TEAEs) (≥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				Total (N=1032) n (%)
		50 mg (N=160) n (%)	100 mg (N=288) n (%)	200 mg (N=293) n (%)	Total (N=741) n (%)	
Infections and infestations	19 (6.5)	13 (8.1)	29 (10.1)	28 (9.6)	70 (9.4)	89 (8.6)
Nasopharyngitis	8 (2.7)	1 (0.6)	6 (2.1)	10 (3.4)	17 (2.3)	25 (2.4)
Sinusitis	3 (1.0)	0 (0.0)	5 (1.7)	3 (1.0)	8 (1.1)	11 (1.1)
Bronchitis	1 (0.3)	3 (1.9)	1 (0.3)	4 (1.4)	8 (1.1)	9 (0.9)
Influenza	0 (0.0)	1 (0.6)	5 (1.7)	1 (0.3)	7 (0.9)	7 (0.7)
Upper respiratory tract infection	1 (0.3)	3 (1.9)	2 (0.7)	1 (0.3)	6 (0.8)	7 (0.7)
Nervous system disorders	9 (3.1)	9 (5.6)	22 (7.6)	34 (11.6)	65 (8.8)	74 (7.2)
Headache	4 (1.4)	7 (4.4)	17 (5.9)	30 (10.2)	54 (7.3)	58 (5.6)
Musculoskeletal & connective tissue disorders	14 (4.8)	11 (6.9)	16 (5.6)	11 (3.8)	38 (5.1)	52 (5.0)
Back pain	4 (1.4)	4 (2.5)	6 (2.1)	4 (1.4)	14 (1.9)	18 (1.7)
Pain in extremity	2 (0.7)	0 (0.0)	2 (0.7)	3 (1.0)	5 (0.7)	7 (0.7)
Gastrointestinal disorders	7 (2.4)	9 (5.6)	12 (4.2)	15 (5.1)	36 (4.9)	43 (4.2)
Diarrhea	0 (0.0)	1 (0.6)	1 (0.3)	4 (1.4)	6 (0.8)	6 (0.6)
Dyspepsia	0 (0.0)	1 (0.6)	1 (0.3)	4 (1.4)	6 (0.8)	6 (0.6)
Nausea	0 (0.0)	0 (0.0)	2 (0.7)	3 (1.0)	5 (0.7)	5 (0.5)
Constipation	1 (0.3)	3 (1.9)	0 (0.0)	0 (0.0)	3 (0.4)	4 (0.4)
Stomach discomfort	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.3)	3 (0.4)	3 (0.3)
Vascular disorders	1 (0.3)	7 (4.4)	18 (6.3)	11 (3.8)	36 (4.9)	37 (3.6)
Flushing	0 (0.0)	6 (3.8)	12 (4.2)	11 (3.8)	29 (3.9)	29 (2.8)
Hypertension	0 (0.0)	1 (0.6)	4 (1.4)	0 (0.0)	5 (0.7)	5 (0.5)
Respiratory, thoracic, and mediastinal disorders	5 (1.7)	4 (2.5)	14 (4.9)	15 (5.1)	33 (4.5)	38 (3.7)
Nasal congestion	2 (0.7)	1 (0.6)	7 (2.4)	4 (1.4)	12 (1.6)	14 (1.4)
Sinus congestion	1 (0.3)	1 (0.6)	2 (0.7)	5 (1.7)	8 (1.1)	9 (0.9)
Injury, poisoning, and procedural complications	10 (3.4)	3 (1.9)	8 (2.8)	4 (1.4)	15 (2.0)	25 (2.4)
Skin laceration	0 (0.0)	1 (0.6)	3 (1.0)	0 (0.0)	4 (0.5)	4 (0.4)
Skin & subcutaneous tissue disorders	4 (1.4)	3 (1.9)	3 (1.0)	4 (1.4)	10 (1.3)	14 (1.4)
Rash	1 (0.3)	2 (1.3)	0 (0.0)	1 (0.3)	3 (0.4)	4 (0.4)

Treatment-emergent adverse events were defined as adverse events occurring after the first dose of study drug or after the first drug dispense date (if the first dose date was missing) and up to 28 days after the last dose of study drug.

The most common system organ classes of TEAEs were infections and infestations (8.6%), nervous system disorders (7.2%), and musculoskeletal and connective tissue disorders (5.0%).

The incidences of TEAEs in the following system organ classes were higher in the avanafil groups than in the placebo group:

- Infections and infestations (placebo, 6.5%; avanafil 50 mg, 8.1%; avanafil 100 mg, 10.1%; and avanafil 200 mg, 9.6%);
- Nervous system disorders (placebo, 3.1%; avanafil 50 mg, 5.6%; avanafil 100 mg, 7.6%; and avanafil 200 mg, 11.6%);
- Gastrointestinal disorders (placebo, 2.4%; avanafil 50 mg, 5.6%; avanafil 100 mg, 4.2%; and avanafil 200 mg, 5.1%);
- Vascular disorders (placebo, 0.3%; avanafil 50 mg, 4.4%; avanafil 100 mg, 6.3%; and avanafil 200 mg, 3.8%); and
- Respiratory, thoracic, and mediastinal disorders (placebo, 1.7%; avanafil 50 mg, 2.5%; avanafil 100 mg, 4.9%; and avanafil 200 mg, 5.1%).

The incidences of the following TEAEs were higher in the avanafil groups than in the placebo group:

- Influenza (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 1.7%; and avanafil 200 mg, 0.3%);
- Headache (placebo, 1.4%; avanafil 50 mg, 4.4%; avanafil 100 mg, 5.9%; and avanafil 200 mg, 10.2%);
- Dyspepsia (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 0.3%; and avanafil 200 mg, 1.4%); and
- Flushing (placebo, 0.0%; avanafil 50 mg, 3.8%; avanafil 100 mg, 4.2%; and avanafil 200 mg, 3.8%).

Table 7.3.4.3 TEAEs Higher in avanafil groups vs. in the placebo group – Phase 3 Double Blind Cohort (TA-301 + TA-302)

	Placebo (N=291) n (%)	Avanafil 50 mg (N=160) n (%)	Avanafil 100 mg (N=288) n (%)	Avanafil 200 mg (N=293) n (%)
Influrenza	0 (0.0)	1 (0.6)	5 (1.7)	1 (0.3)
Headache	4 (1.4)	7 (4.4)	17 (5.9)	30 (10.2)
Dyspepsia	0 (0.0)	1 (0.6)	1 (0.3)	4 (1.4)
Flushing	0 (0.0)	6 (3.8)	12 (4.2)	11 (3.8)

Most of the TEAEs were mild or moderate in severity. The most frequently reported severe TEAE was headache (2 subjects); no other specific severe TEAEs were reported by more than 1 subject.

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Reviewer's comment: The noticeable TEAE in the Phase 3 double blind studies was headache occurring in the placebo, and avanafil 50 mg, 100 mg and 200 mg groups at incidences of 1.4% and 4.4%, 5.9% and 10.2%, respectively.

7.3.4.2 Individual Phase 3, Open-Label, Long-Term Study TA-314

By definition, the Safety Population included all subjects who signed informed consent. However, for the summary of adverse events by onset treatment in study TA-314, only subjects who were actually dispensed study drug were considered for analysis. One subject, Subject #215-054, was not dispensed study drug and is excluded from these analyses. This subject did not experience any adverse events following informed consent for study TA-314.

All adverse events reported in this study were considered treatment-emergent. In total, 275 (38.7%) subjects had a TEAE and 79 (11.1%) subjects had a TEAE that was considered by the investigators to be related to study drug. The most frequently reported TEAEs (PT) were headache (5.6%), flushing (3.5%), nasopharyngitis (3.4%), nasal congestion (2.1%), upper respiratory tract infection (1.5%), influenza (1.5%), and back pain (1.5%). All other TEAEs were reported by 10 (1.4%) or fewer subjects. The incidence of these events was higher with avanafil 200 mg treatment than with avanafil 100 mg treatment. Most of the TEAEs were mild or moderate in severity. Twenty-one (3.0%) subjects had a TEAE that was considered severe in severity. No subject died during the study. Eleven (1.5%) subjects had an SAE. No subject had an SAE that was considered by the investigator to be related to study drug. Twenty (2.8%) subjects discontinued study drug due to a TEAE. For 10 (1.4%) subjects, the adverse event that led to discontinuation was considered by the investigator to be related to study drug.

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Table 7.3.4.4 Summary of TEAEs (≥1% of Subjects Overall) by Treatment at Onset, System Organ Class, and PT – TA-314 – Safety Population

System Organ Class Preferred Term (PT)	TA 314 Avanafil			
	50 mg (N=4) n (%)	100 mg (N=711) n (%)	200 mg (N=514) n (%)	Total (N=711) n (%)
Infections and infestations	0 (0.0)	27 (3.8)	66 (12.8)	87 (12.2)
Nasopharyngitis	0 (0.0)	5 (0.7)	20 (3.9)	24 (3.4)
Upper respiratory tract infection	0 (0.0)	5 (0.7)	7 (1.4)	11 (1.5)
Influenza	0 (0.0)	3 (0.4)	8 (1.6)	11 (1.5)
Sinusitis	0 (0.0)	5 (0.7)	6 (1.2)	10 (1.4)
Bronchitis	0 (0.0)	0 (0.0)	8 (1.6)	8 (1.1)
Nervous system disorders	2 (50.0)	26 (3.7)	36 (7.0)	56 (7.9)
Headache	1 (25.0)	19 (2.7)	27 (5.3)	40 (5.6)
Dizziness	1 (25.0)	6 (0.8)	3 (0.6)	9 (1.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	20 (2.8)	24 (4.7)	39 (5.5)
Back pain	0 (0.0)	4 (0.6)	8 (1.6)	11 (1.5)
Arthralgia	0 (0.0)	2 (0.3)	5 (1.0)	7 (1.0)
Vascular disorders	0 (0.0)	18 (2.5)	22 (4.3)	38 (5.3)
Flushing	0 (0.0)	10 (1.4)	17 (3.3)	25 (3.5)
Hypertension	0 (0.0)	4 (0.6)	5 (1.0)	9 (1.3)
Gastrointestinal disorders	0 (0.0)	12 (1.7)	26 (5.1)	36 (5.1)
Diarrhea	0 (0.0)	3 (0.4)	6 (1.2)	9 (1.3)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	14 (2.0)	19 (3.7)	30 (4.2)
Nasal congestion	0 (0.0)	8 (1.1)	10 (1.9)	15 (2.1)

All AEs reported in TA-314 are considered treatment-emergent. AEs were reported from the date of informed consent until 28 days after the last dose of study drug or until the subject was discontinued from the study, whichever was later. Only AEs occurring on or after the first study drug dispensation date in TA-314 are included. Note that subjects may be included under more than one treatment.

Reviewer's comment: It should be noted that TA-314 was an open-label study in which subjects had the option to titrate their dose up or down. Accordingly, study TA-314 provides reliable assessments of adverse event rates over the range of doses included in the study, but was not designed to provide robust comparisons between specific avanafil doses.

In total, 79 (11.1%) subjects had a TEAE considered by the investigator to be related to study drug in study TA-314. The most frequently reported drug-related TEAEs were headache (4.4%), flushing (3.4%), nasal congestion (1.5%), dizziness (0.7%), dyspepsia (0.6%), and nausea (0.4%). All other drug-related TEAEs were reported by 2 (0.3%) or fewer subjects.

Table 7.3.4.5 Study TA-314: Most Frequently Reported Drug-Related TEAEs – Safety Population

TA-314	Avanafil 50 mg (N=4) n (%)	Avanafil 100 mg (N=711) n (%)	Avanafil 200 mg (N=514) n (%)	Total (N=711) n (%)
Headache	1 (25.0)	15 (2.1)	22 (4.3)	31 (4.4)
Flushing	0 (0.0)	9 (1.3)	17 (3.3)	24 (3.4)
Nasal congestion	0 (0.0)	7 (1.0)	7 (1.4)	11 (1.5)
Dizziness	1 (25.0)	4 (0.6)	1 (0.2)	5 (0.7)
Despepsia	0 (0.0)	1 (0.1)	3 (0.6)	4 (0.6)
Nausea	0 (0.0)	2 (0.3)	3 (0.6)	3 (0.4)

Most of the TEAEs were mild or moderate in severity. Twenty-one (3.0%) subjects had a severe TEAE. Two (0.3%) subjects had 1 or more severe drug-related TEAEs (dyspepsia, headache, and diarrhea for Subject #123-030 while taking avanafil 100 mg and flushing for Subject #127-029 while taking avanafil 200 mg). The severe drug-related TEAEs of dyspepsia, headache, and diarrhea for Subject # 123-030 resulted in discontinuation of study drug. The severe drug-related TEAE of flushing for Subject # 127-029 did not result in a change in study drug. The TEAEs for these 2 subjects resolved.

Twenty (2.8%) subjects discontinued study drug due to a TEAE. For 10 (1.4%) subjects, the AE that led to discontinuation was considered by the investigator to be related to study drug.

In addition, the most common AEs with avanafil treatment from other studies including Phase 2 study TA-01 and TA-03 as well as phase 1 studies, were flushing, headache and nausea.

Reviewer's comment: The common adverse event profile includes headache, flushing, nasal congestion, as well as dizziness, dyspepsia, and nausea. The profile of common adverse events is similar to other marketed PDE 5 inhibitors.

7.3.5 Significant Adverse Events

It is not possible to rule out the role of avanafil in two serious cardiovascular adverse events, one from study TA-301 (Subject 130-012: moderate non obstructive coronary artery disease) and one from study TA-302 (Subject 203-031: unstable angina). Both these subjects were taking avanafil 200 mg. These are the only two cardiovascular events reported in the NDA where the role of avanafil could not be ruled out. Both patients had known serious underlying coronary artery disease, and both had undergone previous angioplasty. It is worth noting that no similar events were reported in Study TA-05 or Study TA-303 and none were reported among > 700 men treated for 9 months or longer in the long-term safety study (TA-314).

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7.3.6 Submission Specific Primary Safety Concerns

The primary safety concerns for avanafil are the same as for all marketed PDE5 inhibitors. No new specific primary safety concerns had been determined in the submission.

7.4 Supportive Safety Results

7.4.1 Laboratory Findings

Clinical Laboratory Evaluations

Analysis conducted by the Sponsor showed in the double-blind cohort including Studies TA-05, TA-301, and TA-302, the numbers and percentages of subjects with abnormal laboratory measurements were low, and no meaningful differences among the treatment groups were observed.

Table 7.4.1 Number (%) of Subjects Who Had Marked Laboratory Abnormalities During the Treatment Period – Double-Blind Cohort (TA-05+TA-301+TA-302)

Laboratory Parameter Category	Placebo n/N' (%)	Avanafil 50 mg n/N' (%)	Avanafil 100 mg n/N' (%)	Avanafil 200 mg n/N' (%)	Total n/N' (%)
ALT					
>3 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	1/321 (0.3)	1/1150 (0.1)
AST					
>3 × ULN	0/313 (0.0)	0/196 (0.0)	1/320 (0.3)	2/321 (0.6)	3/1150 (0.3)
Total bilirubin					
>1.5 × ULN	3/313 (1.0)	1/196 (0.5)	2/320 (0.6)	5/321 (1.6)	11/1150 (1.0)
Alkaline phosphatase					
>1.5 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	1/321 (0.3)	1/1150 (0.1)
Serum creatinine					
High	26/313 (8.3)	13/196 (6.6)	28/320 (8.8)	31/321 (9.7)	98/1150 (8.5)
Hematocrit					
High	3/310 (1.0)	1/197 (0.5)	4/318 (1.3)	5/315 (1.6)	13/1140 (1.1)

N' is the number of subjects with a baseline and post-baseline value for a given parameter.
ALT = alanine transaminase; AST= aspartate transaminase; ULN = upper limit of normal.

Integrated Phase 3 Double-Blind Cohort (TA-301 and TA-302)

The number and percentage of subjects in the Phase 3 double-blind cohort who had a marked abnormal laboratory measurement during the treatment period were similar to those in the double-blind cohort. Mean increases in glucose from baseline to end of study were observed in study TA-301 and TA-302. In these studies, the differences in mean increases in glucose between the avanafil groups and placebo group were not clinically meaningful.

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Table 7.4.4 summarizes changes in selected laboratory parameters from baseline to end of treatment in Study TA-314 by titration dose. Mean changes in safety laboratory parameters were not clinically meaningful.

Table 7.4.2 Changes in Selected Laboratory Parameters From Baseline to End of Treatment by TA-314 Titration Dose – Safety Population

Parameter Statistic	TA-314 100 mg only (N=171)	TA-314 100 mg and 200 mg (N=536)	TA-314 Other (N=5)	Total (N=712)
Alanine transaminase (IU/L)	n [1] = 145	n [1] = 524	n [1] = 3	n [1] = 672
Baseline [2] mean (SD)	30.6 (15.24)	29.5 (13.42)	26.0 (14.42)	29.7 (13.82)
End of treatment [3] mean (SD)	30.5 (17.09)	29.6 (19.95)	38.0 (13.08)	29.8 (19.34)
Mean change (SD)	-0.1 (14.81)	0.1 (15.88)	12.0 (18.19)	0.1 (15.66)
Aspartate transaminase (IU/L)	n [1] = 145	n [1] = 524	n [1] = 3	n [1] = 672
Baseline [2] mean (SD)	25.8 (9.06)	24.6 (8.32)	28.7 (15.14)	24.9 (8.52)
End of treatment [3] mean (SD)	25.3 (9.49)	24.6 (15.45)	31.0 (10.58)	24.8 (14.35)
Mean change (SD)	-0.4 (8.79)	-0.0 (14.57)	2.3 (6.11)	-0.1 (13.50)
Creatinine (mg/dL)	n [1] = 145	n [1] = 524	n [1] = 3	n [1] = 672
Baseline [2] mean (SD)	1.00 (0.153)	1.04 (0.180)	1.09 (0.036)	1.03 (0.175)
End of treatment [3] mean (SD)	1.03 (0.162)	1.08 (0.184)	1.11 (0.057)	1.07 (0.181)
Mean change (SD)	0.03 (0.094)	0.04 (0.110)	0.02 (0.067)	0.04 (0.106)
Bilirubin (mg/dL)	n [1] = 145	n [1] = 524	n [1] = 3	n [1] = 672
Baseline [2] mean (SD)	0.65 (0.345)	0.59 (0.271)	0.43 (0.058)	0.61 (0.289)
End of treatment [3] mean (SD)	0.63 (0.360)	0.59 (0.286)	0.67 (0.462)	0.60 (0.304)
Mean change (SD)	-0.02 (0.250)	-0.01 (0.217)	0.23 (0.404)	-0.01 (0.226)
Glucose (mg/dL)	n [1] = 145	n [1] = 524	n [1] = 3	n [1] = 672
Baseline [2] mean (SD)	109.1 (36.57)	107.1 (26.59)	85.7 (9.29)	107.4 (29.01)
End of treatment [3] mean (SD)	119.3 (48.42)	115.9 (41.86)	90.3 (9.50)	116.5 (43.29)
Mean change (SD)	10.2 (42.51)	8.8 (34.41)	4.7 (2.08)	9.1 (36.21)
Blood urea nitrogen (mg/dL)	n [1] = 145	n [1] = 524	n [1] = 3	n [1] = 672
Baseline [2] mean (SD)	15.3 (4.32)	15.8 (4.54)	19.7 (3.21)	15.7 (4.50)
End of treatment [3] mean (SD)	15.6 (5.08)	16.3 (4.62)	21.0 (2.00)	16.2 (4.73)
Mean change (SD)	0.3 (3.70)	0.5 (3.99)	1.3 (2.08)	0.5 (3.92)

1. n is the number of subjects with measurements at both baseline and end of treatment.
2. Baseline is the last measurement prior to the first dose of study drug in the qualifying study.
3. End of treatment is the last study visit.

Individual Subject Changes: No clinically important findings were noted from shift summaries of laboratory parameters.

Individual Clinically Significant Abnormalities: No subject had an SAE related to laboratory abnormalities; one subject (Subject 221-006) had a laboratory-related adverse event (hyperkalemia) that led to study drug discontinuation; this adverse event was considered by the investigator to be mild in severity and not related to study drug.

Individual Phase 2 Study TA-01

For Group 1 (avanafil 50 mg) and Group 2 (avanafil 100 mg) in study TA-01, mean glucose concentrations increased from baseline to study exit; however, it should be noted that subjects were not required to fast prior to the blood sample collection. For Group 1, mean glucose concentration was 91.1 mg/dL at baseline and 100.8 mg/dL at study exit. For Group 2, mean

glucose concentration was 93.0 mg/dL at baseline and 101.8 mg/dL at study exit. For Group 3 (avanafil 200 mg), mean glucose concentration remained relatively stable from baseline to study exit. No other meaningful changes in safety laboratory parameters were noted during the study.

Individual Phase 2 Study TA-03

In study TA-03, a mean increase in glucose of 10.9 mg/dL was observed from baseline to study exit. In total, 15 (30.6%) subjects with normal glucose concentrations at baseline had high glucose concentrations at study exit. However, it should be noted that subjects were not required to fast prior to blood sample collection. No other meaningful changes in safety laboratory parameters were noted during the study.

Phase 1 Studies
No clinically meaningful changes in laboratory parameters were observed during the Phase 1 program.

Reviewer's comment: The numbers and percentages of subjects with abnormal laboratory measurements were low, and no meaningful differences among the treatment groups were reported.

7.4.2 Vital Signs

Vital Signs

Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

The incidences of abnormal increases in SBP or DBP in the double-blind cohort were low and similar across treatment groups. In total, 27 (2.1%) subjects had SBP >180 mmHg at any time during the randomized treatment period or SBP >140 mmHg and an increase from baseline >20 mmHg on two or more occasions in studies TA-301 and TA-302 or on one or more occasions in study TA-05: 7 (2.0%) subjects in the placebo group, 4 (1.8%) subjects in the avanafil 50 mg group, 10 (2.9%) subjects in the avanafil 100 mg group, and 6 (1.7%) subjects in the avanafil 200 mg group. In total, 20 (1.6%) subjects had DBP >110 mmHg at any time during the randomized treatment period or an increase in DBP from baseline >15 mmHg on two or more occasions in studies TA-301 and TA-302 or on one or more occasion in study TA-05: 6 (1.7%) subjects in the placebo group, 5 (2.3%) subjects in the avanafil 50 mg group, 9 (2.6%) subjects in the avanafil 100 mg group, and 0 (0.0%) subjects in the avanafil 200 mg group.

The incidences of abnormal decreases in SBP or DBP in the double-blind cohort were also low and similar across treatment groups. Only 1 subject (in the avanafil 50 mg group) had an abnormal decrease in SBP (defined as SBP <100 mmHg on two or more occasions during the randomized treatment period in studies TA-301 or TA-302 or on one or more occasion during

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the randomized treatment period in study TA-05). In total, 5 (0.4%) subjects had DBP <60 mmHg on two or more occasions during the randomized treatment period in studies TA-301 or TA-302 or on one or more occasion during the randomized treatment period in study TA-05: 1 (0.3%) subject in the placebo group, 0 (0.0%) subjects in the avanafil 50 mg group, 2 (0.6%) subjects in the avanafil 100 mg group, and 2 (0.6%) subjects in the avanafil 200 mg group.

In study TA-05, mean heart rate values at the end of treatment were slightly higher than those at screening for each treatment group. In study TA-301, mean heart rate values at the end of treatment were slightly lower than those at randomization for each treatment group. In study TA-302, mean heart rate values at the end of treatment were similar to those at randomization for each treatment group.

Individual Phase 3, Open-Label, Long-Term Study TA-314

In study TA-314, mean SBP, DBP, and heart rate values at the end of treatment were similar to those at enrollment.
In total, 31 (4.4%) subjects had an abnormal increase in SBP during treatment, defined as an increase of >20 mmHg from baseline and >140 mmHg on two or more occasions or any value >180 mmHg. Twenty-six (3.7%) subjects had abnormal increases in DBP during treatment, defined as an increase of >15 mmHg from baseline on two or more occasions or any value >110 mmHg.

In total, 5 (0.7%) subjects had an abnormal decrease in SBP during treatment, defined as SBP <100 mmHg on two or more occasions. Seven (1.0%) subjects had an abnormal decrease in DBP during treatment, defined as DBP <60 mmHg on two or more occasions.

Individual Phase 2 Study TA-01

In study TA-01, no statistically significant differences in mean changes in SBP from pre-dose to any post-dose time point were observed between the treatments. In Group 1, statistically significant differences in mean change in DBP from pre-dose were observed between sildenafil 50 mg and placebo and between sildenafil 50 mg and avanafil 50 mg at 80 minutes post-dose. In Group 2, statistically significant differences in mean change in heart rate from pre-dose were observed between avanafil 100 mg and placebo and between avanafil 100 mg and sildenafil 50 mg at each time point except 100 minutes post-dose.

The mean maximum decreases in SBP with avanafil 50 mg (5.2 mmHg), avanafil 100 mg (5.9 mmHg), and avanafil 200 mg (6.9 mmHg) were similar to those observed with placebo (4.0 mmHg to 7.4 mmHg) and generally lower than those observed with sildenafil 50 mg (6.0 mmHg to 9.3 mmHg). The mean maximum decreases in DBP with avanafil 50 mg (4.8 mmHg), avanafil 100 mg (4.1 mmHg), and avanafil 200 mg (4.7 mmHg) were similar to those observed with placebo (3.8 mmHg to 5.1 mmHg) and generally lower than those observed with sildenafil 50 mg (4.2 mmHg to 6.2 mmHg).The mean maximum increases in heart rate with avanafil 50 mg

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(5.9 bpm), avanafil 100 mg (8.0 bpm), and avanafil 200 mg (6.8 bpm) were higher than those observed with placebo (2.4 bpm to 4.5 bpm) and sildenafil 50 mg (4.7 bpm to 5.7 bpm).

Reviewer's comment: It is notable that the BP drop with avanafil 200 mg (6.9 mm Hg) was larger than with avanafil 50 mg (5.2 mm Hg) or with avanafil 100 mg (5.9 mm Hg). All three avanafil doses dropped blood pressure more than placebo did in this trial (placebo decreases ranged from 4.0 – 7.4 mm Hg).

Individual Phase 2 Study TA-03

In study TA-03, no clinically meaningful changes in blood pressure, respiratory rate, pulse, temperature, or body weight from baseline to study exit were noted for any subject.

Phase 1 Studies

In study TA-02, single oral doses of avanafil 200 mg were administered to healthy male volunteers on Day 1, then multiple doses starting on Day 4 to Day 16, were administered to the same subjects, and the sitting blood pressure and pulse were monitored and recorded at multiple time points. In the following table, these results are shown as group mean changes from the baselines for the first several hours after single doses on Days 1 and 4:

Table 7.4.3 Mean Changes from Baseline of Sitting Blood Pressue and Pulse in Subjects in the First Several Hours After Administration of Single Doses of Avanafil 200 mg on Days 1 and 4 In Study TA-02

Day #	Hours Post-dose	Systolic BP (SBP) (mmHg)			Diastolic (DBP) (mmHg)			Pulse (P) (bpm)		
		Placebo	200 mg	Ava-P	Placebo	200 mg	Ava-P	Placebo	200 mg	Ava-P
1	0.5	–2.67	–2.25	+0.42	–0.17	–4.75	–4.58	–3.67	+9.33	+13.0
	1.83	–2.08	–4.75	–2.67	+0.17	–3.08	–3.25	–1.0	+0.83	+1.83
	3.83	–0.67	–5.50	–4.83	–0.92	–6.17	–5.25	+7.0	+8.33	+1.33
4	1.0	+2.67	–5.33	–8.0	–0.42	–3.67	–3.25	–1.33	+3.17	+4.5
	2.0	–0.58	–5.33	–4.75	–0.33	–3.25	–2.92	–3.0	–1.0	+2.0

200 mg: avanafil 200 mg single dose
Ava-P: Difference between avanafil 200 mg and placebo in changes from baseline.

In this study, it was observed that single oral doses of avanafil 200 mg administered to healthy male volunteers on Day 4 resulted in mean changes from baseline in systolic/diastolic blood pressure (SBP/DBP) of –5.3/–3.7 mmHg at 1 hour after dosing, compared to mean changes from baseline in the placebo group of +2.7/–0.4 mm Hg. The reductions in SBP/DBP at 1 hour after dosing of avanafil 200 mg compared to placebo were –8.0/–3.3 mm Hg. On Day 1, the avanafil-related reductions in blood pressure were smaller than on Day 4, bur nonetheless, on Day 1 at 3.83 hours after a single dose of avanafil 200 mg, the maximum mean reductions of SBP/DBP from the baseline compared to placebo were –4.8/–5.3 mmHg.

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Reviewer's comment: The results from Study TA-02 demonstrate that like other PDE5 inhibitors, avanafil is associated with a transient decrease in blood pressure soon after dosing. Additional information relevant to blood pressure was also collected in other Phase 1 studies (either in extrinsic factor studies or in drug-drug interaction studies - see below).

7.4.3 Electrocardiograms (ECGs)

From the individual studies during clinical development, no important differences among the treatment groups in changes in ECG parameters were noted. A thorough QT/QTc study was required and was conducted by the Sponsor.

QT Prolongation

TA-140: A Phase 1, Blinded, Randomized Crossover Trial to Define the ECG Effects of TA-1790 (Avanafil) Using a Single Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (MOX) in Healthy Men.

This thorough QT study was designed with therapeutic and supra-therapeutic doses of avanafil (100 mg and 800 mg, respectively) vs. MOX as a Randomized, double-blind, placebo- & active controlled (MOX 400 mg), 4-arm crossover study.

The subjects were healthy male, 18- 45 years of age (inclusive), with a body mass index (BMI) 19 - 28 kg/m^2 (inclusive).

Methodology: The sponsor evaluated the effect of avanafil on QT prolongation in a double-blind (except for the use of MOX), randomized, single site, four-arm crossover design in healthy male subjects. MOX was used as a positive control in this study to validate the sensitivity of the assay to detect small increases from baseline QTcI duration. The central electrocardiogram (ECG) laboratory [redacted] (b) (6) was blinded to treatment. Subjects were randomized to receive four treatments (placebo, 400 mg MOX, 100 mg avanafil [therapeutic dose], and 800 mg avanafil [supratherapeutic dose]) in one of four sequences. Each treatment consisted of a single dose with at least a 3-day washout period between treatments. For each of the four periods, subjects were confined from morning of Day -1 through completion of the 23-hour post-dose procedures. Conduct of the study took place over a period of approximately 21 days (from check-in of Period 1 through discharge in Period 4). The Investigator and subjects were not blinded to MOX treatment because over encapsulation of MOX might have changed its ECG QTc profile, making assessment of assay sensitivity difficult. Furthermore, endpoint ECG data was defined by the analysis of the central laboratory which was blinded to all treatments.

In this crossover design, fifty-seven subjects received avanafil 100 mg, avanafil 800 mg, placebo, and MOX 400 mg (positive control), and 52 completed the study. 2 subjects were discontinued due to compliance issues, 2 subjects withdrew consent, and one subject discontinued due to an adverse event (AE). For the supratherapeutic dose (800 mg), the least-

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squares (LS) mean of ΔΔQTcF was 9.4 ms and the 90% CI for ΔΔQTcF was 7.2 – 11.6 ms. The upper bound of the 90% CI for ΔΔQTcF for the 800 mg dose exceeded 10 ms (11.6 ms) at one time point for the supratherapeutic dose and therefore, technically failed to exclude a 10 ms increase in QT.

Justification of supratherapeutic dose: The supratherapeutic dose (800 mg) produces C_{max} values 6.8-fold greater than the mean C_{max} for the therapeutic dose (100 mg). Only single dose treatment with avanafil was evaluated in this study; however, there is minimal accumulation of the drug (accumulation ratio: 1.09) after 14 days of dosing. Interaction with strong CYP3A4 inhibitors such as ketoconazole and ritonavir increased C_{max} by 3.1- and 2.4-fold, respectively, while $AUC_{0\text{-}inf}$ increased by approximately 13-fold. Renal and hepatic impairment did not significantly increase avanafil concentrations. The supratherapeutic dose of 800 mg avanafil was considered sufficient to cover the 13-fold increase in avanafil AUC exposure from administration of 100 mg avanafil with a strong CYP3A4 inhibitor and an accumulation ratio of 1.09. After accounting for known intrinsic and extrinsic factors, the therapeutic dose is not expected to cause >10 ms increase in QT. To address the drug-drug interaction with strong CYP 3A4 inhibitors, the sponsor recommended reducing avanafil dose to 50 mg every other day. All together, the supratherapeutic dose of 800 mg is sufficient to describe the steady state high exposure scenario anticipated in patients administered avanafil 50 mg every other day with a potent concomitant CYP3A4 inhibitor (i.e., ketoconazole).

Assay sensitivity was demonstrated in that the QTcI placebo-corrected mean change from baseline value for MOX was +5.9 msec (expected 5 msec to 10 msec). The results from this thorough QT/QTc study demonstrated that avanafil does not cause any significant changes in QTc interval or ventricular repolarization over an 8-fold exposure range above an expected therapeutic dose.

Table 7.4.4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Therapeutic and Supratherapeutic Avanafil and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
Therapeutic Avanafil	0.5	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)

The QT Interdisciplinary Review Team (QT-IRT) made the following comments to the Review Division:

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 of 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.

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Figure 7.4.1 Observed Median-Quantile Avanafil Concentration and Associated Mean (90% CI) ΔΔQTcF (colored dots) Together with the Mean (90% CI) Predicted ΔΔQTcF (black line with shaded grey area)

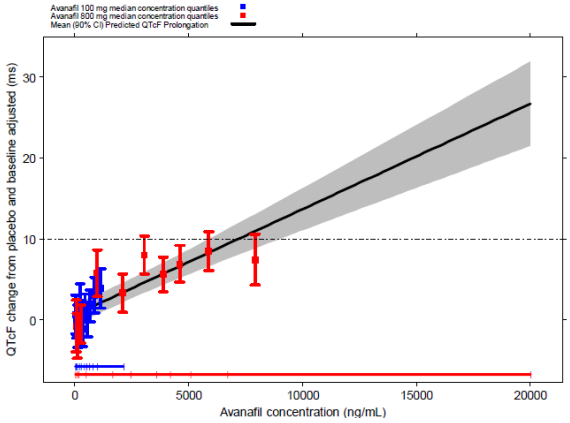
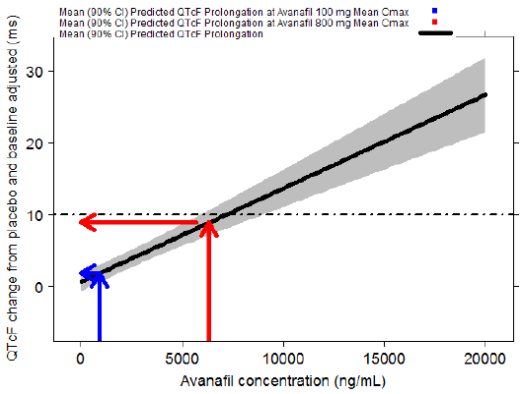


Figure 7.4.2 Mean (90% CI) Predicted ΔΔQTcF at Geometric Mean Cmax. Predicted Cmax for the High Exposure Scenario was Interpolated from the Sponsor's Highlights of Clinical Pharmacology (orange)



The QT-IRT further recommended the following related labeling for the Effects on Cardiac Electrophysiology subsection:

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

Reviewer's comment: The results from this thorough QT/QTc study demonstrated that avanafil does not cause significant changes in QTc interval or ventricular repolarization over an 8-fold exposure range above an expected therapeutic dose. The results are acceptable.

7.4.4 Special Safety Studies/Clinical Trials

7.4.4.1 Intrinsic Factors

7.4.4.1.1 Hepatic Impairment (Study TA-012)

The effects of mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment on the PK of avanafil following a single oral dose of 200 mg were evaluated in an open-label, non-randomized, single dose, parallel-cohort study (TA-012). The sponsor did not evaluate the effect of severe hepatic impairment on PK of avanafil.

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The following table summarizes the PK parameters of avanafil for patients with mild and moderate hepatic impairment and normal hepatic function with the geometric mean (SD) avanafil concentrations vs. time profile (data from Study TA-012).

PK parameter*	Normal Hepatic Function (N=8)	Mild Hepatic Impairment (N=8)	Moderate Hepatic Impairment (N=8)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	9260 (2210)	9610 (3660)	10300 (4490)
C_{max} (ng/mL)	2610 (796)	2540 (886)	1270 (739)
t_{max} (hr)[1]	0.5 (0.5, 1.0)	0.5 (0.5, 2.1)	1.1 (0.5, 3.0)
$t_{1/2}$ (hr)	7.5 (2.8)	6.9 (1.8)	6.1 (1.9)
CL/F (mL/min)	22.5 (4.8)	23.4 (8.6)	24.5 (15.6)

*arithmetic mean (SD)
[1]tmax: median and range

Reviewer's comment: A single dose of avanafil 200 mg appeared to be safe in subjects with mild to moderate hepatic impairment. However, the sponsor did not evaluate the effect of severe hepatic impairment on avanafil PK. There does not appear to be a need for dose adjustment in patients with mild and moderate hepatic impairment.

7.4.4.1.2 Renal Impairment (Study TA-013)

The effect of mild renal impairment (creatinine clearance [CLcr]: 60-89 mL/min) and moderate renal impairment ([CLcr]: 30-59 mL/min) on the PK of avanafil was evaluated by the sponsor and compared against subjects with normal renal function ([CLcr] $\geq$ 90 mL/min). Patients were administered a single oral dose of 200 mg in a single-center, open-label, parallel group, non-randomized study (TA-013). The sponsor did not evaluate the effect of severe renal impairment or end stage renal disease on PK of avanafil.

The following table summarizes the PK parameters of avanafil for patients with mild and moderate renal impairment and normal renal function (data from Study TA-013).

PK parameter*	Normal Renal Function (N=5)	Mild Renal Impairment (N=9)	Moderate Renal Impairment (N=10)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	8490 (1180)	8240 (2800)	9260 (2920)
C (ng/mL)	2870 (1060)	2950 (1090)	2790 (1010)
t_{max} (hr)[1]	0.75 (0.5, 1.0)	0.5 (0.5, 0.5)	0.75 (0.5, 1.5)
$t_{1/2}$ (hr)	6.4 (4.4)	6.2 (3.0)	4.9 (2.2)
CL/F (mL/min)	23.9 (3.5)	27.8 (12.6)	23.8 (8.6)

*arithmetic mean (SD)
[1]tmax: median and range

Reviewer's comment: A single dose of avanafil 200 mg appeared to be safe and tolerated by subjects with mild to moderate renal impairment. However, the sponsor did not evaluate

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the effect of severe and end stage renal impairment on avanafil PK. There does not appear to be a need for dose adjustment in patients with mild and moderate renal impairment.

7.4.4.2 Extrinsic Factors

7.4.4.2.1 Effect of Food

Effect of food on avanafil PK (Study TA-020)
Compared to the fasted condition, the exposure ($AUC_{0\text{-}inf}$) of a single 200 mg dose of avanafil decreased by 1.5% after subjects received a high fat/high caloric meal. C_{max} decreased by 40%. T_{max} increased by 1.25 hrs from 0.75 to 2.0 hrs and $t_{1/2}$ was decreased slightly by 0.6 hr from 5.1 to 4.5 hrs. Though C_{max} decreased by 40%, the total exposure changed to a negligible degree (1.5%).

Table 7.4.5 Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters Following Treatment B (Fed) Versus Treatment A (Fasted)

Pharmacokinetic Parameters	Treatment B[a]	N	Treatment A[a]	N	90% CI	% Mean Ratio
C_{max} (ng/mL)	1690	23	2760	23	(52.57, 70.79)	61.00
$AUC_{0\text{-}t}$ (ng•hr/mL)	7720	23	7660	23	(92.29, 109.95)	100.74
$AUC_{0\text{-}inf}$ (ng•hr/mL)	7990	22	8310	17	(88.86, 104.14)	96.20

Treatment A = a single oral dose of two 100 mg avanafil tablets (Formulation II), fasted (Reference)
Treatment B = a single oral dose of two 100 mg avanafil tablets (Formulation II), fed (Test)
a. Cmax, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ are presented as geometric least-squares means (LS Means) with three significant figures, calculated by exponentiating the LS Means from the ANOVA. Parameters were log-transformed prior to analysis.
% Mean Ratio = 100*(test/reference).

Reviewer's comment: Based on these small changes, no dose adjustment or special dosing instructions in the presence of food is necessary. Additionally, the Phase 3 study was conducted with no restrictions on food intake.

7.4.4.2.2 Effect of alcohol (Study TA-015)

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

The dependent variables to be analyzed using ANOVA were maximum decrease in SBP and DBP, and maximum increase in pulse rate as well as $AUEC_{0\text{-}t}$ of SBP, DBP, and pulse rate. All

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statistical tests were carried out using two-sided tests. Ninety-five percent (95%) confidence interval (CI) for mean difference was also calculated.

The results showed that mean maximum percent blood alcohol levels occurred at Hour 0.5 for Treatments A and B, with values of 0.0569% and 0.0547%, respectively. At Hour 2, mean levels had decreased to 0.0259% and 0.0245% for Treatments A and B, respectively. By Hour 6, mean alcohol levels had returned to baseline (0.0000%).

At most postdose time points through Hour 2, there were larger mean blood pressure decreases (SBP and DBP) and larger mean pulse rate increases following Treatment A (alcohol + avanafil), compared to Treatment C (avanafil + placebo). Treatment B (alcohol alone) actually showed the least change from baseline for BP and pulse across time points. By Hour 4, mean BP and pulse measurements were near baseline values for all treatments.

Table 7.4.6 Mean Hemodynamic Parameters

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

There were also statistically significant differences in diastolic pressure maximum decrease (-4.54 mmHg) ($p < 0.05$) and pulse rate maximum increase (+9.33 bpm) ($p < 0.005$) when comparing Treatments A and B.

Table 7.4.7 Statistical Comparisons of the Maximum Changes in Supine Blood Pressure and Pulse Rate: Treatment A versus B

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Treatment A	Treatment B	Mean Difference		
Max decrease systolic (mmHg)	-14.46	-10.93	-3.53	-9.68, 2.63	0.2483
Max decrease diastolic (mmHg)	-14.14	-9.60	-4.54	-8.98, -0.10	0.0454
Max increase pulse rate (bpm)	+19.53	+10.20	+9.33	3.35, 15.31	0.0037

Treatment A = a single oral dose of one 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 = a single oral dose of one placebo tablet plus an oral alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kilogram of body weight)

While the decreases in standing systolic and diastolic BP (-2.88 mmHg), and increases in standing pulse rate (+3.67) were greater for Treatment A (avanafil + alcohol) compared to Treatment C (avanafil alone), there were no statistically significant differences in blood pressure maximum decreases ($p > 0.05$) and pulse rate maximum increases ($p > 0.05$) when comparing Treatments A and C.

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Table 7.4.8 Statistical Comparisons of the Maximum Changes in Supine Blood Pressure and Pulse Rate: Treatment A versus C

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Treatment A	Treatment C	Mean Difference		
Max decrease systolic (mmHg)	-14.46	-11.58	-2.88	-9.13, 3.38	0.3520
Max decrease diastolic (mmHg)	-14.14	-11.20	-2.94	-7.44, 1.56	0.1902
Max increase pulse rate (bpm)	+19.53	+15.86	+3.67	-2.38, 9.72	0.2231

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

There did not appear to be numerically nor statistically significant differences in blood pressure maximum decreases ($p > 0.05$) and pulse rate maximum increases ($p > 0.05$) when comparing Treatments B (alcohol alone) and C (avanafil alone).

Table 7.4.9 Statistical Comparisons of the Maximum Changes in Supine Blood Pressure and Pulse Rate: Treatment B versus C

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Treatment B	Treatment C	Mean Difference		
Max decrease systolic (mmHg)	-10.93	-11.58	0.65	-5.50 , 6.80	0.8291
Max decrease diastolic (mmHg)	-9.60	-11.20	1.60	-2.84 , 6.04	0.4636
Max increase pulse rate (bpm)	+10.20	+15.86	-5.66	-11.64 , 0.32	0.0625

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

Summary of clinical safety results: Overall, headache occurred with the same frequency (14%) in subjects given avanafil + alcohol compared to avanafil + placebo drink, and occurred less frequently (7%) in subjects given placebo + alcohol.

Reviewer's Comments:
The Clinical Pharmacology Reviewer believes that there was an additive hypotensive effect from alcohol + avanafil treatment compared to alcohol alone, with an additional decrease SBP/DBP of approximately 3.5/4.5 mmHg. (b) (4) **. The Clinical Pharmacology reviewer disagreed with the proposed labeling based on the available data indicating a decrease in both systolic and diastolic blood pressure and recommended labeling the findings (a decrease SBP/DBP of approximately 3.5/4.5 mmHg) from this alcohol study.**

This Clinical Reviewer agrees with Clin Pharm Reviewer's opinion that the study data of an additional decrease in both systolic and diastolic blood pressure of approximately 3.5/4.5 mmHg should be presented in the labeling. A precaution in labeling is also necessary for excessive consumption of alcohol and avanafil, similar to the Precaution which exists for the currently marketed PDE5 inhibitors.

7.4.4.2.3 Effects of CYP3A4 Inhibitors (Study TA-011):

The Sponsor conducted study TA-011 to evaluate the effect of ketoconazole (a strong CYP3A4 inhibitor), ritonavir (a strong CYP3A4 inhibitor), and erythromycin (a moderate CYP3A4 inhibitor) on the PK of avanafil.

The Sponsor concluded:

- The mean maximum (C_{max}) and overall extent ($AUC_{0\text{-}inf}$) of avanafil exposures were approximately 3-fold and 14-fold higher, respectively, when avanafil was co-administered with ketoconazole, a strong CYP3A4 inhibitor.
- The mean maximum (C_{max}) and overall extent ($AUC_{0\text{-}inf}$) of avanafil exposures were approximately 2-fold and 13-fold higher, respectively, when avanafil was co-administered with ritonavir, another strong CYP3A inhibitor.
- The mean maximum (C_{max}) and overall extent ($AUC_{0\text{-}inf}$) of avanafil exposures were approximately 2-fold and 3-fold higher, respectively, when avanafil was co-administered with erythromycin, a moderate CYP3A4 inhibitor.
- Based on examination of SAEs, discontinuations related to AEs and frequency of severe AEs, administration of avanafil appeared to be safe when co-administered with ketoconazole, ritonavir, or erythromycin, for the healthy male subjects in this study.

Reviewer's comment: The results of study TA-011 demonstrate a clear effect of strong and moderate CYP3A4 inhibitors on the PK of avanafil. The Clinical Pharmacology reviewer believes that dose adjustment is needed and the Clinical Reviewer agrees.

7.4.5. Studies of Effect on Vision

No dedicated vision study was conducted to evaluate avanafil's effects on vision. Effects of avanafil on color discrimination were evaluated and included in two phase 1 studies, HP-01 and TA-016. The results of these limited vision investigations are shown here.

7.4.5.1 Study HP-01

Study HP-01 was a double-blind, ascending single oral dose, safety, tolerability and pharmacokinetic study of avanafil in healthy male volunteers, which included examination of colour discrimination after administration of avanafil.

Modification of colour vision test (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 built-up for each panel of colour at each time of evaluation, the investigator quoted yes for any defective colour vision test and no for any nondetected defective colour vision. Subjects presenting at least one abnormal test for each panel of colour, whatever the time after dosing, were counted per dose group. A summary table of error scores from this part of the study is shown below:

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Table 7.4.10 Summary of Farnsworth-Munsell 100 Hue Test

Treatment group	Adm. cond.	Visit or/day	Scheduled time	Panel 1		Panel 2				Panel 3				Panel 4			
				No		No		Yes		No		Yes		No		Yes	
				N	%	N	%	N	%	N	%	N	%	N	%	N	%
Placebo	Fasting	Day 1	H0	16	100.0	16	100.0	.	.	16	100.0	.	.	16	100.0	.	.
			H1.5	16	100.0	15	93.8	1	6.3	15	93.8	1	6.3	15	93.8	1	6.3
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
12.5 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	5	83.3	1	16.7
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
25 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
50 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
TA-1790	Fasting	Day 1	H0	7	100.0	7	100.0	.	.	7	100.0	.	.	7	100.0	.	.
100mg			H1.5	7	100.0	7	100.0	.	.	7	100.0	.	.	7	100.0	.	.
	Fed	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
200 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
400 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
600 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
TA-1790	Fasting	Day 1	H0	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.
800 mg			H1.5	6	100.0	6	100.0	.	.	6	100.0	.	.	6	100.0	.	.

The Sponsor reported that:

- One subject in the 12.5 mg group presented abnormal result at panel 4 at HL.5.
- One subject under placebo had defective colour vision for panel 2, 3 and 4 at 1.5 hour after administration. This abnormality observed on the left eye was considered as consistent with the same finding at screen on the right eye. The investigator believed that thisd efective colour version was not related to the study drug.

As only one subject presented an abnormality in the 12.5 mg dose group and also because no furter abnormalities were observed at any other doses, including doses greater than 12.5 mg, this abnormality in the 12.5 mg group was considered consequently as not related to study drug by the investigator.

Reviewer's comment: There is only limited vision safety data available from this study.

7.4.5.2 Study TA-016

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

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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, and at approximately 0.667 hours postdose on Day 1. The analytical parameters of 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). Postdose (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 was no statistically significant results in comparisons of postdose (0.67 hour) values between the two treatments. The p-value for that comparison was 0.056 (see table below). One marginally significant p-value was observed in mean change in square root transformed total error score in an analysis excluding an outlier. That p-value for that comparions 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 7.4.11 Farnsworth-Munsell 100-Hue Test Summary and Change From Predose Treatment A vs. Treatment B (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±17.60	39.5±21.70			
Day 1 0.67 hr	45.3±19.77	39.2±19.09	12.0±19.28	–0.3±14.82	0.056
Total Error Square Root					
Day –1 pre-dose	5.59±1.45	6.03±1.81			
Day 1 0.67 hr	6.55±1.55	6.05±1.65	0.96±1.50	0.02±1.19	0.047

Therefore, the investigator determined that there were no suggestions of any subtle color deficiencies of any type following warfarin + avanafil compared to warfarin + placebo. The Sponsor believes that overall results are below any area of clinical concern.

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Reviewer's comment: The reviewer believes that from the study design, the purpose of ths study was to compare the effects on colour deficiency from warfarin + avanafil when comparing with warfarin + placebo; from this study no conclusions could be reached whether avanafil itself had any effects on vision.

This Reviewer believes that a special designed, dedicated study to evaluate effects of avanafil on vision, including but not limited to visual acuity, intraocular pressure, pupillometry and color vision discrimination, should be conducted by the Sponsor as a postmarketing requirement (PMR).

7.5 Other Safety Explorations

No other safety explorations were planned.

7.5.1 Dose Dependency for Adverse Events

No special designed studies on dose-dependency for adverse events were conducted; However, the trend of occurrence of dose-dependent adverse events was observed in Phase 3 double blind studies and open-label, long-term safety study. In particular, headache appears to be a dose-related adverse event.

7.5.2 Time Dependency for Adverse Events

No specific designed studies on time dependency for adverse events were conducted.

7.5.3 Drug-Demographic Interactions

7.5.3.1 Effect of Age

Effect of age on avanafil PK
The arithmetic mean AUC_{0-t} for avanafil was 1.2-fold higher in elderly (65-80 yrs) subjects, compared to young (19-43 yrs) subjects. The arithmetic mean AUC_{0-t} for avanafil was 1.1-fold higher in elderly subjects, compared to young subjects. Median t_{max} increased by 0.19 hr from 0.56 to 0.75 hr and mean $t_{1/2}$ decreased by 0.9 hr from 6.5 to 5.6 hrs in elderly subjects, compared to young subjects. Overall differences observed between the elderly and young subjects are not significant given the variability observed between subjects.

Effect of age on the adverse events:

The following is an overview of adverse events for the subgroups of subjects <50 years of age, subjects ≥50 years and <65 years of age, and subjects ≥65 years of age in the double-blind cohort.

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No important differences between the age subgroups in the incidences of TEAEs or those categorized as targeted medical events were observed.

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Table 7.5.1 Summary of Adverse Events and TMEs by Class and PT – Age Subgroups – Double-Blind Cohort (TA-301 + TA- 302 + TA-05)

	Subjects < 50 Years of Age				Subjects ≥50 Years and < 65 Years of Age				Subjects ≥65 Years of Age			
	Placebo (N=88) n (%)	Avanafil 50 mg (N=66) n (%)	Avanafil 100 mg (N=94) n (%)	Avanafil 200 mg (N=83) n (%)	Placebo (N=178) n (%)	Avanafil 50 mg (N=116) n (%)	Avanafil 100 mg (N=169) n (%)	Avanafil 200 mg (N=186) n (%)	Placebo (N=83) n (%)	Avanafil 50 mg (N=35) n (%)	Avanafil 100 mg (N=86) n (%)	Avanafil 200 mg (N=83) n (%)
Subjects with TEAEs												
Any TEAE	24 (27.3)	25 (37.9)	36 (38.3)	24 (28.9)	47 (26.4)	33 (28.4)	66 (39.1)	71 (38.2)	18 (21.7)	10 (28.6)	38 (44.2)	33 (39.8)
Maximum severity of TEAEs												
Severe	1 (1.1)	0 (0.0)	2 (2.1)	0 (0.0)	3 (1.7)	1 (0.9)	5 (3.0)	2 (1.1)	0 (0.0)	1 (2.9)	2 (2.3)	2 (2.4)
Subjects with SAEs												
Any treatment-emergent SAE	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)	2 (1.7)	3 (1.8)	5 (2.7)	0 (0.0)	0 (0.0)	2 (2.3)	2 (2.4)
Study drug discontinuations due to adverse events												
Any TEAE	2 (2.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)	3 (2.6)	3 (1.8)	3 (1.6)	2 (2.4)	0 (0.0)	3 (3.5)	3 (3.6)
Any SAE	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (1.2)	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)
TME Class Preferred Term												
Upper respiratory events	9 (10.2)	4 (6.1)	9 (9.6)	8 (9.6)	11 (6.2)	12 (10.3)	24 (14.2)	22 (11.8)	3 (3.6)	1 (2.9)	11 (12.8)	13 (15.7)
Nasal congestion	1 (1.1)	1 (1.5)	3 (3.2)	1 (1.2)	1 (0.6)	3 (2.6)	3 (1.8)	5 (2.7)	2 (2.4)	0 (0.0)	4 (4.7)	1 (1.2)
Hemodynamic changes	0 (0.0)	1 (1.5)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.9)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Dizziness	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

7.5.4 Drug-Disease Interactions

7.5.4.1 By Baseline Diabetic Status

No meaningful differences in the incidences of TEAEs and SAEs were observed between the baseline diabetic status subgroups for any treatment group. No important differences between the baseline diabetic status subgroups in the types of TEAEs or the incidences of specific TEAEs with avanafil treatment were observed. No important differences between the baseline diabetic status subgroups in the types of drug-related TEAEs or the incidences of specific drug-related TEAEs with avanafil treatment were observed. No important differences were observed between the baseline diabetic status subgroups in the incidences of TEAEs in the upper respiratory events class, hemodynamic changes class, major cardiac events class, special sensory effects (hearing) class, or special sensory effects (vision) class.

7.5.4.2 By Baseline Coronary Artery Disease Status

For subjects with coronary artery disease at baseline (total n=145), the overall incidences of TEAEs were lower in the placebo (n=41), avanafil 50 mg (n=14), and avanafil 100 mg group (n=40) compared to subjects without coronary artery disease at baseline. No subject with coronary artery disease at baseline treated with avanafil 50 mg or avanafil 100 mg reported a drug-related adverse event compared to 23 (11.3%) subjects and 50 (16.2%) subjects without coronary artery disease at baseline treated with avanafil 50 mg and avanafil 100 mg, respectively. Three (6.0%) subjects with coronary artery disease at baseline treated with avanafil 200 mg reported an SAE compared to 4 (1.3%) subjects without coronary artery disease at baseline treated with avanafil 200 mg. Four (8.0%) subjects with coronary artery disease at baseline treated with avanafil 200 mg experienced adverse events resulting in study drug discontinuation compared to 2 (0.7%) subjects without coronary artery disease at baseline treated with avanafil 200 mg.

Reviewer's comment: Of the three serious adverse events (SAEs) in patients with coronary artery disease and randomized to avanafil 200 mg, two were cardiovascular adverse events: one occurred in Study TA-301 (Subjects 130-012 with moderate non obstructive coronary artery disease) and one in Study TA-302 (Subjects 203-031 with unstable angina). Both these patients were taking avanafil 200 mg. In both these cases, it is not possible to rule out a role of avanafil in the adverse event because the event was reported within 24 hours of taking avanafil. These are the only two cardiovascular events reported in the NDA where the role of avanafil could not be ruled out. Both patients had known serious underlying coronary artery disease, and both had undergone previous angioplasty. It is worth noting that no similar events were reported in Study TA-05 or in Study TA-303, and none were reported among > 700 men treated for 9 months or longer in the long-term safety study (TA-314). In summary, the role of avanafil in the cardiovascular AEs in these 2 patients remains unclear.

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7.5.4.3 By Baseline Hypertension Status

For subjects with hypertension at baseline, the overall incidences of TEAEs and drug-related TEAEs were slightly lower in the avanafil 50 mg and avanafil 100 mg groups compared to subjects without hypertension. The incidence of SAEs with avanafil was slightly higher among subjects with hypertension compared to subjects without hypertension. No meaningful differences in the incidences of adverse events resulting in study drug discontinuation were observed between the baseline hypertension status subgroups. A higher percentage of subjects without hypertension who received avanafil 50 mg reported upper respiratory events (9.7%) compared to subjects with hypertension who received avanafil 50 mg (3.2%).

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Table 7.5.2 Summary of Adverse Events and TMEs (by class and PT) – Baseline Diabetic Status Subgroups – Double-Blind Cohort (TA-301+TA-302+TA-05)

	Subjects With Diabetes at Baseline				Subjects Without Diabetes at Baseline			
	Placebo (N=130) n (%)	Avanafil 50 mg (N=0) n (%)	Avanafil 100 mg (N=127) n (%)	Avanafil 200 mg (N=131) n (%)	Placebo (N=219) n (%)	Avanafil 50 mg (N=217) n (%)	Avanafil 100 mg (N=222) n (%)	Avanafil 200 mg (N=221) n (%)
Subjects with SAEs								
Any treatment-emergent SAE	1 (0.8)	0	3 (2.4)	4 (3.1)	1 (0.5)	2 (0.9)	3 (1.4)	3 (1.4)
Any drug-related SAE	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study drug discontinuations due to adverse events								
Any TEAE	0 (0.0)	0	1 (0.8)	2 (1.5)	5 (2.3)	3 (1.4)	6 (2.7)	4 (1.8)
Any drug-related TEAE	0 (0.0)	0	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.5)	2 (0.9)	2 (0.9)
Any SAE	0 (0.0)	0	1 (0.8)	1 (0.8)	1 (0.5)	1 (0.5)	2 (0.9)	1 (0.5)
TME Class Preferred Term								
Upper respiratory events	7 (5.4)	0	13 (10.2)	11 (8.4)	16 (7.3)	17 (7.8)	31 (14.0)	32 (14.5)
Nasal congestion	0 (0.0)	0	0 (0.0)	1 (0.8)	4 (1.8)	4 (1.8)	10 (4.5)	6 (2.7)
Sinus congestion	1 (0.8)	0	1 (0.8)	4 (3.1)	0 (0.0)	1 (0.5)	2 (0.9)	2 (0.9)
Sinusitis	0 (0.0)	0	4 (3.1)	1 (0.8)	4 (1.8)	0 (0.0)	1 (0.5)	2 (0.9)
Pneumonia	0 (0.0)	0	0 (0.0)	2 (1.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Table 7.5.3 Summary of Adverse Events and TMEs (by class and PT) – Coronary Artery Disease Subgroups – Double-Blind Cohort (TA-301+TA-302+TA-05)

	Subjects With Coronary Artery Disease				Subjects Without Coronary Artery Disease			
	Placebo (N=41) n (%)	Avanafil 50 mg (N=14) n (%)	Avanafil 100 mg (N=40) n (%)	Avanafil 200 mg (N=50) n (%)	Placebo (N=308) n (%)	Avanafil 50 mg (N=203) n (%)	Avanafil 100 mg (N=309) n (%)	Avanafil 200 mg (N=302) n (%)
Subjects with TEAEs								
Any TEAE	7 (17.1)	3 (21.4)	12 (30.0)	20 (40.0)	82 (26.6)	65 (32.0)	128 (41.4)	108 (35.8)
Any drug-related TEAE	2 (4.9)	0 (0.0)	0 (0.0)	9 (18.0)	13 (4.2)	23 (11.3)	50 (16.2)	52 (17.2)
Maximum severity of TEAEs								
Severe	0 (0.0)	0 (0.0)	1 (2.5)	3 (6.0)	4 (1.3)	2 (1.0)	8 (2.6)	1 (0.3)
Subjects with SAEs								
Any treatment-emergent SAE	0 (0.0)	1 (7.1)	1 (2.5)	3 (6.0)	2 (0.6)	1 (0.5)	5 (1.6)	4 (1.3)
Study drug discontinuations due to adverse events								
Any TEAE	0 (0.0)	0 (0.0)	1 (2.5)	4 (8.0)	5 (1.6)	3 (1.5)	6 (1.9)	2 (0.7)
TME Class Preferred Term								
Upper respiratory events	2 (4.9)	1 (7.1)	5 (12.5)	6 (12.0)	21 (6.8)	16 (7.9)	39 (12.6)	37 (12.3)
Nasal congestion	1 (2.4)	0 (0.0)	0 (0.0)	2 (4.0)	3 (1.0)	4 (2.0)	10 (3.2)	5 (1.7)
Hemodynamic changes	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	3 (1.0)	0 (0.0)
Dizziness	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.6)	0 (0.0)

Table 7.5.4 Summary of Adverse Events and TMEs (by class and PT) – Baseline Hypertension Status Subgroups – Double-Blind Cohort (TA-301+TA-302+TA-05)

	Subjects With Hypertension				Subjects Without Hypertension			
	Placebo (N=156) (%)	Avanafil 50 mg (N=62) n (%)	Avanafil 100 mg (N=164) n (%)	Avanafil 200 mg (N=161) n (%)	Placebo (N=193) n (%)	Avanafil 50 mg (N=155) n (%)	Avanafil 100 mg (N=185) n (%)	Avanafil 200 mg (N=191) n (%)
Subjects with TEAEs								
Any TEAE	37 (23.7)	17 (27.4)	59 (36.0)	60 (37.3)	52 (26.9)	51 (32.9)	81 (43.8)	68 (35.6)
Maximum severity of TEAEs								
Severe	0 (0.0)	2 (3.2)	6 (3.7)	4 (2.5)	4 (2.1)	0 (0.0)	3 (1.6)	0 (0.0)
Subjects with SAEs	0 (0.0)	2 (3.2)	5 (3.0)	5 (3.1)	3 (1.6)	0 (0.0)	1 (0.5)	2 (1.0)
Any SAE	0 (0.0)	2 (3.2)	5 (3.0)	5 (3.1)	2 (1.0)	0 (0.0)	1 (0.5)	2 (1.0)
Study drug discontinuations due to adverse events	2 (1.3)	1 (1.6)	4 (2.4)	3 (1.9)	3 (1.6)	2 (1.3)	4 (2.2)	3 (1.6)
Any drug-related TEAE	0 (0.0)	1 (1.6)	2 (1.)	2 (1.2)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
TME Class Preferred Term								
Upper respiratory events	8 (5.1)	2 (3.2)	21 (12.8)	23 (14.3)	15 (7.8)	15 (9.7)	23 (12.4)	20 (10.5)
Nasal congestion	0 (0.0)	0 (0.0)	5 (3.0)	3 (1.9)	4 (2.1)	4 (2.6)	5 (2.7)	4 (2.1)
Hemodynamic changes	0 (0.0)	1 (1.6)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	2 (1.1)	0 (0.0)
Dizziness	0 (0.0)	1 (1.6)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.5)	0 (0.0)

Treatment-emergent adverse events were defined as adverse events occurring after the first dose of study drug or after the first drug dispense date (if the first dose date was missing) and up to 28 days after the last dose of study drug.

7.5.5 Drug-Drug Interactions

7.5.5.1 Avanafil with Nitrates (Glyceryl trinitrate) (Study TA-04)

The sponsor evaluated the hemodynamic response to a sublingual dose of glyceryl trinitrate in subjects receiving oral avanafil, sildenafil, and placebo (Study TA-04) in 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, with the study groups differing in the time interval (0.5 [n=23], 1 [n=20], 4 [n=19], 8 [n=13], and 12 [n=13] hrs) between treatment with avanafil (200 mg), sildenafil (100 mg), or placebo and glyceryl trinitrate (0.4 mg) administration. Usual dose of nitroglycerin is 0.3 to 0.6 mg.

A single oral dose of avanafil 200 mg was shown to potentiate the hypotensive effect of glyceryl trinitrate (0.4 mg tablet administered sublingually). A statistically significant interaction between avanafil and glyceryl trinitrate was observed at the **0.5-hour time point** for blood pressure and pulse rate.

The mean maximum change in SBP and DBP occurred in the group administered avanafil and glyceryl trinitrate with 0.5 hr separation. The mean maximum decreases from predose to postdose in <u>sitting SBP</u> were 19.2, 17.8, and 14.3 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The difference observed with avanafil and sildenafil was determined to be statistically significant from placebo. The mean maximum decreases from predose to postdose in <u>standing DBP</u> were 21.5, 20.3, and 17.5 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The change in standing DBP with avanafil + glyceryl trinitrate co-administration was statistically different from placebo + glyceryl trinitrate.

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Table 7.5.5 Mean Maximum Change from predose to postdose in Systolic and Diastolic Blood Pressure (mmHg) and Pulse (bpm) by Study Group Following Glyceryl Trinitrate Administration by Group

	Sitting			Standing		
Group	**Avanafil**	**Sildenafil**	**Placebo**	**Avanafil**	**Sildenafil**	**Placebo**
Systolic Blood Pressure (mmHg)						
1 (12-hour)	-14.38	-19.57	-16.44	-18.67	-26.36	-20.02
2 (8-hour)	-14.67	-18.62	-17.24	-20.78	-25.04	-23.44
3 (4-hour)	-19.00	-19.51	-20.24	-21.20	-25.83	-20.38
4 (1-hour)	-17.74§	-22.29	-16.76	-17.84	-25.72	-20.96
5 (0.5-hour)	-19.17*	-17.77*	-14.26	-24.13	-24.80	-22.71
1-5 combined	-17.38	-19.63*	-16.96	-20.67	-25.52*	-21.51
3-5 combined	-18.64	-19.86*	-17.01	-21.10	-25.45	-21.39
4-5 combined	-18.47	-20.03*	-15.43	-21.05	-25.26	-21.89
Diastolic Blood Pressure (mmHg)						
1 (12-hour)	-12.63	-14.36	-13.07	-15.25	-17.48	-16.07
2 (8-hour)	-10.47	-13.00	-12.38	-12.67*	-16.87	-20.07
3 (4-hour)	-16.42	-18.07	-17.55	-21.35	-22.28	-18.14
4 (1-hour)	-13.82	-15.30	-14.15	-15.14	-20.37	-15.70
5 (0.5-hour)	-16.69	-17.41	-14.33	-21.54*	-20.26	-17.50
1-5 combined	-14.41§	-15.96*	-14.54	-17.73	-19.84*	-17.44
3-5 combined	-15.66	-16.93	-15.33	-19.38*	-20.97*	-17.14
4-5 combined	-15.29	-16.36	-14.25	-18.41*	-20.31*	-16.66
Pulse (bpm)						
1 (12-hour)	15.65	13.98	16.50	16.08	20.67	19.62
2 (8-hour)	18.60	15.73	19.13	19.84	24.73*	16.78
3 (4-hour)	17.71	17.37	16.20	17.94	19.05	18.50
4 (1-hour)	11.30	15.36	13.27	15.70§	23.08*	18.07
5 (0.5-hour)	16.17*	20.06*	13.01	18.69§	26.87	20.32
1-5 combined	15.69	16.79*	15.26	17.60§	22.93*	18.76
3-5 combined	15.08	17.60*	14.14	17.46§	23.00*	19.02
4-5 combined	13.79§	17.71*	13.14	17.23§	24.97*	19.27

Groups 1, 2, 3, 4, and 5 = Glyceryl trinitrate at 12, 8, 4, 1, and 0.5 hrs post study drug administration, respectively.
N = 14-16, 15, 22-23, 21-23, and 23-24 for Groups 1, 2, 3, 4, and 5, respectively.
* significant difference from placebo
§ significant difference from sildenafil citrate

The mean maximum increase in pulse rate occurred in the group administered avanafil and glyceryl trinitrate separated by 8 hrs. The mean maximum increases from predose to postdose in sitting pulse rate were 18.6, 15.7, and 19.1 bpm in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 8 hrs later. The mean maximum increases from predose to postdose in standing pulse rate were 19.8, 24.7, and 16.8 bpm in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 8 hrs later. In addition, at 0.5 hr time point, the change in standing pulse rate with avanafil + glyceryl trinitrate co-administration (+16.2 bpm) was statistically different from placebo + glyceryl trinitrate (+13.0 bpm). It is of interest to note that despite differences observed at 0.5 and 8 hours, sitting and standing blood pulse rates were not significantly different between avanafil and placebo groups at 1 and 4 hours.

Summary of Study TA-04:

- Overall, 11 (12%) subjects with placebo, 15 (15%) subjects with avanafil, and 28 (29%) subjects with sildenafil had clinically significant drops in standing SBP (≥30 mmHg) after glyceryl trinitrate administration.
- Overall, the number (%) of subjects with symptomatic hypotension AEs after administration of glyceryl trinitrate was 11 (11%) for placebo, 24 (24%) for avanafil, and 26 (27%) for sildenafil. Thus, the occurrence of symptomatic hypotension AEs in male subjects administered avanafil coadministered with a sublingual dose of glyceryl trinitrate was more than with placebo + glyceryl trinatrate, and comparable to sildenafil citrate coadministered with glyceryl trinitrate.

Sponsor's conclusions:

- (b) (4)
- The concomitant use of avanafil with any form of nitrates should be avoided.

Reviewer's comment: With the administration of glyceryl trinitrate, the number of subjects with symptomatic hypotension increased in subjects who received avanafil, compared to placebo. Overall, the potentiation of hypotension is a concern in patients requiring sublingual glyceryl trinitrate and taking avanafil; therefore, avanafil should not be used with nitroglycerin. The sponsor proposed to include a cautionary statement in the full prescribing label regarding the potentiation of hypotensive effects of nitrates by avanafil and a contraindication in Highlights of the label. This reviewer agrees and recommends also to include the corresponding data to convey the decrease in sitting and standing SBP/DBP after administration of avanafil and glyceryl trinitrate separated by 30 min. The safe timepoint at which nitroglycerin may be taken after taking avanafil is not entirely clear from this study. The data show sporadic statistically significant differences between avanafil and placebo groups at timepoints after 0.5 hours, but based upon an abundance of caution, it seems reasonable to wait at least 12 hours between avanafil and nitroglycerin and even then to monitor vital signs carefully.

7.5.5.2 With Antihypertensives (TA-019)

7.5.5.2.1 With Enalapril (10 mg BID) (an ACE inhibitor)

A single 200 mg dose of avanafil was given to subjects who received 10 mg doses of enalapril twice daily for 11 days had a minor additional effect on BP and pulse rate. The results showed that standing SBP decreased by -0.8 mmHg, DBP increased by +0.2 mmHg, and pulse rate increased by +0.6 bpm in subjects who received avanafil and enalapril, compared to placebo and enalapril. A mean maximum decrease in supine SBP/DBP of -1.8/-3.5 mmHg and increase in pulse rate of +1.0 bpm was observed in subjects co-administered with avanafil and enalapril, compared to placebo and enalapril.

Table 7.5.6: Incidence of Potentially Clinically Important Blood Pressure-Related Events Following Co-Administration Avanafil + Enalapril Versus Placebo + Enalapril – TA-019

Parameter	Number of Subjects	
	Avanafil + Enalapril (N = 24)	Placebo + Enalapril (N=24)
Standing SBP <85 mmHg	0	0
Standing SBP decrease >30 mmHg	0	0
Standing DBP <45 mmHg	0	0
Standing DBP decrease >20 mmHg	0	1
Supine SBP <85 mmHg	0	0
Supine SBP decrease >30 mmHg	1	0
Supine DBP <45 mmHg	1	0
Supine DBP decrease >20 mmHg	1	0

Treatment consisted of enalapril 10 mg BID on Days 1-11 plus a single dose of 200 mg avanafil or placebo on Days 8 and 11. BID = twice daily;
DBP= diastolic blood pressure; SBP= systolic blood pressure.

- A single oral dose of avanafil 200 mg co-administered with enalapril (10 mg twice daily) resulted in a mean maximum decrease in supine SBP/DBP of -1.75/-3.46 mmHg compared to placebo, accompanied by a mean maximum increase in pulse rate of 0.96 bpm. No statistically significant difference in the maximum decrease from baseline in standing SBP was observed following co-administration of avanafil with enalapril compared to placebo.
- A statistically significant difference in the maximum decrease from baseline in supine DBP (a secondary endpoint) was observed following co-administration of avanafil with enalapril versus placebo with enalapril (not shown in Table 3.3.3.29). Supine DBP returned to baseline by 4 hours post-avanafil dosing.

7.5.5.2.2 **With Amlodipine (5 mg, QD)** (a calcium channel blocker)

A single 200 mg dose of avanafil given to subjects who received 5 mg doses of amlodipine once daily for 18 days had minor effect on BP. Standing SBP / DBP decreased by -1.6 mmHg / -1.4 mmHg, respectively, in subjects who received avanafil and amlodipine, compared to placebo and amlodipine. The effect on standing pulse rate was a little more significant, which increased by +5.4 bpm in subjects who received avanafil and amlodipine, compared to placebo and amlodipine. A mean maximum decrease in supine SBP of -1.18 mmHg and increase in DBP of +1.5 mmHg was observed in subjects co-administered with avanafil and amlodipine, compared to placebo and amlodipine.

Table 7.5.7: Incidence of Potentially Clinically Important Blood Pressure-Related Events Following Co-Administration of Avanafil + Amlodipine versus Placebo + Amlodipine – TA-019

Parameter	Number of Subjects	
	Avanafil + Amlodipine (N = 23)	Placebo + Amlodipine (N=23)
Standing SBP <85 mmHg	0	0
Standing SBP decrease >30 mmHg	0	0
Standing DBP <45 mmHg	0	0
Standing DBP decrease >20 mmHg	0	1
Supine SBP <85 mmHg	0	1
Supine SBP decrease >30 mmHg	0	1
Supine DBP <45 mmHg	0	3
Supine DBP decrease >20 mmHg	1	3

Treatment consisted of amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil or placebo on Days 12 and 19.
DBP= diastolic blood pressure; SBP= systolic blood pressure.

- A single oral dose of avanafil 200 mg co-administered with amlodipine (5 mg once daily) resulted in a mean maximum change in supine SBP/DBP of 1/-1 mmHg compared to placebo. No statistically significant difference in the maximum decrease from baseline in standing SBP was observed following co-administration of avanafil with amlodipine compared to placebo.
- A statistically significant difference in the maximum increase from baseline in standing pulse rate (secondary endpoint) was observed following co-administration of avanafil with amlodipine versus placebo with amlodipine (not shown in Table 3.3.3.28) Treatment differences were most notable in the first 4 hours postdose, and remained slightly higher than placebo from Hours 5.0 to 10.

Clinical Safety Results: Amlodipine+placebo / Enalopril+Placebo: One subject in each cohort experienced potentially clinically important decreases in BP following co-administration of enalapril or amlodipine with placebo. In both cases, the events resolved within 1 hour after onset and were not accompanied by concurrent symptoms of hypotension.

Headache was the most common adverse event in both cohorts and was more prevalent in subjects who received avanafil + amlodipine, and avanafil alone, compared to placebo + enalapril and placebo + amlodipine. Number of subjects reporting dizziness was the same in subjects who received enalapril only and avanafil + enalapril; 1 of 24 subjects in Cohort A. In contrast, there were 2 of 24 subjects who reported dizziness in the amlodipine only group of Cohort B. Co-administration with amlodipine did not result in a corresponding increase in adverse events.

The Sponsor concludes that a single oral 200 mg dose of avanafil, administered with 10 mg enalapril or 5 mg amlodipine, appeared to be safe and generally well tolerated by the healthy male subjects in this study. The Sponsor states that small reductions in blood pressure occurred following co-administration of avanafil with these blood pressure-lowering agents compared with placebo, but no clinically significant hemodynamic events or changes. The Sponsor

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concludes that physicians should discuss the potential for avanafil to enhance the blood pressure-lowering effect of antihypertensive medications with subjects.

Reviewer's comment: The interaction potential of avanafil with anti-hypertensive agents amlodipine and enalapril appears small. Specific labeling will be drafted.

The sponsor proposes to state in the label that avanafil has the potential to augment the blood pressure lowering effect of alpha-blockers and other antihypertensives. For patients who are stable on alpha-blocker therapy, the sponsor recommends the initial avanafil dose be the lowest dose (50 mg). The reader is referred to the next section of this review for information concerning alpha blockers.

Reviewer's comment: This reviewer also recommends adding in the label the mean maximum changes in standing SBP/DBP following antihypertensive or alpha-blocker therapy concomitant with avanafil administration to convey the numerical changes in blood pressure.

7.5.5.3 With α-Blockers (Study TA-017)

7.5.5.3.1 Doxazosin+avanafil

A Phase 1, single-center, double-blind, randomized, placebo-controlled, two-Cohort, 2wo-period crossover study of the hemodynamic interactions between avanafil and two α-adrenergic blockers, doxazosin and tamsulosin, in middle-aged healthy male subjects

Doxazosin was given once daily in the morning at 1 mg for 1 day (Day 1), 2 mg for 2 days (Days 2-3), 4 mg for 4 days (Days 4-7), and 8 mg for 11 days (Days 8-18) and a single oral dose of either 200 mg avanafil or placebo administered after the doxazosin on Days 15 and 18. Doxazosin has a terminal elimination $t_{1/2}$ of about 22 hours. The initial dosage of doxazosin in patients with hypertension and/or benign prostatic hyperplasia (BPH) is 1 mg given once daily with maintenance dose ranging from 1 to 16 mg once daily. The starting dose of 1 mg is intended to minimize the frequency of postural hypotension and first-dose syncope associated with doxazosin therapy.

Reviewer's comment: The design of this study between doxazosin and avanafil is appropriate as doxazosin is titrated for safety and the dose is a clinically relevant dose, and avanafil is the anticipated highest clinical dose.

7.5.5.3.2 Tamsulosin+avanafil

Tamsulosin 0.4 mg was administered once daily in the morning for 11 consecutive days (Days 1-11) and a single oral dose of either 200 mg avanafil or placebo. Recalling that avanafil t_{max} is 0.5-0.7 hrs, administration of avanafil 3.3 hrs after tamsulosin will coincide with the t_{max} of tamsulosin of 4-5 hrs and thereby maximizing the additive hypotensive effects of both drugs.

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The recommended dose is 0.4 mg once daily, and can increase to 0.8 mg once daily for patients who fail to respond to 0.4 mg dose. Postural hypotension, dizziness, and vertigo are concerns with tamsulosin therapy. In combination with avanafil, orthostasis can be a concern if a pharmacodynamic interaction is shown; therefore, the initial dose of 0,4 mg was preferred over the maximum dose of 0.8 mg.

Reviewer's comment: The design of the tamsulosin study was appropriate.

Overall, blood pressure decreased and pulse rate increased with the administration of avanafil after subjects were given doxazosin or tamsulosin for multiple days prior to avanafil dosing. The clinical effect appeared to have diminished after several hours with blood pressure and pulse rate returning to baseline. The mean age of the subjects enrolled in this study was 46.5 yrs (range 40-61 yrs). The vital signs data from these studies are summarized in the next few tables.

Doxazosin + avanafil

Table 7.5.8 Statistical Comparisons of the Maximum Changes in Standing Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort A: Doxazosin)

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Doxazosin + Avanafil	Doxazosin + Placebo	Mean Difference		
Max decrease systolic (mmHg)	-14.46	-11.96	-2.50	-6.53 - +1.53	0.2114
Max decrease diastolic (mmHg)	-14.50	-8.08	-6.42	-9.54 - -3.30	0.0003
Max increase pulse rate (bpm)	+19.17	+11.96	+7.21	+3.82 - +10.60	0.0002

Cohort A: rising doses of doxazosin daily (Days 1-18) plus a single dose of 200 mg avanafil or placebo on Days 15 and 18.

Table 7.5.9 Statistical Comparisons of the Maximum Changes in Supine Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort A: Doxazosin)

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

Cohort A: rising doses of doxazosin daily (Days 1-18) plus a single dose of 200 mg avanafil or placebo on Days 15 and 18.

A statistically significant difference in the maximum decrease from baseline in supine SBP ($p = 0.0005$) was observed following avanafil versus placebo. The difference in the LSM was -6.00 mmHg.

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Table 7.5.10 Incidence of Potentially Clinically Important Hemodynamic Results (Cohort A: Doxazosin)

Parameter	Number of Subjects	
	Doxazosin + Avanafil (N = 24)	Doxazosin + Placebo (N = 24)
Standing SBP < 85 mmHg	3	0
Standing SBP decrease > 30 mmHg	1	0
Standing DBP < 45 mmHg	2	0
Standing DBP decrease > 20 mmHg	4	1
Supine SBP < 85 mmHg	0	0
Supine SBP decrease > 30 mmHg	0	0
Supine DBP < 45 mmHg	0	0
Supine DBP decrease > 20 mmHg	0	0

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.

Although doxazosin + avanafil decreased standing systolic BP more than doxazosin + placebo, there were no statistically significant difference observed in the maximum decrease from baseline in standing SBP ($p = 0.2114$). The 95% CIs of differences contained zero for the comparisons.

However, statistically significant differences in the maximum decrease from baseline in standing DBP ($p = 0.0003$) was observed following doxazosin + avanafil versus doxazosin + placebo. The difference in the LSM for maximum decrease in standing DBP was –6.42 mmHg. Likewise, statistically significant difference in the maximum increase from baseline in pulse rate ($p = 0.0002$) was observed following avanafil versus placebo. The differences in the LSM for maximum increase in standing pulse rate was +7.21 bpm.

The largest mean supine SBP decreases following avanafil occurred from Hours 0.5 to 1.75, ranging from –6.0 to –4.5 mmHg. Mean SBP changes from baseline following placebo ranged from –2.0 to +4.9 mmHg over the same period. The largest mean supine DBP decreases following avanafil occurred from Hours 0.25 to 1.25, ranging from –6.0 to –4.7 mmHg. Mean DBP changes from baseline following placebo ranged from –0.8 to +2.0 mmHg over the same period. The largest mean increases in supine pulse rate in the immediate postdose period following avanafil occurred from Hours 0.25 to 1.0, ranging from +4.4 to +7.5 bpm. Mean pulse rate changes from baseline following placebo ranged from –4.2 to –0.5 bpm over the same period.

Statistically significant differences were observed in the maximum decrease from baseline in the supine SBP. Maximum decrease in supine SBP was 6.0 mmHg. The maximum decrease in supine DBP was 3.6 mmHg.

Statistically significant differences were not observed in the maximum decrease from baseline in the supine pulse rate between subjects who received avanafil or placebo. The maximum increase in supine pulse rate was 7.2 bpm.

Reviewer's Comment: There is a pharmacodynamic reaction between avanafil and doxazosin, occurring soon after concomitant dosing, and resolving soon thereafter. This will need to be shown in labeling, with an appropriate precaution.

tamsulosin + avanafil

The following are key summary points from the tamsulosin interaction study:

1) Statistically significant differences were not observed in the maximum decrease from baseline in the supine SBP between subjects who received avanafil or placebo.
2) Statistically significant differences were observed in the maximum decrease from baseline in the supine DBP between subjects who received avanafil or placebo. The maximum decrease in supine DBP was 3.3 mmHg.
3) Statistically significant differences were observed in the maximum increase from baseline in the supine pulse rate of 4.7 bpm.

Table 7.5.11 Statistical Comparisons of the Maximum Changes in Standing Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort B: Tamsulosin)

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Tamsulosin + Avanafil	Tamsulosin + Placebo	Mean Difference		
Max decrease systolic (mmHg)	-14.50	-10.88	-3.63	-8.14 - +0.89	0.1101
Max decrease diastolic (mmHg)	-13.13	-9.46	-3.67	-7.86 - +0.53	0.0835
Max increase pulse rate (bpm)	+22.25	+19.79	+2.46	-1.32 - +6.24	0.1913

Cohort B: tamsulosin 0.4 mg daily (Days 1-11) plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.

There were no statistically significant differences observed in the maximum decrease from baseline in standing SBP (p = 0.1101) or DBP (p = 0.0835), or the maximum increase from baseline in standing pulse rate (p = 0.1913) following avanafil versus placebo.

Table 7.5.12 Statistical Comparisons of the Maximum Changes in Supine Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort B: Tamsulosin)

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

Cohort B: tamsulosin 0.4 mg daily (Days 1-11) plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.

A statistically significant difference in the maximum decrease from baseline in supine DBP (p = 0.0392) was observed following avanafil versus placebo. The difference in the LSM was -3.33

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mmHg. Statistically significant difference in the maximum increase from baseline in supine pulse rate (p = 0.0344) was also observed following tamsulosin + avanafil compared to tamsulosin + placebo. The difference in the LSMs for these parameters was +4.67 bpm.

Table 7.5.13 Incidence of Potentially Clinically Important Hemodynamic Results (Cohort B: Tamsulosin)

Parameter	Number of Subjects	
	Tamsulosin + Avanafil (N = 24)	Tamsulosin + Placebo (N = 24)
Standing SBP < 85 mmHg	2	0
Standing SBP decrease > 30 mmHg	1	0
Standing DBP < 45 mmHg	2	0
Standing DBP decrease > 20 mmHg	4	1
Supine SBP < 85 mmHg	0	0
Supine SBP decrease > 30 mmHg	0	0
Supine DBP < 45 mmHg	0	1
Supine DBP decrease > 20 mmHg	1	1

SBP= systolic blood pressure; DBP= diastolic blood pressure
Cohort B: tamsulosin 0.4 mg daily (Days 1-11) plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.

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 postdose 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 those farther removed from the time of dosing (Hours 7.0, 8.0, and 24.0).

Two subjects experienced potentially clinically important supine hemodynamic events. One subject had a single isolated potentially clinically important supine DBP event at Hour 24.0 following placebo and one subject experienced decreases in supine DBP at multiple time points following avanafil from Hours 0.25 to 3.5 and Hours 6.0 to 12.0.

Reviewer's Comments: There is a modest pharmacodynamic interaction between avanafil and tamsulosin, which is less than the interaction between doxazosin and avanafil.

In summary, the effect of avanafil on blood pressure and heart rate in patients taking a avanafil and either the α-blockers doxazosin or tamsulosin is larger than with avanafil alone. As expected, doxazosin has a larger effect compared to tamsulosin. Based on these results, and the known class effect, the Sponsor advises caution when avanafil is co-administered with α-blockers. Subjects should be stable on α-blocker therapy prior to initiating treatment with avanafil, and avanafil should be initiated at the 50 mg dose. The Reviewer agrees. The potential risk of co-administration of avanafil and α-blockers should be included in the Precautions section, and the lower starting dose of avanafil for α-blocker user at initiating stage should be inserted in labeling.

As a final overview of pharmacodynamic interaction studies, the following table summarizes the hemodynamic changes (maximum decreases in BP and maximum increases in pulse rate) from 200 mg avanafil co-administered with nitrates, alpha blockers, selected anti-hypertensives and alcohol (Studies TA-04, TA-015, TA-017 and TA-019).

Table 7.5.14 Mean Maximum Hemodynamic Changes: Co-Administering 200 mg avanafil with Commonly Used Drugs and Alcohol

	Standing SBP/DBP (mmHg)	Supine SBP/DBP (mmHg)	Standing Pulse Rate (bpm)	Supine Pulse Rate (bpm)
With Nitrates				
Glyceryl Trinitrate + Avanafil	–24.1/–21.5	–19.2/–16.7*	+18.7	+16.2*
Glyceryl Trinitrate	–22.7/–17.5	–14.3/–14.3*	+20.3	+13.0*
With α-Blockers				
Doxazosin + Avanafil	–14.5/–14.5	–13.2/–10.6	+19.2	+17.1
Doxazosin	–12.0/–8.1	–7.2/–7.0	+12.0	+13.4
Tamsulosin + Avanafil	–14.5/–13.1	–11.0/–10.0	+22.3	+20.8
Tamsulosin	–10.9/–9.5	–7.9/–6.7	+19.8	+16.1
With Anti-hypertensives				
Enalapril + Avanafil	–9.3/–8.1	–9.4/–9.3	+18.2	+14.0
Enalapril	–8.5/–8.3	–7.6/–5.9	+17.6	+13.1
Amlodipine + Avanafil	–10.4/–9.4	–10.1/–8.8	+17.8	+12.0
Amlodipine	–8.9/–8.0	–8.9/–10.3	+12.4	+11.0
With Alcohol				
Alcohol + Avanafil	n/a	–14.5/–14.6	n/a	+19.3
Alcohol	n/a	–10.9/–9.6	n/a	+10.2

*sitting (not supine) SBP/DBP, sitting (not supine) pulse rate

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenecity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

7.6.2.1 Safety Studies for Sperm (Studies TA-014 and TA-021)

Safety Studies for Sperm (Studies TA-014 and TA-021)

Study TA-014 (effects of age on PK, and acute effect on sperm function in young men) 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 19 to

Reference ID: 3117872

43 y/o, while the subjects in the elderly group were 65-80 y/o. Avanafil semen exposure and the acute effect of avanafil on sperm function in healthy, young male subjects were also evaluated. The Sponsor concluded the following:

- Pharmacokinetics of avanafil and its metabolites were generally comparable in elderly and young subjects
- Avanafil was highly bound to plasma proteins in young and elderly subjects (mean plasma protein binding at ~99%) and was age and concentration independent;
- Mean total amount of avanafil in seminal fluid collected at 1 hour postdose was minimal (<0.0002% of the 200 mg administered);
- Mean sperm motility remained within the reference range and was not considered to be significantly affected by a single dose of avanafil 200 mg (did not change by >20% from baseline) and there was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress.
- Two subjects 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. These sperm motility values were still higher than the 20% abnormality criterion. It is possible that these 2 subjects had a pre-existing condition (e.g., leukocytospermia) that could have affected sperm motility and that the low sperm motility values were not related to study drug.
- Following a single oral dose of avanafil 200 mg, systemic exposures to avanafil, and the metabolites M4 and M16 were generally comparable in elderly and young subjects. However, there was slightly greater exposure of M16 in the elderly, compared to avanafil and M4.

Reviewer's comment: In this study, a single dose (not multiple doses) of avanafil 200 mg appeared to be safe and generally tolerated by the young and elderly male subjects. A single dose sperm study is not sufficient to assess the potential effect of avanafil on human sperm.

Study TA-021 (sperm motility and concentration) 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.

Reference ID: 3117872

Table 7.6.1 Summary of Semen Parameters by Time Point and Treatment

Semen Parameter (Mean ± SD)	Normal Range*	Screening (N = 17)	Predose (Day -2) (N = 17)	Avanafil (N = 17)	Placebo (N = 17)
Volume (mL)	2 - 6	3.1 ± 0.8	3.3 ± 0.8	2.8 ± 0.8	3.1 ± 0.9
Concentration (Mil/mL)	20 - 250	255 ± 158	251 ± 129	284 ± 166	297 ± 163
Total Sperm Count (Mil)	> 40	780 ± 520	859 ± 525	812 ± 550	937 ± 618
Normal Forms (%)	> 14	15 ± 5	13 ± 5	12 ± 4	13 ± 5
Total Motile Count (Mil)	> 20	584 ± 397	647 ± 420	607 ± 466	717 ± 510
Motility (%)	> 50	74 ± 6	74 ± 8	70 ± 10	73 ± 9
Forward Progression (%)	> 50	95 ± 2	95 ± 2	94 ± 2	94 ± 3
WHO Calculated Forward Progression (%)		71 ± 6	70 ± 9	66 ± 11	69 ± 10
Vitality (%)	> 50	91 ± 3	93 ± 3	91 ± 6	91 ± 4

* Normal ranges provided by Heartland Center for Reproductive Medicine Laboratories
@ Forward progression (%) = forward moving sperm / total moving sperm (method used by Heartland)
# WHO calculated forward progression (%) = forward moving sperm / total sperm (method using WHO criteria)

Table 7.6.2 Arithmetic Pharmacokinetic Parameters (Mean ± SD) of Avanafil for Plasma and Seminal Fluid

Matrix	Parameter	Avanafil Mean ± SD (N)
Plasma	Concentration (ng/mL)	3200 ± 1150 (17)
Seminal Fluid	Concentration (ng/mL)	185 ±89.4 (17)
	Volume (mL)	2.81 ± 0.798 (17)
	Total Amount (ng)	512 ± 260 (17)
	% Dose (%)	0.000256 ± 0.000130
Seminal Fluid / Plasma	Concentration Ratio	0.06 ± 0.02

The Sponsor concluded the following:

- While a very small percent of the avanafil dose (~0.0002%) was detected in seminal fluid, 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.

Reviewer's Comments: Both Studies TA-014 and TA-021 were single-dose studies, and the efforts from longer term use are unknown at this moment. As discussed with the Sponsor at the Pre-NDA meeting, a longer-term sperm study (e.g., 12 weeks treatment) is necessary.

7.6.2.2 Data on Pregnancy

Avanafil is not indicated for use in women; therefore, the effects of avanafil during pregnancy and lactation were not evaluated.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Sponsor submitted a request for waiver of pediatric studies for avanafil on February 29, 2012. The Division forwarded the waiver to the Pediatric Review Committee. The Division supported the waiver because the disease/condition does not exist in the pediatric population and is indicated for the treatment of erectile dysfunction. The PeRC PREA subcommittee conducted a review and on March 27, 2012, PeRC agreed with the Division to grant a full waiver for this indication. (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
No overdoses occurred in the avanafil clinical development program. Single avanafil doses up to 800 mg have been given to healthy subjects and multiple daily avanafil doses up to 300 mg have been given to subjects with erectile dysfunction. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance because avanafil is highly bound to plasma proteins and is not significantly eliminated in urine.

Drug Abuse
No studies were specifically performed to assess the abuse potential of avanafil. No adverse events of drug abuse were reported during the clinical development program. In general, PDE5 inhibitors do not pose a significant potential for abuse or dependence.

Withdrawal and Rebound
No studies were specifically performed to assess the withdrawal effects of avanafil. However, given that avanafil is intended to be used on an as needed basis, there was essentially a "withdrawal period" after every dose recorded in the clinical development program, and information from each of these periods is included in the overall safety database. Accordingly, there were no withdrawal issues associated with avanafil observed during the clinical development program. No PDE5 inhibitors are reported to be associated with withdrawal effects.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability
No studies were specifically performed to assess the effects of avanafil on mental ability or on the ability to drive or operate machinery. No PDE5 inhibitors are reported to be associated with mental impairment or inability to drive or operate machinery and no evidence was observed during the clinical development program to indicate these are issues with avanafil treatment.

Reference ID: 3117872

7.7 Additional Submissions / Safety Issues

After the 12-Day Safety Update, no additional safety submissions were received.

8 Postmarket Experience

Avanfil has not been approved in the US, no postmarket experience is available.

9 Appendices

9.1 Literature Review/References

No literature review/references are inserted here.

9.2 Labeling Recommendations

Clinical edits to product labeling were conveyed to Sponsor on April 12, 2012. Several points were emphasized in the labeling:

- The product is similar to all other PDE5 inhibitors in its side effect profile, drug interactions, effects on blood pressure, and effects on vision.
- The recommended use of the product will be as it was used in the Phase 3 studies. (b) (4)
- Study TA-05 is not considered a Phase 3 study for purposes of efficacy
- The safety results from Study 303 (radical prostatectomy) will be included in labeling.
- Clinical agrees with Clinical Pharmacology that the product should not be used in patients taking strong CYP 3 A4 inhibitors due to the reduced clearance of avanafil. and the current lack of availability of a 25 mg dosage strength.

If required, a Clinical labeling Addendum can be completed after the labeling negotiations have finished.

9.3 Advisory Committee Meeting

No advisory committee meetings were held for this application, as the side effect profile and risk/benefit issues were the same as for the marketed PDE5 inhibitors

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

/s/

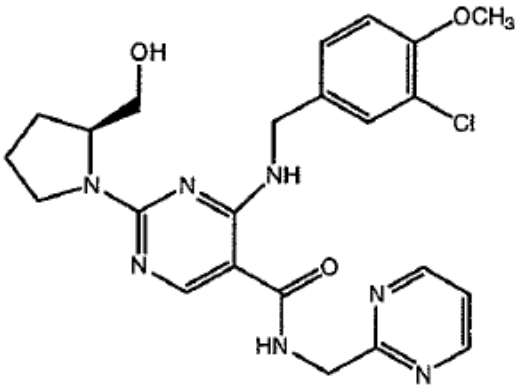
GUODONG FANG
04/17/2012

MARK S HIRSCH
04/17/2012
I concur.

Medical Officer's NDA Filing Memorandum
Prepared for 45-day Filing Meeting on August 10, 2011

NDA 202,276

NDA submission Date:	June 29, 2011
45-Day Filing Review Date:	August 13, 2011
Mid-Cycle Review Date:	November 21, 2011
PDUFA Goal Date:	April 29, 2012
Sponsor:	Vivus Inc., 1172 Castro St., Mountain View, CA
Generic Name:	Avanafil
Proposed Trade Name:	(b) (4)
Internal development name:	TA-1790
Chemical Name:	(S)-4-(3-Chloro-4-methoxybenaylamino)-2-(2-hydroxymethylpyrrolidin-1-yl)-N-pyrimidin-2-ylmethyl-5-pyrimidinecarboxamide
Empirical formula:	$C_{23}H_{26}ClN_7O_3$
Molecular Weight:	483.95
Dose strength:	50 mg, 100 mg, 200 mg
Route of Administration:	Oral
Indication:	Male erectile dysfunction
Related Submissions:	IND 51235
Structure:	



According to the Sponsor, avanafil is a potent inhibitor of cGMP-specific PDE5 and is highly selective for the PDE5 isoenzyme relative to other phosphodiesterases. Avanafil is rapidly absorbed following oral administration and achieves maximum plasma concentrations from 30 to 45 minutes in the fasted state. Avanafil has a half-life ($t_{½}$) of approximately (b) (4) 5 hours.

1. Summary

1.1. Purpose:

Reference ID: 2997438

This review is conducted to fulfill a regulatory requirement of assessing and determining whether this NDA 202,276 (b) (4) [Avanfil]) is eligible for filing under 21 CFR 314.101, "the filing means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review." This document also serves as the basis for communicating to sponsor potential clinical review issues identified during this initial review period.

1.2. Conclusion:

Following a preliminary review of three pivotal adequate and controlled studies of efficacy and safety (TA-301, TA-302 and TA-05), one open-label, long-term safety study (TA-314), the draft label, and financial disclosures for investigators of Studies of TA-301, TA-302, and TA-314, this reviewer has not identified any major deficiencies that would constitute the basis for a Refusal-to-file (RTF) action as described in the FDA guidance consistent with 21 CFR 314.101 (d) (3). **This reviewer concludes that**

- **The submitted NDA 202,276 application is sufficiently complete to permit a substantive clinical review, therefore, is filable, and should be filed from a Clinical perspective. Several Clinical comments to Sponsor for the 74-Day letter are listed in final section of this memo.**

The following is a brief clinical outline of this NME NDA submission including the contents of the Clinical section and current preliminary comments from the Clinical review team.

2. Background

2.1. Clinical regulatory history of Vivus's avanafil (TA-1790) for ED

Avanafil has undergone evaluation for the treatment of erectile dysfunction (ED) under IND 51,235, which was originally submitted on November 30, 2001, after a pre-IND meeting with the Division on November 07, 2001. With the opening IND, the Sponsor included a Protocol # TA-01, "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 between the Sponsor and DRUP. The sponsor proposed to conduct two, pivotal, Phase 3 studies and a 12-month open label safety extension study. This proposal was considered generally 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

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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 included in labeling.

3. Drug interaction studies, including nitroglycerin, alpha-blockers, and ketoconazole (400 mg QD) should be conducted.

During the Phase 3 clinical trial development, the Division responded with advice to the Sponsor's proposed "pivotal" clinical trials TA-301 (in the general ED population), TA-302 (in diabetic men) and TA-303 (in radical prostatectomy patients) through special protocol assessments. The Division also reviewed the protocol for TA-314 (long-term safety and tolerability)

On October 20, 2010, the Division met with the Sponsor for a Pre-NDA meeting. The Clinical review team had several comments and recommendations:

1. Due to slower than expected enrollment, the Sponsor asked whether the NDA could be submitted without Study 303 (in radical prostatectomy patients). The Division stated that even without inclusion of Study 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 (treatment of ED). In addition, there appeared to be sufficient patient exposure to support safety even without inclusion of Study TA-303. However, the Division do not agree (b) (4)

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

3. (b) (4)

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

5. All pooling of efficacy data in the ISE would be considered exploratory.

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3. In addition to safety data presented by individual phase 1 study, the Division requested an overall narrative summary of safety from the seventeen phase 1 studies.

4. The Sponsor was asked to conduct a pre-defined analyses of safety data from the open-label, safety extension study TA-314 and to keep this analysis separate from the controlled studies in the ISS.

5. The Sponsor was asked to provide individual narratives for the targeted medical events (TMEs).

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

7. 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.

8. The Sponsor was informed to submit a request for pediatric waiver in the NDA submission, and it would be conveyed to the Pediatric Review Committee (PeRC). (b) (4)

The Clinical Pharmacology team had several comments as well:

1. The impact of severe renal impairment including End State Renal Disease (ESRD) on avanafil PK was not assessed. This would become a review issue and might become a post-marketing requirement (PMR) given that avanafil is an NME. The Sponsor was requested to address this in the NDA submission.

2. The impact of severe hepatic impairment on avanafil PK was not assessed. This would become a review issue. The Sponsor was requested to address this in the NDA submission.

3. The Pre-NDA meeting package stated that avanafil can be taken without regard to food. However, food appears to delay the time to maximum plasma concentration. Therefore, food effect would be a review issue.

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

5. Regarding **Drug-Drug Interaction** (DDI) studies
   - (b) (4), the NDA would need to include information supporting the previous DDI studies TA-016, TA-018, TA-015, TA-017, and TA-019.
   - The NDA should include information to address the effect of CYP 3A4 inducer (e.g., rifampin) co-administration on avanafil PK.

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- The NDA should include information to address the effect of avanafil on P-glycoprotein (e.g., digoxin).
- The NDA should include information to describe the effect of mild, moderate and strong CYP3A4 inhibitors on avanafil PK.

6. The NDA would need to include information on the following additional clinical pharmacology issues:
   - The effect of age on avanafil exposure.
   - The starting dose of avanafil and how it was determined.
   - The safety of (b) (4) administration of avanafil, if such a dosing regimen was requested.

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.

3. NDA Filing Review

Formulations

Two avanafil immediate-release tablet formulations (Formulations I and II) were used in studies conducted in support of this NDA. (b) (4) vanafil Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and it is the proposed commercial formulation.

Key PK parameters:

T_{max}: 0.5-0.75 hrs (fasted); $t_{1/2}$: 2.8-5.1 hrs
High-fat meal: Delays t_{max} by 1.25 hrs; and decreases C_{max} by 39%; no effect on AUC

3.1. Methods of RTF Review:

This medical officer's filing review is based on three criteria proposed in the FDA Guidance for the filing review that represents FDA's interpretation of 21 CFR314.101 (d)(3):

- Omission of a section of the NDA required under 21 CFR 314.50, including 314.50(b), (c), (d) (1)-(6), or presentation of a section in so haphazard a manner as to render it incomplete on its face
- Clear failure to include evidence of effectiveness compatible with the statute and regulations [21 CFR 314.50; 314.126]
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use

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Submitted Materials:

The principal analyses of efficacy and safety included in this NDA include data from 3 pivotal clinical studies, 3 supportive clinical studies, and 17 Phase 1 studies.

- "Pivotal" clinical studies (N = 3): TA-05 (Phase 2), TA-301 (Phase 3), and TA-302 (Phase 3);
- Supportive studies (N = 3): TA-01 (Phase 2), TA-03 (Phase 2), and TA-314 (Phase 3);
- Phase 1 clinical pharmacology studies (N = 17); HP-01, TA-02, TA-04, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, and TA-140.

Table 3.1.1 "Pivotal" Clinical studies (n=3)

Protocol	Primary end points	Treatment groups /doses/patients	N	Subjects
Phase 2 studies				
TA-05	Dose-ranging, safety and efficacy (9-12 weeks)	Randomized, active-controlled, double-blind, 3-way crossover	295	Mild to moderate ED
Phase 3 studies				
TA-301	Efficacy and safety in general ED (12 weeks)*	Randomized, placebo-controlled, double-blind, parallel with doses (50, 100, 200, 300 mg)	646	Mild to severe ED
TA-302	Efficacy and safety in diabetic patients (12 weeks)	Randomized, placebo-controlled, double-blind, parallel with doses (100, 200 mg)	390	Mild to severe ED

*patients with diabetes and ED caused by spinal cord injury or radical prostatectomy were excluded.

Table 3.1.2 Supportive Clinical studies (n=3)

Protocol	Primary end points	Treatment groups /doses/patients	N	Subjects
Phase 2 studies				
TA-01	Preliminary safety and efficacy (3 dose levels) using RigiScan™ monitoring	Randomized, single-blind; randomized, placebo, and active (sildenafil, SIL)–controlled, crossover (TA1970 50, 100, 200 mg), single dose	89	Mild to moderate ED
TA-03	(1) Onset of effect of 200 mg dose; (2) effective duration of action	Randomized, active -controlled, double-blind, 3-way crossover (TA1970 200 mg, SIL 100 mg) 9-12 weeks	51	Mild to moderate ED
Phase 3 studies				
TA-314	Long-term safety and efficacy (52 weeks)	Open-label extension (TA1970 50, 100, 200, mg)	712	Completed TA-301,302

The Sponsor classified Study **TA-05** as one of the "pivotal" clinical trials, even though TA -05 was a Phase 2 study. TA-05 was a Phase 2, randomized, double-blind, parallel-design, placebo-controlled, multicenter study in adult male subjects with mild to moderate ED of ≥ 6 months duration and who were in a monogamous heterosexual relationship for at least 3 months. Subjects with diabetes and subjects with erectile dysfunction caused by spinal cord injury or radical prostatectomy were excluded from participation. 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

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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 regarding the administration of study drug and sexual experience in a diary.

The other 2 "pivotal" clinical studies are Phase 3 studies **TA-301** and **TA 302**. In the two Phase 3 studies patients had mild to severe ED, while in the Phase 2 study, patients had mild to moderate ED. Disease severity was determined by the International Index of Erectile Function (IIEF) erectile function domain score (mild=IIEF score of 17 to 25; moderate=IIEF score of 11 to 16; severe=IIEF score ≤ 10) at the randomization visit. In the 12-week, 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 302 were randomized in a 1:1:1 ratio to placebo, avanafil 100, and 200 mg.

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Table 3.1.3 Phase 1 Clinical Pharmacology studies (n=3)

Protocol	Primary end points	Treatment groups /doses/patients	N	Subjects
HP-01	Safety, tolerability, PK profile, metabolites, food effect	Randomized, double-blind, placebo-controlled, single ascending dose, parallel (12.5, 25, 50, 100, 200, 400, 600, 800 mg)	65	Healthy male
TA-02	PK of single and multiple doses; Safety, tolerability,	Randomized, double-blind, single- and multiple-dose, paralleldoses (50, 100, 200 mg) (72 hr to 17 days)	48	Healthy male
TA-04	hemodynamic effects of sublingual glyceryl trinitrate on avanafil relative to sildenafil	Randomized, placebo-controlled, double-blind, 3-way crossover (200 mg) (sildenafil 100 mg, placebo) single dose	106	Healthy male
TA-07	PK ofsingle and steady –state; bid dose	Non-radomized, open-label (200 mg single D); washout 48 hrs, per 12 hr dose of 200 mg x 7 days	15	Healthy male
TA-010	[^{14}C] TA-1790 Mass balance & absorption, distribution, metabolism, excretion profile	Single-dose, non-randomized, open-label, mass balance study (600 mg suspension oral)	6	Healthy male
TA-011	Safety and PK co-administered with ketoconazole, ritanovir, or erythromycin	Randomized, open-label, 1-sequence, 3-parallel group (various doses on different days with single dose TA-1790 50-200 mg)	44	Healthy male
TA-012	PK+tolerability in hepatic impairment	Non-randomized, open-label, single-dose, parallel-group, matched-control (200 mg)	24	Male of normal, or hepatic impairment mild to moderate
TA-013	PK+tolerability in renal impairment	Non-randomized, open-label, single-dose, parallel-group, match-controlled, (200 mg)	24	Male of normal, or renal impairment mild to moderate
TA-014	Age effect, semen exposure, acute effect on sperm; age on the PK, safety in young/elderly	Open-label, non-randomized, 2-cohort, single-dose (200 mg)	32	Healthy male (young & elderly)
TA-015	Hemodynamic interactions of concomitant TA-1790+alcohol	Randomized, double-blind, placebo-controlled, 3-period, 3-way crossover (200 mg) single dose	15	Healthy male
TA-016	Effects of daily avanafil dosing on the PK & PD of a single dose of warfarin.	Randomized, double-blind, placebo-controlled, 2-way crossover (200 mg) single dose	24	Healthy male
TA-017	Effects of the co-administration of avanafil on the hemodynamic effects of 2 α-adrenergic blockers doxazosin or tamsulosin	Randomized, double-blind, placebo-controlled, 2-cohort, 2-period, crossover; various doses of DOX (Cohort A) and TAM (Cohort B) or placebo with TA-1790 (200 mg single dose)	48	Healthy male
TA-018	effect of a single dose of avanafil on the single -dose PK of desipramine and rosiglitazone and multiple-dose PK of omeprazole	All open-label, crossover; doses of OME, single dose of ROSI, DESI , with single dose of TA-1790 (200 mg); Cohort A: Non-randomized, 1-sequence; Cohort B and C: randomized, 2-period;	60	Healthy male
TA-019	PK and hemodynamic effects of the co-administration of avanafil with 2 BP medications enalapril or amlodipine	Randomized, double-blind, placebo-controlled, 2-cohort, 2-period crossover; Cohort A: ENAL + TA-1790 (200 mg single dose); Cohort B: AML + TA-1790 (200 mg single D)	48	Healthy male
TA-020	Effect of food on the PK; relative BA of 2 formulations; and dose-proportionality of avanafil	Randomized open-label, 4-period crossover (2x100 mg formulation II fasted or fed; 2x100 mg formulation I, 1x50 mg formulation II, fasted; single dose)	24	Healthy male, BW ≥50 kg BMI 18-30 kg/m^2
TA-021	Acute effect on sperm, semen exposure; safety & tolerability in young male	Double-blind, placebo-controlled, randomized, 2-period crossover; 200 mg, single dose	17	Healthy male, BW ≥50 kg BMI 18-30 kg/m^2
TA-140	Thorough QT study with therapeutic and supra-therapeutic dose of avanafil vs. MOX	Randomized, double-blind, placebo- & active controlled (MOX 400 mg), 4-arm crossover, avanafil 100 mg, 800 mg; single dose	57	Healthy male, 18- 45 years of age, BMI 19-28 kg/m^2

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The supportive studies include 2 Phase 2 studies and 1 Phase 3 long term safety study. One of the 2 Phase 2 studies is Study **TA-01**, which was a single blind, randomized, crossover study to evaluate the safety and efficacy of 3 dose level of avanafil given in conjunction with visual sexual stimulation in patients with mild to moderate ED in conjunction with RigiScan monitoring. The other Phase 2 study was **TA-03** study, which was a double-blind, randomized, active-controlled, 3-way crossover study to evaluate the onset of effect of avanafil 200 mg administered at home in patients with ED; and to determine the effective duration of action of avanafil in the at-home setting. In addition, **TA-314**, was a Phase 3, open-label extension study to evaluate the long-term safety, 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. All Patients in Study TA-314 had completed a previous Phase 3 avanafil study; either TA-301 or TA-302.

The remaining 17 Phase 1 studies include:

- A biopharmaceutics study – Study **TA-020** comparing avanafil Formulations I and II,
- A food effect arm in the first-in-human study (**Study HP-01**) to determine the effect of food on the avanafil PK and the dose proportionality.
- Pharmacokinetics studies
  - To evaluate absorption, distribution, metabolism, and excretion – Studies TA-020, HP-01, and **TA-010**
  - Single dose and steady-state PK of avanafil – **TA-07**
- To evaluate drug-drug interaction
  - Effect of other drugs on the PK of avanafil – co-administered with ketoconazole and ritonavir in **TA-011**; co-administered with erythromycin in **TA-019**
  - Effect of avanafil on the pharmacokinetics of other drugs – co-administered with omeprazole (a CYP2C19 substrate), rosiglitazone (a CYP2C8 substrate) or desipramine (a CYP2D6 substrate) in **TA-018**, and with amlodipine (a CYP3A4 substrate) in TA-019
  - Effect of avanafil on warfarin (S-warfarin is a 2C9 substrate), including on the prothrombin time and international normalized ratio (INR) or collagen-induced platelet aggregation in **TA-016**,
- In special populations
  - Renal impairment – **TA-013**
  - Hepatic impairment – **TA-012**
  - Age – **TA-014**
- Pharmacodynamics: Effects on blood pressure and heart rate – avanafil alone in **TA-02**; with nitrates in **TA-04**; with alpha blockers in **TA-017**; with anti-hypertensives, including ACE inhihibitors and calcium channel blockers in TA-019**,** and with alcohol in **TA-015;**

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- Effect on sperm functions – **TA-021**
- TQT study – **TA-140**

In addition, the following critical sections of the NDA submission were submitted:

- Draft labeling
- Financial disclosure information for covered studies

3.2. Proposed indication:

The treatment of erectile dysfunction (ED).

Exposure requirement
The regulatory requirements for total exposure have been met (i.e., at least 300 subjects with at least 6 months of total exposure and 100 subjects with at least 12 months of total exposure to avanafil, including exposure in the "qualifying" studies).

3.3. Results of Filing Review

3.3.1. Does the NDA 202,276 omit a section required under CFR 314.50, or were any of the sections of the NDA presented in so haphazard a manner as to render it incomplete on its face for a sufficient clinical review? Was a particular section presented in such a manner as to render it incomplete for the clinical review?

Answer: No. The NDA contains critical sections in sufficient detail (see Table 3). Certification (Form 3454) and investigator lists are provided for the 23 covered studies in the US under IND #51,235 (also see "CLINICAL: 45 day checklist" in Appendix 1).

Table 3.3.1 Checklist for the critical sections of NDA for a sufficient clinical review

Required Sections (21 CFR 314.50)	Location
The proposed text of the labeling (c)(2)(i)	Module 1
An overview of the data (c)(2)(viii)	2.3, 2.4, 2.5 & 2.6
The technical sections and integrated summaries (d) • Controlled clinical studies (d)(5)(ii) • Summary of efficacy (d)(5)(v) • Summary of safety (d)(5)(vi) • Benefits and risks conclusion (d)(5(viii)	Module 2, 3, 4 & 5 2.7.6 and 5.3.5.1 2.7.3 and 5.3.5.3 2.7.4 and 5.3.5.3 2.5.6
Required case report forms and tabulations (f)	5.3.5.1
Financial certification or disclosure statement (k)	Module 1

3.3.2. Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

a. **Lack of any adequate and well-controlled studies (21 CFR 314.126), including use of obviously inappropriate or clinically irrelevant study endpoints**
b. **Presentation or what appears to be only a single adequate and well-controlled trial without adequate explanation of why the trial should be**

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regarded as fulfilling the legal requirement for adequate and well-controlled investigations

c. **Use of a study design clearly inappropriate (as reflected in regulations or well-established agency interpretation) for the particular claim**

Answer: No. The sponsor provides data supporting the efficacy of avanafil primarily from pivotal clinical studies including two Phase 3, and one Phase 2 study, which were multi-center, double blind, randomized, parallel group, placebo-controlled studies, with supportive evidence from two Phase 2 studies, as well as from one long term safety and efficacy study. A total of 2,183 patients were enrolled in the Phase 2 and 3 studies conducted in the U.S., which covered a broad range of etiologies of erectile dysfunction as well as the full range of ED severities from mild to severe.

The following section of the filing review summarizes the efficacy findings of the 3 "pivotal" clinical studies including one Phase 2 and two Phase 3 studies, which provide evidence of effectiveness compatible with statute and regulations.

3.3.2.1. Pivotal Double-Blind Studies (TA-301, TA-302, and TA-05)

3.3.2.1.1. General study design:

Since the methodology of these studies was almost identical, a single summary will be performed for this preliminary review. The objective of these studies was to evaluate the clinical efficacy and safety of avanafil versus placebo for the treatment of patients with ED. These were multicenter, randomized, double-blind, placebo-controlled, parallel group studies conducted entirely within the United States. In combination, in these three studies, 1228 patients were randomized, and 1081 (88.0%) completed the study and 147 (12.0%) discontinued from the study with primary reasons of protocol non-compliance, and "other". Subjects who took at least one dose of study medication or placebo and could, therefore, be included in the intent-to-treat (ITT) population. The evaluable efficacy population of the three combined studies was 1228 patients and was defined as all patients who received at least one dose of study medication and had at least one post baseline efficacy evaluation.

3.3.2.1.2. Efficacy endpoints:

There were **three co-primary efficacy endpoints:**

1) Change in IIEF erectile function (EF) domain score from baseline to end of treatment;
2) Changes in percentage of sexual attempts resulting in successful vaginal penetration (SEP2);
3) Change in percentage of sexual attempts resulting in successful intercourse (SEP3).

The secondary endpoints included

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1) Changes in other IIEF domain scores from baseline to end of treatment;
2) Percentage of successful response to diary questions by time interval between dose administration and sexual attempt.

3.3.2.1.3. Results:

3.3.2.1.3.1.1. Primary endpoints:

Co-Primary Endpoint 1 (EF Domain Score)

Table 3.3.3 Change in IIEF Erectile Function Domain Score From Baseline to End of Treatment –ITT Population – Individual Phase 3 Studies TA-301 and TA-302

TA-301 Primary Efficacy Endpoint (1)

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 (5.11)	15.3 (7.79)	2.9 (6.38)	2.9 (0.57)	<0.0001
Avanafil 50 mg	152	12.6 (5.20)	18.1 (7.94)	5.4 (7.54)	5.4 (0.57)	<0.0001
Avanafil 100 mg	156	12.6 (5.39)	20.9 (7.90)	8.3 (7.67)	8.3 (0.56)	<0.0001
Avanafil 200 mg	155	12.8 (5.00)	22.2 (7.73)	9.5 (7.03)	9.5 (0.56)	<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
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)				4.1 (0.80)	(2.5 , 5.6)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)				2.9 (0.80)	(1.3 , 4.5)	0.0003
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				1.2 (0.79)	(-0.4 , 2.7)	0.1366

TA-302 Primary Efficacy Endpoint (1)

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 (5.01)	13.2 (7.72)	1.8 (6.24)	1.8 (0.64)	0.0066
Avanafil 100 mg	125	11.2 (4.78)	15.8 (8.26)	4.6 (7.00)	4.5 (0.64)	<0.0001
Avanafil 200 mg	125	12.0 (5.10)	17.3 (8.65)	5.3 (7.50)	5.4 (0.66)	<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
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				0.8 (0.88)	(-0.9, 2.6)	0.3387

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;

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TA-05 Primary Efficacy Endpoint (1)

Treatment	N		Baseline Score (SD)	ScoreAt the End (SD)	Change from Baseline (SD)	LS Mean (SE)	p-value [1]
Placebo	55		15.8 (4.0)	16.9 (7.3)	1.1 (6.4)	0.9 (0.95)	–
Avanafil 50 mg	56		16.1 (3.5)	19.4 (7.5)	3.2 (7.6)	3.2 (0.94)	0.0915
Avanafil 100 mg	60		16.2 (4.1)	22.3 (7.0)	6.1 (6.7)	6.1 (0.90)	0.0001
Avanafil 200 mg	56		16.5 (3.8)	22.4 (7.4)	5.9 (7.1)	6.0 (0.94)	0.0002
Avanafil 300 mg	57		16.5 (3.8)	22.5 (7.2)	6.0 (7.9)	6.1 (0.94)	0.0001

Adult male subjects 35 to 70 years of age with mild to moderate erectile dysfunction;
N = 295 (249 completed, 84.4%)
1. Two-sided p-value from treatment comparison of avanafil with placebo.

Co-Primary Endpoint 2 (SEP2)

Table 3.3.2 Change in % of Sexual Attempts Subjects Were Able to Achieve Successful Vaginal Penetration (SEP2) Between the Run-in Period and the Treatment Period – – ITT Population- Individual Phase 3 Studies TA-301 and TA-302

TA-301 Primary efficacy Endpoint (2)

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 (36.34)	53.8 (37.88)	7.1 (32.07)	7.1 (2.33)	0.0025
Avanafil 50 mg	154	45.4 (36.72)	64.3 (37.21)	18.9 (35.51)	18.2 (2.34)	<0.0001
Avanafil 100 mg	157	46.6 (38.24)	73.9 (32.26)	27.3 (35.17)	27.2 (2.32)	<0.0001
Avanafil 200 mg	156	48.3 (38.22)	77.3 (31.44)	29.0 (35.90)	29.8 (2.33)	<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 (3.30)	(16.3 , 29.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				20.1 (3.29)	(13.6 , 26.5)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)				11.1 (3.31)	(4.6 , 17.6)	0.0009
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)				11.7 (3.30)	(5.2 , 18.1)	0.0004
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)				9.0 (3.29)	(2.5 , 15.5)	0.0064
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				2.6 (3.28)	(-3.8 , 9.1)	0.4221

TA-302 Primary Efficacy Endpoint (2)

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 (36.63)	42.0 (39.34)	5.9 (31.16)	7.5 (2.85)	0.0088
Avanafil 100 mg	126	32.5 (35.19)	54.0 (39.40)	21.5 (37.19)	21.5 (2.85)	<0.0001
Avanafil 200 mg	126	41.5 (37.66)	63.5 (38.67)	22.0 (35.00)	25.9 (2.90)	<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
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				4.4 (3.97)	(-3.4, 12.2)	0.2719

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.

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

TA-05 Primary Efficacy Endpoint (2)

Treatment	N	Baseline Rate (SD)	At the End Rate (%)	Change from Baseline (%)	LS Mean (SE)	p-value [1]
Placebo	55	56.3 (36.0)	60.5 (36.6)	4.2 (35.8)	-0.2 (3.53)	–
Avanafil 50 mg	56	67.8 (29.7)	76.1 (30.0)	8.4 (31.2)	11.5 (3.51)	0.0200
Avanafil 100 mg	60	61.7 (34.7)	79.2 (26.5)	17.5 (30.5)	16.7 (3.37)	0.0006
Avanafil 200 mg	56	66.8 (31.0)	79.8 (27.9)	13.0 (34.1)	15.4 (3.50)	0.0019
Avanafil 300 mg	57	62.8 (32.6)	83.7 (20.5)	20.9 (33.8)	20.8 (3.46)	<0.0001

Adult male subjects 35 to 70 years of age with mild to moderate erectile dysfunction;
N = 295 (249 completed, 84.4%)
1. Two-sided p-value from treatment comparison of avanafil with placebo.

Co-Primary Endpoint 3 (SEP3)

Table 3.3.1 Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period Resulting in Successful Intercourse (SEP3) – ITT Population – Individual Phase 3 Studies TA-301 and TA-302

TA-301 Primary efficacy Point (3)

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 (17.82)	27.0 (31.41)	14.4 (27.63)	14.1 (2.57)	<0.0001
Avanafil 50 mg	154	13.5 (18.58)	41.3 (35.94)	27.8 (33.86)	27.8 (2.58)	<0.0001
Avanafil 100 mg	157	13.9 (18.87)	57.1 (36.05)	43.2 (33.86)	43.4 (2.56)	<0.0001
Avanafil 200 mg	156	12.4 (18.52)	57.0 (37.78)	44.6 (35.67)	44.2 (2.57)	<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
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)				16.4 (3.64)	(9.3, 23.6)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)				15.6 (3.63)	(8.5, 22.7)	<0.0001
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				0.8 (3.62)	(-6.3, 7.9)	0.8198

TA-302 Primary Efficacy Endpoint (3)

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 (16.41)	20.5 (29.10)	10.5 (27.73)	13.6 (2.77)	<0.0001
Avanafil 100 mg	126	8.2 (17.42)	34.4 (36.37)	26.2 (33.71)	28.7 (2.78)	<0.0001
Avanafil 200 mg	126	8.0 (14.91)	40.0 (36.34)	32.1 (32.94)	34.0 (2.76)	<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
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				5.3 (3.84)	(-2.3, 12.8)	0.1724

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.

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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;

TA-05 Primary Efficacy Endpoint (3)

Treatment	N	Baseline Rate (SD)	At the End Rate (%)	Change from Baseline (%)	LS Mean (SE)	p-value [1]
Placebo	55	16.9 (19.6)	28.9 (30.2)	12.1 (29.9)	11.2 (4.21)	–
Avanafil 50 mg	56	21.2 (19.6)	53.4 (33.9)	32.2 (33.8)	34.4 (4.19)	0.0001
Avanafil 100 mg	60	19.0 (20.4)	58.6 (33.6)	39.6 (34.7)	40.0 (4.03)	<0.0001
Avanafil 200 mg	56	20.4 (18.9)	62.1 (33.0)	41.7 (33.6)	43.0 (4.18)	<0.0001
Avanafil 300 mg	57	18.1 (20.1)	64.3 (32.3)	46.1 (34.3)	46.0 (4.14)	<0.0001

Adult male subjects 35 to 70 years of age with mild to moderate erectile dysfunction;
N = 295 (249 completed, 84.4%)
1. Two-sided p-value from treatment comparison of avanafil with placebo.

3.3.2.1.3.2.Secondary endpoints:

Changes in other IIEF domain scores from baseline to end of treatment

Table 3.3.4 Changes in IIEF Orgasmic Function, Sexual Desire, Intercourse Satisfaction, and Overall Satisfaction Domain Scores From Baseline to End of Treatment – Integrated Analysis of Studies TA-301 and TA-302 and TA-05 – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Orgasmic function domain score						
Placebo	331	5.0 (2.68)	5.4 (3.06)	0.4 (2.80)	0.4 (0.15)	0.0152
Avanafil 50 mg	208	5.1 (2.53)	6.6 (2.89)	1.5 (2.83)	1.2 (0.20)	<0.0001
Avanafil 100 mg	341	5.0 (2.66)	6.9 (3.04)	2.0 (3.15)	2.0 (0.15)	<0.0001
Avanafil 200 mg	336	5.0 (2.73)	7.1 (3.08)	2.0 (3.16)	2.0 (0.15)	<0.0001
Sexual desire domain score						
Placebo	331	6.8 (1.98)	6.9 (2.09)	0.1 (1.97)	0.1 (0.09)	0.3272
Avanafil 50 mg	208	6.4 (2.03)	7.0 (1.93)	0.6 (1.81)	0.4 (0.12)	0.0026
Avanafil 100 mg	341	6.9 (2.04)	7.3 (1.92)	0.5 (1.89)	0.5 (0.09)	<0.0001
Avanafil 200 mg	336	6.8 (1.99)	7.4 (1.93)	0.6 (1.88)	0.6 (0.09)	<0.0001
Intercourse satisfaction domain score						
Placebo	331	6.6 (1.96)	7.6 (2.99)	1.0 (2.69)	0.9 (0.16)	<0.0001
Avanafil 50 mg	208	6.7 (1.91)	8.7 (3.11)	2.0 (2.89)	1.6 (0.21)	<0.0001
Avanafil 100 mg	341	6.6 (1.92)	9.3 (3.39)	2.7 (3.10)	2.6 (0.16)	<0.0001
Avanafil 200 mg	336	6.6 (1.94)	9.4 (3.31)	2.9 (3.01)	2.8 (0.16)	<0.0001
Overall satisfaction domain score						
Placebo	331	4.2 (2.03)	5.1 (2.54)	0.9 (2.33)	0.9 (0.13)	<0.0001
Avanafil 50 mg	208	4.1 (1.98)	5.8 (2.58)	1.7 (2.54)	1.3 (0.17)	<0.0001
Avanafil 100 mg	341	4.3 (1.99)	6.4 (2.68)	2.1 (2.68)	2.1 (0.13)	<0.0001
Avanafil 200 mg	336	4.3 (2.06)	6.6 (2.71)	2.3 (2.77)	2.3 (0.13)	<0.0001

1. n is the number of subjects with values at both time points.
2. Baseline value was obtained at Visit 2 (Week 0).
3. End of treatment value is the last available value during the treatment period.
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.

LS = least squares; SD = standard deviation; SE = standard error.

Reference ID: 2997438

Percentage of successful response to diary questions by time interval between dose administration and sexual attempt.

Table 3.3.5 Summary of Attempts in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse by Time Interval (SEP3) – Integrated Analysis of Studies TA-301 and TA-302 and TA-05 – ITT Population

Time Interval From Dose to Attempt Statistic	Placebo (N=337)	Avanafil 50 mg (N=210)	Avanafil 100 mg (N=343)	Avanafil 200 mg (N=338)	Total Avanafil (N=891)
≤15 minutes					
Number of attempts	123	85	200	112	397
Successful intercourse [1] n (%)	34 (27.6)	53 (62.4)	121 (60.5)	63 (56.3)	237 (59.7)
95% CI for treatment difference [2]	–	(21.7, 47.7)	(22.5, 43.3)	(16.5, 40.7)	
>15 minutes and ≤30 minutes					
Number of attempts	1915	1301	1987	2056	5344
Successful intercourse [1] n (%)	571 (29.8)	665 (51.1)	1077 (54.2)	1107 (53.8)	2849 (53.3)
95% CI for treatment difference [2]	–	(17.9, 24.7)	(21.4, 27.4)	(21.1, 27.0)	
≤30 minutes					
Number of attempts	2038	1386	2187	2168	5741
Successful intercourse [1] n (%)	605 (29.7)	718 (51.8)	1198 (54.8)	1170 (54.0)	3086 (53.8)
95% CI for treatment difference [2]	–	(18.8, 25.4)	(22.2, 28.0)	(21.4, 27.2)	
>30 minutes and ≤45 minutes					
Number of attempts	1529	1009	1804	1699	4512
Successful intercourse [1] n (%)	380 (24.9)	472 (46.8)	958 (53.1)	910 (53.6)	2340 (51.9)
95% CI for treatment difference [2]	–	(18.2, 25.7)	(25.1, 31.4)	(25.5, 31.9)	
>45 minutes and ≤60 minutes					
Number of attempts	967	610	1125	1027	2762
Successful intercourse [1] n (%)	287 (29.7)	251 (41.1)	586 (52.1)	546 (53.2)	1383 (50.1)
95% CI for treatment difference [2]	–	(6.6, 16.3)	(18.3, 26.5)	(19.3, 27.7)	
>60 minutes and ≤120 minutes					
Number of attempts	810	478	967	921	2366
Successful intercourse [1] n (%)	240 (29.6)	221 (46.2)	538 (55.6)	542 (58.8)	1301 (55.0)
95% CI for treatment difference [2]	–	(11.1, 22.1)	(21.6, 30.4)	(24.8, 33.7)	
>120 minutes					
Number of attempts	272	186	261	363	810
Successful intercourse [1] n (%)	61 (22.4)	98 (52.7)	134 (51.3)	230 (63.4)	462 (57.0)
95% CI for treatment difference [2]	–	(21.5, 39.0)	(21.1, 36.8)	(33.9, 47.9)	
>120 minutes and ≤240 minutes					
Number of attempts	185	133	200	246	579
Successful intercourse [1] n (%)	46 (24.9)	66 (49.6)	99 (49.5)	152 (61.8)	317 (54.7)
95% CI for treatment difference [2]	–	(14.2, 35.3)	(15.3, 34.0)	(28.2, 45.6)	
>240 minutes and ≤360 minutes					
Number of attempts	30	25	24	54	103
Successful intercourse [1] n (%)	6 (20.0)	15 (60.0)	10 (41.7)	31 (57.4)	56 (54.4)
95% CI for treatment difference [2]	–	(16.1, 64.0)	(-2.7, 46.0)	(17.9, 56.9)	
>360 minutes					
Number of attempts	57	28	37	63	128
Successful intercourse [1] n (%)	9 (15.8)	17 (60.7)	25 (67.6)	47 (74.6)	89 (69.5)
95% CI for treatment difference [2]	–	(24.5, 65.3)	(34.0, 69.6)	(44.5, 73.1)	

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.

Reference ID: 2997438

1. Successful intercourse defined as a YES response to the diary question "Did your erection last long enough for you to have successful intercourse?"
2. The 95% CI of the difference between avanafil and placebo for the proportion of successes is based on normal approximation.

CI = confidence interval

Table 3.3.6 Summary of Attempts Subjects Were Able to Achieve Successful Vaginal Penetration by Time Interval (SEP2) – Integrated Analysis of Studies TA-301 and TA-302 and TA-05 – ITT Population

Time Interval From Dose to Attempt Statistic	Placebo (N=337)	Avanafil 50 mg (N=210)	Avanafil 100 mg (N=343)	Avanafil 200 mg (N=338)	Total Avanafil (N=891)
≤15 minutes					
Number of attempts	123	85	200	112	397
Successful insertion [1] n (%)	62 (50.4)	65 (76.5)	149 (74.5)	87 (77.7)	301 (75.8)
95% CI for treatment difference [2]	–	(13.4, 38.7)	(13.4, 34.8)	(15.5, 39.0)	
>15 minutes and ≤30 minutes					
Number of attempts	1915	1301	1987	2056	5344
Successful insertion [1] n (%)	1075 (56.1)	990 (76.1)	1398 (70.4)	1584 (77.0)	3972 (74.3)
95% CI for treatment difference [2]	–	(16.8, 23.2)	(11.2, 17.2)	(18.0, 23.8)	
≤30 minutes					
Number of attempts	2038	1386	2187	2168	5741
Successful insertion [1] n (%)	1137 (55.8)	1055 (76.1)	1547 (70.7)	1671 (77.1)	4273 (74.4)
95% CI for treatment difference [2]	–	(17.2, 23.4)	(12.1, 17.8)	(18.5, 24.1)	
>30 minutes and ≤45 minutes					
Number of attempts	1529	1009	1804	1699	4512
Successful insertion [1] n (%)	759 (49.6)	709 (70.3)	1286 (71.3)	1283 (75.5)	3278 (72.7)
95% CI for treatment difference [2]	–	(16.9, 24.4)	(18.4, 24.9)	(22.6, 29.1)	
>45 minutes and ≤60 minutes					
Number of attempts	967	610	1125	1027	2762
Successful insertion [1] n (%)	509 (52.6)	403 (66.1)	782 (69.5)	750 (73.0)	1935 (70.1)
95% CI for treatment difference [2]	–	(8.5, 18.3)	(12.7, 21.0)	(16.2, 24.6)	
>60 minutes and ≤120 minutes					
Number of attempts	810	478	967	921	2366
Successful insertion [1] n (%)	415 (51.2)	314 (65.7)	707 (73.1)	693 (75.2)	1714 (72.4)
95% CI for treatment difference [2]	–	(9.0, 19.9)	(17.4, 26.3)	(19.6, 28.4)	
>120 minutes					
Number of attempts	272	186	261	363	810
Successful insertion [1] n (%)	129 (47.4)	133 (71.5)	188 (72.0)	285 (78.5)	606 (74.8)
95% CI for treatment difference [2]	–	(15.3, 32.9)	(16.6, 32.7)	(23.8, 38.4)	
>120 minutes and ≤240 minutes					
Number of attempts	185	133	200	246	579
Successful insertion [1] n (%)	100 (54.1)	92 (69.2)	140 (70.0)	186 (75.6)	418 (72.2)
95% CI for treatment difference [2]	–	(4.5, 25.8)	(6.4, 25.5)	(12.6, 30.5)	
>240 minutes and ≤360 minutes					
Number of attempts	30	25	24	54	103
Successful insertion [1] n (%)	15 (50.0)	20 (80.0)	17 (70.8)	41 (75.9)	78 (75.7)
95% CI for treatment difference [2]	–	(6.2, 53.8)	(-4.7, 46.3)	(4.7, 47.1)	
>360 minutes					
Number of attempts	57	28	37	63	128
Successful insertion [1] n (%)	14 (24.6)	21 (75.0)	31 (83.8)	58 (92.1)	110 (85.9)
95% CI for treatment difference [2]	–	(30.9, 70.0)	(42.9, 75.5)	(54.5, 80.5)	

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.

Reference ID: 2997438

1. Successful intercourse defined as a YES response to the diary question "Did your erection last long enough for you to have successful intercourse?"
2. The 95% CI of the difference between avanafil and placebo for the proportion of successes is based on normal approximation.

CI = confidence interval

3.3.2.2. Other supportive studies for efficacy

3.3.2.2.1. Phase 2 Studies TA-01 and TA-03:

3.3.2.2.1.1. Instrumental Monitoring Study TA-01:

- Statistically significant differences between avanafil treatment and placebo treatment for the objective efficacy assessments were generally noted most frequently during the early (20- to 40-minute) interval from dosing. During the 20- to 40-minute interval, the majority of values for duration of ≥60% rigidity with avanafil 50 mg, 100 mg, and 200 mg treatments were statistically superior to placebo.
- While all avanafil treatments showed some degree of efficacy during the middle (60- to 80-minute) interval, avanafil 200 mg continued to show efficacy during the late (100- to 120-minute) interval.

3.3.2.2.2. Phase 3 Study TA-314

Reviewer's Comment: The efficacy results from this study are not suitable to be counted into efficacy database to support the NDA because of the open label nature of the study.

3.3.2.3. Preliminary efficacy conclusions:

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.

1. Avanafil appears to have met all three co-primary endpoints at all three doses studied in the general ED population, and at both doses studied in diabetic men with ED. The two Phase 2 studies provide supportive evidence of benefit.
2. The efficacy results from the long term (6 month) study are not suitable to be counted into efficacy database to support the NDA because of the open label nature;
3. The results from the instrumental monitoring study suggest that peak response to avanafil occurs soon after dosing (e.g, in the interval from 20-40 minutes after dosing).

3.3.3. Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:

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a. **total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
b. **clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets**
c. **absence of a comprehensive analysis of safety data**
d. **absence of an analysis of data supporting the proposed dose and dose interval**

Answer: No. The following section of the filing memorandum reviews the total patient exposure and safety database for avanafil.

The safety of avanafil was studied in 23 clinical studies, including 17 Phase 1 trials, three Phase 2 trials, two pivotal Phase 3 trials, and one long term Phase 3 open label trial with predominantly patients rolled over from the earlier 2 pivotal Phase 3 studies.

- For the integrated analyses of double-blind studies TA-301, TA-302, and TA-05, the Safety Population was defined as all subjects who took at least one dose of study drug and had safety data available. Subjects were considered to have taken a dose of study drug if the number of tablets returned was less than the number of tablets dispensed.
- For study TA-314, the Safety Population was defined as all roll-over subjects who signed the TA-314 informed consent, irrespective of the receipt of study drug during the study itself. All enrolled subjects received study drug in the qualifying study and were thus included in the Safety Population for study TA-314.

3.3.3.1. Overall extent of exposure

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.

3.3.3.1.1. Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

Reference ID: 2997438

Table 3.3.7 Summary of Exposure – Double-Blind Studies (TA-05 and TA-301 and TA-302)

	Placebo (N=349)	Avanafil 50 mg (N=217)	Avanafil 100 mg (N=349)	Avanafil 200 mg (N=352)	Total (N=1267)
Duration of exposure (weeks) [1]					
n	349	217	349	352	1267
Mean (SD)	11.8 (2.69)	11.9 (2.56)	12.3 (3.44)	12.3 (2.68)	12.1 (2.90)
Median	12.1	12.3	12.3	12.3	12.3
Number (%) in specified exposure range					
<4 weeks	5 (1.4)	3 (1.4)	4 (1.1)	6 (1.7)	18 (1.4)
≥4 weeks and <8 weeks	24 (6.9)	14 (6.5)	13 (3.7)	11 (3.1)	62 (4.9)
≥8 weeks and <12 weeks	65 (18.6)	40 (18.4)	60 (17.2)	55 (15.6)	220 (17.4)
≥12 weeks	255 (73.1)	160 (73.7)	272 (77.9)	280 (79.5)	967 (76.3)
Number of doses taken					
n	337	210	343	338	1228
Mean (SD)	16.7 (7.47)	17.5 (8.51)	18.5 (8.64)	18.4 (7.80)	17.8 (8.11)
Median	16.0	17.0	17.0	18.0	17.0
Number of times study drug taken within 24 hrs of previous dose					
n	171	113	179	166	629
Mean (SD)	3.0 (3.46)	3.6 (4.06)	3.4 (4.43)	2.8 (3.11)	3.2 (3.79)
Number (%) who took 2 doses within 24 hours					
1 time to ≤5 times	148 (42.4)	92 (42.4)	155 (44.4)	146 (41.5)	541 (42.7)
5 times to ≤10 times	15 (4.3)	11 (5.1)	11 (3.2)	14 (4.0)	51 (4.0)
10 times to ≤20 times	7 (2.0)	9 (4.1)	11 (3.2)	6 (1.7)	33 (2.6)
20 times to ≤30 times	1 (0.3)	1 (0.5)	1 (0.3)	0 (0.0)	3 (0.2)
≥30 times	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Data from studies TA-05, TA-301, and TA-302 are included.

1. Duration of exposure is the number of weeks between the first drug dispense date and the study termination or completion date.

SD = standard deviation.

For the double-blind cohort, the mean duration of exposure was 12.1 weeks. For the majority of subjects in each treatment group, the duration of exposure was ≥ 12 weeks. Overall mean time on treatment, or the time between the first and last dose of study drug, was 10.6 weeks, and overall median time on treatment was 11.3 weeks. In general, exposure to treatment was similar across all treatment groups.

Overall, the mean total number of doses taken was 17.8: 16.7 doses for the placebo group, 17.5 doses for the avanafil 50 mg group, 18.5 doses for the avanafil 100 mg group, and 18.4 doses for the avanafil 200 mg group.

For the two Phase 3 studies alone, the total exposure is showing as Table 3.3.8.

Reference ID: 2997438

Table 3.3.7 Summary of Duration of Exposure – Phase 3 Double-Blind Cohort – (TA-301+TA-302)

	Placebo (N=291)	Avanafil 50 mg (N=160)	Avanafil 100 mg (N=288)	Avanafil 200 mg (N=293)	Total (N=1032)
Duration of exposure (weeks) [1]					
n	291	160	288	293	1032
Mean (SD)	12.1 (2.37)	12.0 (2.43)	12.1 (2.57)	12.4 (2.42)	12.2 (2.45)
Median	12.1	12.2	12.1	12.3	12.3
Number (%) in specified exposure range					
<4 weeks	3 (1.0)	2 (1.3)	4 (1.4)	2 (0.7)	11 (1.1)
≥4 weeks and <8 weeks	14 (4.8)	10 (6.3)	12 (4.2)	10 (3.4)	46 (4.5)
≥8 weeks and <12 weeks	57 (19.6)	31 (19.4)	49 (17.0)	51 (17.4)	188 (18.2)
≥12 weeks	217 (74.6)	117 (73.1)	223 (77.4)	230 (78.5)	787 (76.3)
Number of doses taken					
n	282	154	283	282	1001
Mean (SD)	17.5 (7.64)	18.6 (9.35)	19.3 (9.22)	19.2 (8.12)	18.6 (8.53)
Median	16.0	17.0	17.0	18.0	17.0
Number of times study drug taken within 24 hrs of previous dose					
n	158	88	151	152	549
Mean (SD)	3.1 (3.56)	4.1 (4.41)	3.7 (4.74)	2.9 (3.21)	3.4 (3.99)
Number (%) who took 2 doses within 24 hours					
1 time to ≤5 times	135 (46.4)	67 (41.9)	127 (44.1)	132 (45.1)	461 (44.7)
5 times to ≤10 times	15 (5.2)	11 (6.9)	11 (3.8)	14 (4.8)	51 (4.9)
10 times to ≤20 times	7 (2.4)	9 (5.6)	11 (3.8)	6 (2.0)	33 (3.2)
20 times to ≤30 times	1 (0.3)	1 (0.6)	1 (0.3)	0 (0.0)	3 (0.3)
≥30 times	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Data from studies TA-301 and TA-302 are included.

1. Duration of exposure is the number of weeks between the first drug dispense date and the study termination or completion date.

SD = standard deviation.

Overall, with two Phase 3 studies, the mean total number of doses taken was 18.6: 17.5 doses for the placebo group, 18.6 doses for the avanafil 50 mg group, 19.3 doses for the avanafil 100 mg group, and 19.2 doses for the avanafil 200 mg group.

3.3.3.1.2. Individual Phase 3, Open-label, Long term Study TA-314

Reference ID: 2997438

Table 3.3.8 Summary of Duration of Exposure by TA-314 Titration Dose – TA-314 Safety Population

	TA-314 100 mg only (N=171)	TA-314 100 & 200 mg (N=536)	TA-314 Other (N=5)	Total (N=712)
Duration of exposure (weeks) [1]				
n	171	536	5	712
Mean (SD)	28.6 (17.19)	37.4 (14.01)	34.4 (22.04)	35.3 (15.33)
Median	24.3	39.0	40.7	38.1
Number (%) in specified exposure range				
<3 months (12 weeks)	27 (15.8)	27 (5.0)	1 (20.0)	55 (7.7)
≥3 months (12 weeks) and <6 months (26 weeks)	62 (36.3)	101 (18.8)	1 (20.0)	164 (23.0)
≥6 months (26 weeks) and <9 months (38 weeks)	22 (12.9)	94 (17.5)	0 (0.0)	116 (16.3)
≥9 months (38 weeks) and <12 months (52 weeks)	28 (16.4)	195 (36.4)	1 (20.0)	224 (31.5)
≥12 months (52 weeks)	32 (18.7)	119 (22.2)	2 (40.0)	153 (21.5)

1. Duration of exposure is the number of weeks between the first drug dispense date and the study termination or completion date. The summary includes treatment in the qualifying period. For subjects who received placebo in the qualifying study, the first drug dispense date is the first drug dispense date in TA-314.

SD = standard deviation.

For study TA-314, the mean duration of exposure to avanafil was 35.3 weeks, and the median duration of exposure was 38.1 weeks. 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). Mean and median duration of exposure were longer for subjects who received avanafil 100 mg and 200 mg than for subjects who received avanafil 100 mg only.

In total, 536 (75.3%) subjects were dispensed avanafil 100 mg and 200 mg during study TA-314; 171 (24.0%) subjects were dispensed avanafil 100 mg only; 3 (0.4%) subjects were dispensed avanafil 100 mg and 50 mg; 1 (0.1%) subject was dispensed all three doses of avanafil; and 1 (0.1%) subject was not dispensed study drug during this study.

Overall, the mean total number of doses taken was 68.6: 47.5 doses for subjects who received avanafil 100 mg only during this study; 75.4 doses for subjects who received avanafil 100 mg and 200 mg during this study; and 58.2 doses for other subjects (i.e., subjects who received avanafil 100 mg and 50 mg and subjects who received all three doses of avanafil).

3.3.3.1.3. Phase 1 Studies

In total, 621 subjects were exposed to avanafil: 83 subjects received a dose of avanafil ≤ 50 mg, 73 subjects received avanafil 100 mg, 462 subjects received avanafil 200 mg, and 80 subjects received a dose of avanafil >200 mg.

Reference ID: 2997438

Table 3.3.9 Number of Subjects Exposed to Study Drug During the Phase 1 Program

	Placebo	Avanafil ≤50 mg	Avanafil 100 mg	Avanafil 200 mg	Avanafil >200 mg	Total Avanafil
HP-01	16	18	7	6	18	49
TA-02	12	12	12	12	–	36
TA-04	97	–	–	102	–	102
TA-07	–	–	–	15	–	15
TA-010	–	–	–	–	6	6
TA-011	–	29	–	15	–	44
TA-012	–	–	–	24	–	24
TA-013	–	–	–	24	–	24
TA-014	–	–	–	32	–	32
TA-015	15	–	–	14	–	14
TA-016	24	–	–	23	–	23
TA-017	48	–	–	48	–	48
TA-018	–	–	–	59	–	59
TA-019	47	–	–	48	–	48
TA-020	–	24	–	23	–	24
TA-021	17	–	–	17	–	17
TA-140	54	–	54	–	56	56
Total	330	83	73	462	80	621

Sources: HP-01 CSR, TA-02 CSR, TA-04 CSR, TA-07 CSR, TA-010 CSR, TA-011 CSR, TA-012 CSR, TA-013 CSR, TA-014 CSR, TA-015 CSR, TA-016 CSR, TA-017 CSR, TA-018 CSR, TA-019 CSR, TA-020 CSR, TA-021 CSR, TA-140 CSR

3.3.3.1.4. Exposure during the Clinical Developent Program

Reference ID: 2997438

Table3.3.10 Summary of Avanafil Exposure During the Clinical Development Program

		Total Exposure	Avanafil Exposure					Placebo
			Total	≤ 50 mg [1]	100 mg	200 mg	300-800 mg [2]	
Phase 1 Studies								
Total	17 Phase 1 Studies	**657**	**621**	**83**	**73**	**462**	**80**	**330**
Phase 2 Studies								
TA-01	Visual stimulation (cross-over study)	83	82	27	27	28	NA	82
TA-03	Home administration (crossover)	49	49	NA	NA	49	NA	NA
TA-05	Safety and efficacy	284	229	56	60	56	57	55
Total		**416**	**360**	**83**	**87**	**133**	**57**	**137**
Phase 3 Studies								
TA-301	Generalized ED	644	483	160	161	162	NA	161
TA-302	Subjects with diabetes	388	258	NA	127	131	NA	130
TA-314	Open-label, long-term roll over from TA-301 & TA-302		201 [3]	–	–	–	NA	NA
Total		**1032**	**942**	**160**	**288**	**293**	**0**	**291**
Program TOTAL		**2105**	**1923**	**326**	**448**	**888**	**137**	**758**

Reviewer's Comment: This reviewer believes that for NDA 202,276, the total population exposure requirement is sufficient including the long term exposure.

3.3.3.2. Safety and Tolerability

3.3.3.2.1. Adverse Events

3.3.3.2.1.1 Common Adverse Events

<u>An Overview</u>

Reference ID: 2997438

Table 3.3.3.11 Overview of Adverse Events – Double-Blind Cohort (TA-05+TA-301+TA-302)

	Placebo (N=349) n (%)	Avanafil				Total (N=1267) n (%)
		50 mg (N=217 n (%)	100 mg (N=349) n (%)	200 mg (N=352) n (%)	Total (N=918) n (%)	
Subjects with TEAEs						
Any TEAE	89 (25.5)	68 (31.3)	140 (40.1)	128 (36.4)	336 (36.6)	425 (33.5)
Any drug-related TEAE	15 (4.3)	23 (10.6)	50 (14.3)	61 (17.3)	134 (14.6)	149 (11.8)
Maximum severity of TEAEs						
Mild	51 (14.6)	41 (18.9)	77 (22.1)	75 (21.3)	193 (21.0)	244 (19.3)
Moderate	34 (9.7)	25 (11.5)	54 (15.5)	49 (13.9)	128 (13.9)	162 (12.8)
Severe	4 (1.1)	2 (0.9)	9 (2.6)	4 (1.1)	15 (1.6)	19 (1.5)
Maximum severity of drug-related TEAEs						
Mild	12 (3.4)	17 (7.8)	37 (10.6)	45 (12.8)	99 (10.8)	111 (8.8)
Moderate	3 (0.9)	6 (2.8)	11 (3.2)	16 (4.5)	33 (3.6)	36 (2.8)
Severe	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)	2 (0.2)
Deaths	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Subjects with SAEs						
Any SAE	3 (0.9)	2 (0.9)	6 (1.7)	7 (2.0)	15 (1.6)	18 (1.4)
Any treatment-emergent SAE	2 (0.6)	2 (0.9)	6 (1.7)	7 (2.0)	15 (1.6)	17 (1.3)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study drug discontinuations due to adverse events						
Any adverse event	5 (1.4)	3 (1.4)	8 (2.3)	6 (1.7)	17 (1.9)	22 (1.7)
Any TEAE	5 (1.4)	3 (1.4)	7 (2.0)	6 (1.7)	16 (1.7)	21 (1.7)
Any drug-related TEAE	0 (0.0)	1 (0.5)	2 (0.6)	3 (0.9)	6 (0.7)	6 (0.5)
Any SAE	1 (0.3)	1 (0.5)	3 (0.9)	2 (0.6)	6 (0.7)	7 (0.6)

An overview of adverse events for the double-blind cohort (TA-05+TA-301+TA-302):

- In total, 425 (33.5%) subjects reported at least one TEAE during the study. The incidence of TEAEs was higher in the avanafil groups (31.3% to 40.1%) than in the placebo group (25.5%).
- In total, 149 (11.8%) subjects had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (10.6% to 17.3%) than in the placebo group (4.3%).
- Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups.
- One subject (in the avanafil 100 mg group) died during study TA-301 from a self-inflicted gunshot wound; the event was considered by the investigator to be not related to study drug. In total, 18 (1.4%) subjects had an SAE. The incidence of SAEs was similar across all treatment groups. No subject had an SAE that was considered by the investigators to be related to study drug.
- In total, 22 (1.7%) subjects discontinued study drug due to an adverse event. The percentage of subjects who discontinued study drug due to an adverse event was

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similar across all treatment groups. In total, 6 (0.5%) subjects discontinued study drug due to a drug-related TEAE.

3.3.3.2.1.1.1. Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

Table 3.3.3.12 Summary of Treatment-Emergent Adverse Events (TEAEs) (≥1% of Subjects in Any Treatment Group) by System Organ Class and PT – Double-Blind Cohort (TA-05+TA-301+TA-302)

System Organ Class Preferred Term (PT)	Placebo (N=349) n (%)	Avanafil				Total (N=1267) n (%)
		50 mg (N=217) n (%)	100 mg (N=349) n (%)	200 mg (N=352) n (%)	Total (N=918) n (%)	
Infections and infestations	25 (7.2)	16 (7.4)	39 (11.2)	36 (10.2)	91 (9.9)	116 (9.2)
Nasopharyngitis	10 (2.9)	2 (0.9)	9 (2.6)	12 (3.4)	23 (2.5)	33 (2.6)
Upper respiratory tract infection	1 (0.3)	4 (1.8)	4 (1.1)	5 (1.4)	13 (1.4)	14 (1.1)
Bronchitis	1 (0.3)	3 (1.4)	1 (0.3)	4 (1.1)	8 (0.9)	9 (0.7)
Influenza	0 (0.0)	1 (0.5)	6 (1.7)	1 (0.3)	8 (0.9)	8 (0.6)
Sinusitis	4 (1.1)	0 (0.0)	5 (1.4)	3 (0.9)	8 (0.9)	12 (0.9)
Nervous system disorders	12 (3.4)	15 (6.9)	31 (8.9)	41 (11.6)	87 (9.5)	99 (7.8)
Headache	6 (1.7)	11 (5.1)	24 (6.9)	37 (10.5)	72 (7.8)	78 (6.2)
Musculoskeletal & connective tissue disorders	15 (4.3)	15 (6.9)	21 (6.0)	13 (3.7)	49 (5.3)	64 (5.1)
Back pain	4 (1.1)	7 (3.2)	7 (2.0)	4 (1.1)	18 (2.0)	22 (1.7)
Respiratory, thoracic, and mediastinal disorders	7 (2.0)	7 (3.2)	18 (5.2)	20 (5.7)	45 (4.9)	52 (4.1)
Nasal congestion	4 (1.1)	4 (1.8)	10 (2.9)	7 (2.0)	21 (2.3)	25 (2.0)
Sinus congestion	1 (0.3)	1 (0.5)	3 (0.9)	6 (1.7)	10 (1.1)	11 (0.9)
Vascular disorders	2 (0.6)	8 (3.7)	22 (6.3)	14 (4.0)	44 (4.8)	46 (3.6)
Flushing	0 (0.0)	7 (3.2)	15 (4.3)	14 (4.0)	36 (3.9)	36 (2.8)
Hypertension	1 (0.3)	1 (0.5)	5 (1.4)	0 (0.0)	6 (0.7)	7 (0.6)
Gastrointestinal disorders	9 (2.6)	9 (4.1)	15 (4.3)	19 (5.4)	43 (4.7)	52 (4.1)
Dyspepsia	0 (0.0)	1 (0.5)	2 (0.6)	5 (1.4)	8 (0.9)	8 (0.6)
Nausea	0 (0.0)	0 (0.0)	2 (0.6)	4 (1.1)	6 (0.7)	6 (0.5)
Constipation	1 (0.3)	3 (1.4)	0 (0.0)	0 (0.0)	3 (0.3)	4 (0.3)
Skin & subcutaneous tissue disorders	5 (1.4)	5 (2.3)	3 (0.9)	5 (1.4)	13 (1.4)	18 (1.4)
Rash	1 (0.3)	3 (1.4)	0 (0.0)	1 (0.3)	4 (0.4)	5 (0.4)

Treatment-emergent adverse events were defined as adverse events occurring after the first dose of study drug or after the first drug dispense date (if the first dose date was missing) and up to 28 days after the last dose of study drug.

In total, 425 (33.5%) subjects in the double-blind cohort reported at least one TEAE. The incidence of TEAEs was higher in the avanafil groups (31.3% to 40.1%) than in the placebo group (25.5%). The TEAEs that occurred more frequently in the avanafil groups than in the placebo group were upper respiratory tract infection, influenza, headache, nasal congestion, sinus congestion, flushing, and dyspepsia.

In total, 149 (11.8%) subjects in the double-blind cohort had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (10.6% to 17.3%) than in the placebo group (4.3%). The

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incidences of the following drug-related TEAEs were higher in the avanafil groups than in the placebo group:

- Headache (placebo, 1.1%; avanafil 50 mg, 4.6%; avanafil 100 mg, 5.7%; and avanafil 200 mg, 8.8%);
- Flushing (placebo, 0.0%; avanafil 50 mg, 2.8%; avanafil 100 mg, 4.3%; and avanafil 200 mg, 4.0%); and
- Nasal congestion (placebo, 0.9%; avanafil 50 mg, 1.8%; avanafil 100 mg, 2.0%; and avanafil 200 mg, 1.7%).

Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups. In total, 19 (1.5%) subjects in the double-blind cohort had a severe TEAE: 4 (1.1%) subjects in the placebo group, 2 (0.9%) subjects in the avanafil 50 mg group, 9 (2.6%) subjects in the avanafil 100 mg group, and 4 (1.1%) subjects in the avanafil 200 mg group. The most frequently reported severe TEAE was headache (2 subjects); no other specific severe TEAEs were reported by more than 1 subject.

3.3.3.2.1.1.2. Individual Phase 3, Open-Label, Long-Term Study TA-314

By definition, the Safety Population included all subjects who signed informed consent. However, for the summary of adverse events by onset treatment in study TA-314, only subjects who were actually dispensed study drug were considered for analysis. One subject, Subject #215-054, was not dispensed study drug and is excluded from these analyses. This subject did not experience any adverse events following informed consent for study TA-314.

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Table 3.3.3.13 Summary of TEAEts (≥1% of Subjects Overall) by Treatment at Onset, System Organ Class, and PT – TA-314 – Safety Population

System Organ Class Preferred Term (PT)	TA 314 Avanafil			
	50 mg (N=4) n (%)	100 mg (N=711) n (%)	200 mg (N=514) n (%)	Total (N=711) n (%)
Infections and infestations	0 (0.0)	27 (3.8)	66 (12.8)	87 (12.2)
Nasopharyngitis	0 (0.0)	5 (0.7)	20 (3.9)	24 (3.4)
Upper respiratory tract infection	0 (0.0)	5 (0.7)	7 (1.4)	11 (1.5)
Influenza	0 (0.0)	3 (0.4)	8 (1.6)	11 (1.5)
Sinusitis	0 (0.0)	5 (0.7)	6 (1.2)	10 (1.4)
Bronchitis	0 (0.0)	0 (0.0)	8 (1.6)	8 (1.1)
Nervous system disorders	2 (50.0)	26 (3.7)	36 (7.0)	56 (7.9)
Headache	1 (25.0)	19 (2.7)	27 (5.3)	40 (5.6)
Dizziness	1 (25.0)	6 (0.8)	3 (0.6)	9 (1.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	20 (2.8)	24 (4.7)	39 (5.5)
Back pain	0 (0.0)	4 (0.6)	8 (1.6)	11 (1.5)
Arthralgia	0 (0.0)	2 (0.3)	5 (1.0)	7 (1.0)
Vascular disorders	0 (0.0)	18 (2.5)	22 (4.3)	38 (5.3)
Flushing	0 (0.0)	10 (1.4)	17 (3.3)	25 (3.5)
Hypertension	0 (0.0)	4 (0.6)	5 (1.0)	9 (1.3)
Gastrointestinal disorders	0 (0.0)	12 (1.7)	26 (5.1)	36 (5.1)
Diarrhea	0 (0.0)	3 (0.4)	6 (1.2)	9 (1.3)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	14 (2.0)	19 (3.7)	30 (4.2)
Nasal congestion	0 (0.0)	8 (1.1)	10 (1.9)	15 (2.1)

All AEs reported in TA-314 are considered treatment-emergent. AEs were reported from the date of informed consent until 28 days after the last dose of study drug or until the subject was discontinued from the study, whichever was later. Only AEs occurring on or after the first study drug dispensation date in TA-314 are included. Note that subjects may be included under more than one treatment.

In total, 275 (38.7%) subjects had an AE in study TA-314; all AEs reported in this study were considered treatment emergent. The most frequently reported TEAEs (PT) were headache (5.6%), flushing (3.5%), nasopharyngitis (3.4%), nasal congestion (2.1%), upper respiratory tract infection (1.5%), influenza (1.5%), and back pain (1.5%). All other TEAEs were reported by 10 (1.4%) or fewer subjects. The incidence of these events was higher with avanafil 200 mg treatment than with avanafil 100 mg treatment.

It should be noted that TA-314 was an open-label study in which subjects had the option to titrate their dose up or down. Accordingly, study TA-314 provides reliable assessments of adverse event rates over the range of doses included in the study, but was not designed to provide robust comparisons between specific avanafil doses. In total, 79 (11.1%) subjects had a drug-related TEAE in study TA-314. The most frequently reported drug-related TEAEs were headache (4.4%), flushing (3.4%), nasal congestion (1.5%), dizziness (0.7%), dyspepsia (0.6%), and nausea (0.4%). All other drug-related TEAEs were reported by 2 (0.3%) or fewer subjects.

Most of the TEAEs were mild or moderate in severity. Twenty-one (3.0%) subjects had a severe TEAE. Two (0.3%) subjects had 1 or more severe drug-related TEAEs (dyspepsia,

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headache, and diarrhea for Subject #123-030 while taking avanafil 100 mg and flushing for Subject #127-029 while taking avanafil 200 mg). The severe drug-related TEAEs of dyspepsia, headache, and diarrhea for Subject # 123-030 resulted in discontinuation of study drug. The severe drug-related TEAE of flushing for Subject # 127-029 did not result in a change in study drug. The TEAEs for these 2 subjects resolved.

Twenty (2.8%) subjects discontinued study drug due to a TEAE. For 10 (1.4%) subjects, the AE that led to discontinuation was considered by the investigator to be related to study drug.

In addition, the most common AEs with avanafil treatment from other studies

- Phase 2 study TA-01 - flushing;
- Phase 2 study TA-03 – headache;
- Phase 1 studies: headache and nausea.

3.3.3.2.1.2. Deaths and non-fatal serious adverse events (SAE's)

3.3.3.2.1.2.1. Deaths

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

3.3.3.2.1.2.2 Other Serious Adverse Events (SAE's)

3.3.3.2.1.2.2.1 Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

The incidence of SAE's in the double-blind cohort was: 3 (0.9%) subjects in the placebo group, 2 (0.9%) subjects in the avanafil 50 mg group, 6 (1.7%) subjects in the avanafil 100 mg group, and 7 (2.0%) subjects in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group.

In study TA-05, 1 subject in the avanafil 300 mg group had 2 SAE's (abdominal injury and head injury) due to a motor vehicle accident. The incidence of SAEs in the Phase 3 double-blind cohort was low: 3 (1.0%) subjects in the placebo group, 1 (0.6%) subject in the avanafil 50 mg group, 6 (2.1%) subjects in the avanafil 100 mg group, and 7 (2.4%) subjects in the avanafil 200 mg group. No specific SAE was reported by more than 1 subject in any treatment group.

3.3.3.2.1.2.2.2.Individual Phase 3, Open-label, Long-Term Study TA-314

Eleven subjects had an SAE during study TA-314. No subject had an SAE that was considered by the investigators to be related to study drug. The SAE resulted in discontinuation of study drug for 6 subjects: 1 subject with acute psychosis, 1 subject with femoral artery occlusion, 1 subject with coronary artery disease, 1 subject with

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aortic valve stenosis, 1 subject with cervical vertebral fracture, and 1 subject with congestive cardiac failure.

3.3.3.2.1.3. Adverse Events Leading to Discontinuation

3.3.3.2.1.3.1. Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

In total, 22 (1.7%) subjects in the double-blind cohort had an AE that resulted in study drug discontinuation: 5 (1.4%) subjects in the placebo group, 3 (1.4%) subjects in the avanafil 50 mg group, 8 (2.3%) subjects in the avanafil 100 mg group, and 6 (1.7%) subjects in the avanafil 200 mg group. In total, 6 (0.5%) subjects discontinued study drug due to a drug-related TEAE. An adverse event of headache led to discontinuation of study drug for 5 subjects: 2 (0.6%) subjects in the avanafil 100 mg group and 3 (0.9%) subjects in the avanafil 200 mg group. No other specific adverse event led to study drug discontinuation for more than 1 subject in any treatment group.

3.3.3.2.1.3.2. Individual Phase 3, Open-label, Long-term Study TA-314

In study TA-314, 20 subjects had an AE that resulted in study drug discontinuation. For 10 subjects, the AEs that led to discontinuation were considered by the investigators to be related to study drug: 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 pruritus and eye swelling.

The subject with pruritus and eye swelling (Subject # 238-010) had previously completed the TA-302 study during which he received avanafil 100 mg; the subject did not have any AEs during study TA-302. The events of pruritus and eye swelling were reported as itching in the neck area and swelling around the eyes. The subject recovered from the event after 6 days.

3.3.3.2.1.3.3 Other Phase 2 and Phase 1 Studies

In Phase 2 Study TA-03, the partner of 1 subject became pregnant during the study and it was noted that the subject discontinued study drug due to this adverse event; however, “non-compliance with study requirements” was recorded as the reason the subject was discontinued from the study. No subject discontinued study drug due to an adverse event.

One subject discontinued from the study due to an AE during the Phase 1 program. In study TA-02, Subject #16 discontinued due to an SAE of pharyngolaryngeal pain; the investigator considered the event to be unlikely related to study drug. No other subjects discontinued study drug due to an adverse event during the Phase 1 program.

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3.3.3.2.1.4 Analysis of AEs by Organ System and Syndrome

Based on the known effects of PDE5 inhibitors as reported in the product labels or literature, adverse events were specified at the preferred term level, categorized by class, and summarized as targeted medical events (TMEs).

3.3.3.2.1.4.1 Integrated Double-Blind Cohort (TA-05, TA-301, and TA-302)

Table 3.3.14 Summary of TME by Class and PT – Double-Blind Cohort (TA-05+TA 301+TA-302)

Targeted Medical Events (TME) Class and Preferred Term (PT)	Placebo (N=349) n (%)	Avanafil				Total (N=1267) n (%)
		50 mg (N=217) n (%)	100 mg (N=349) n (%)	200 mg (N=352) n (%)	Total (N=918) n (%)	
Upper respiratory (UR) events	23 (6.6)	17 (7.8)	44 (12.6)	43 (12.2)	104 (11.3)	127 (10.0)
Nasopharyngitis	10 (2.9)	2 (0.9)	9 (2.6)	12 (3.4)	23 (2.5)	33 (2.6)
Nasal congestion	4 (1.1)	4 (1.8)	10 (2.9)	7 (2.0)	21 (2.3)	25 (2.0)
UR tract infection	1 (0.3)	4 (1.8)	4 (1.1)	5 (1.4)	13 (1.4)	14 (1.1)
Sinusitis	4 (1.1)	0 (0.0)	5 (1.4)	3 (0.9)	8 (0.9)	12 (0.9)
Sinus congestion	1 (0.3)	1 (0.5)	3 (0.9)	6 (1.7)	10 (1.1)	11 (0.9)
Bronchitis	1 (0.3)	3 (1.4)	1 (0.3)	4 (1.1)	8 (0.9)	9 (0.7)
Influenza	0 (0.0)	1 (0.5)	6 (1.7)	1 (0.3)	8 (0.9)	8 (0.6)
Cough	1 (0.3)	0 (0.0)	2 (0.6)	1 (0.3)	3 (0.3)	4 (0.3)
Lower U tract infection	1 (0.3)	1 (0.5)	0 (0.0)	2 (0.6)	3 (0.3)	4 (0.3)
Sinus headache	1 (0.3)	0 (0.0)	2 (0.6)	1 (0.3)	3 (0.3)	4 (0.3)
Pharyngitis streptococcal	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)	3 (0.3)	3 (0.2)
Pneumonia	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.6)	3 (0.3)	3 (0.2)
Acute sinusitis	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	2 (0.2)	2 (0.2)
UR tract congestion	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.2)	2 (0.2)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
RT infection viral	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Rhinitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Rhinorrhea	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Viral pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	1 (0.1)
Postnasal drip	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hemodynamic changes	0 (0.0)	2 (0.9)	3 (0.9)	1 (0.3)	6 (0.7)	6 (0.5)
Dizziness	0 (0.0)	2 (0.9)	2 (0.6)	1 (0.3)	5 (0.5)	5 (0.4)
Syncope	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Major cardiac events	1 (0.3)	1 (0.5)	0 (0.0)	1 (0.3)	2 (0.2)	3 (0.2)
Transient ischemic attack	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	2 (0.2)
AMI	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Special sensory effects (hearing)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)	2 (0.2)
Tinnitus	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Vertigo positional	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)
Special sensory effects (vision)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)	2 (0.2)
Vision blurred	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	2 (0.2)	2 (0.2)
Other (priapism)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The incidence of TEAEs categorized as upper respiratory events was higher in the avanafil 100 mg and avanafil 200 mg groups than in the avanafil 50 mg and placebo

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groups. The incidence of TEAEs categorized as upper respiratory events was 6.6% in the placebo group, 7.8% in the avanafil 50 mg group, 12.6% in the avanafil 100 mg group, and 12.2% in the avanafil 200 mg group. The incidence of TEAEs categorized as hemodynamic changes was 0.9% in the avanafil 50 mg group, 0.9% in the avanafil 100 mg group, and 0.3% in the avanafil 200 mg group; no subject in the placebo group had a TEAE categorized as a hemodynamic change. No subject in the double-blind cohort had a TEAE of hypotension. The incidences of TEAEs categorized as major cardiac events and special sensory effects were low and similar across treatments. No subject in the double-blind cohort had a TEAE categorized as a priapism targeted medical event.

3.3.3.2.1.4.2 Individual Phase 3, Open-Label, Long-Term Study TA-314

Table 3.3.15 Summary of TMEs by Treatment at Onset, Class, and PT – TA-314 – Safety Population

TME Class Preferred Term (PT)	TA-314 Avanafil			
	50 mg (N=4) n (%)	100 mg (N=711) n (%)	200 mg (N=514) n (%)	Total (N=711) n (%)
Upper respiratory (UR) events	0 (0.0)	29 (4.1)	59 (11.5)	80 (11.3)
Nasopharyngitis	0 (0.0)	5 (0.7)	20 (3.9)	24 (3.4)
Nasal congestion	0 (0.0)	8 (1.1)	10 (1.9)	15 (2.1)
Influenza	0 (0.0)	3 (0.4)	8 (1.6)	11 (1.5)
UR tract infection	0 (0.0)	5 (0.7)	7 (1.4)	11 (1.5)
Sinusitis	0 (0.0)	5 (0.7)	6 (1.2)	10 (1.4)
Bronchitis	0 (0.0)	0 (0.0)	8 (1.6)	8 (1.1)
Cough	0 (0.0)	1 (0.1)	2 (0.4)	3 (0.4)
Epistaxis	0 (0.0)	1 (0.1)	2 (0.4)	3 (0.4)
Sinus congestion	0 (0.0)	1 (0.1)	1 (0.2)	2 (0.3)
Lower RT infection	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Pneumonia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Rhinitis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Snoring	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Viral UR tract infection	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Hemodynamic changes	1 (25.0)	6 (0.8)	4 (0.8)	10 (1.4)
Dizziness	1 (25.0)	6 (0.8)	3 (0.6)	9 (1.3)
Syncope vasovagal	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Special sensory effects (hearing)	0 (0.0)	2 (0.3)	2 (0.4)	4 (0.6)
Vertigo	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)
Motion sickness	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Tinnitus	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Special sensory effects (vision)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.4)
Photophobia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Vision blurred	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Cyanopsia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Other (priapism)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.4)
Erection increased	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.3)
Spontaneous penile erection	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Major cardiac events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Eighty (11.3%) subjects had 1 or more TEAEs categorized as upper respiratory (UR) events. The incidence of TEAEs in the UR events class was higher with avanafil 200 mg

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(11.5%) than with avanafil 100 mg (4.1%). No differences in the incidence of TEAEs categorized as hemodynamic changes were observed with avanafil 100 mg treatment compared to avanafil 200 mg treatment. Three (0.4%) subjects had a TEAE categorized as a priapism TME while taking avanafil 200 mg (2 subjects with erection increased and 1 subject with spontaneous penile erection). One of the TEAEs of erection increased was mild in severity, and the other was moderate in severity; the TEAE of spontaneous penile erection was mild in severity. None of these events met the clinical definition of priapism (i.e., an erection lasting longer than 4 hours). No subject had a TEAE of hypotension in study TA-314. No subject had a TEAE categorized as a major cardiac event in study TA-314.

3.3.3.2.2. Clinical Laboratory Evaluation

3.3.3.2.2.1. Integrated Double-blind Cohort (TA-05+TA-301+TA-301)

Table 3.3.16 Number (%) of Subjects Who Had Marked Laboratory Abnormalities During the Treatment Period – Double-Blind Cohort (TA-05+TA-301+TA-302)

Laboratory Parameter Category	Placebo n/N' (%)	Avanafil			Total n/N' (%)
		50 mg n/N' (%)	100 mg n/N' (%)	200 mg n/N' (%)	
ALT					
>2 × ULN	3/313 (1.0)	2/196 (1.0)	1/320 (0.3)	2/321 (0.6)	8/1150 (0.7)
>3 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	1/321 (0.3)	1/1150 (0.1)
AST					
>2 × ULN	3/313 (1.0)	0/196 (0.0)	2/320 (0.6)	2/321 (0.6)	7/1150 (0.6)
>3 × ULN	0/313 (0.0)	0/196 (0.0)	1/320 (0.3)	2/321 (0.6)	3/1150 (0.3)
Total bilirubin					
>1.5 × ULN	3/313 (1.0)	1/196 (0.5)	2/320 (0.6)	5/321 (1.6)	11/1150 (1.0)
>2 × ULN	1/313 (0.3)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	1/1150 (0.1)
Alkaline phosphatase					
>1.5 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	1/321 (0.3)	1/1150 (0.1)
ALT or AST with total bilirubin					
ALT or AST >3 × ULN & total bilirubin >1.5 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	0/1150 (0.0)
ALT or AST >3 × ULN & total bilirubin >2 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	0/1150 (0.0)
White blood cell count					
Low	26/312 (8.3)	11/197 (5.6)	21/319 (6.6)	24/317 (7.6)	82/1145 (7.2)
High	5/312 (1.6)	2/197 (1.0)	2/319 (0.6)	5/317 (1.6)	14/1145 (1.2)
Serum creatinine					
Low	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	0/1150 (0.0)
High	26/313 (8.3)	13/196 (6.6)	28/320 (8.8)	31/321 (9.7)	98/1150 (8.5)
Hematocrit					
Low	31/310 (10.0)	10/197 (5.1)	30/318 (9.4)	30/315 (9.5)	101/1140 (8.9)
High	3/310 (1.0)	1/197 (0.5)	4/318 (1.3)	5/315 (1.6)	13/1140 (1.1)
Hemoglobin					
Low	19/311 (6.1)	10/197 (5.1)	21/319 (6.6)	21/317 (6.6)	71/1144 (6.2)
High	5/311 (1.6)	0/197 (0.0)	3/319 (0.9)	2/317 (0.6)	10/1144 (0.9)

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The numbers and percentages of subjects with abnormal laboratory measurements were low, and no meaningful differences among the treatment groups were observed.

3.3.3.2.2.2. Individual Phase 3, Open-Label, Long-Term Study TA-314

No meaningful changes in safety laboratory parameters were noted with long-term avanafil treatment during study TA-314.

3.3.3.2.3. Vital Signs

3.3.3.2.3.1 Avanafil administration alone

Overall, the incidences of abnormal increases or abnormal decreases in SBP and DBP were low in the integrated double-blind cohort and in study TA-314. In the double-blind cohort, no meaningful differences in the incidences of abnormal increases or abnormal decreases in SBP and DBP were observed between treatment groups.

In the pivotal avanafil studies, BP was not necessarily measured in the proximity of study drug administration. Therefore, more relevant vital sign results were obtained from the Phase 1 studies that were specifically designed to evaluate the effects of avanafil treatment on these parameters and include vital sign assessments at appropriate time intervals after dosing. In earlier studies evaluating single and repeat doses of up to 800 mg of avanafil, postural hypotension and vasovagal responses have been observed at high avanafil doses, although there has been no consistent or dose-related effect of avanafil on sitting or standing blood pressure or heart rate. Following a single oral dose of avanafil 200 mg to healthy male subjects in Study TA-02, avanafil produced no significant difference compared to placebo in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) (difference in the mean maximal decrease of 0.6 mmHg and 2.4 mmHg, respectively) or pulse rate (difference in the mean maximal increase of 3.7 bpm).

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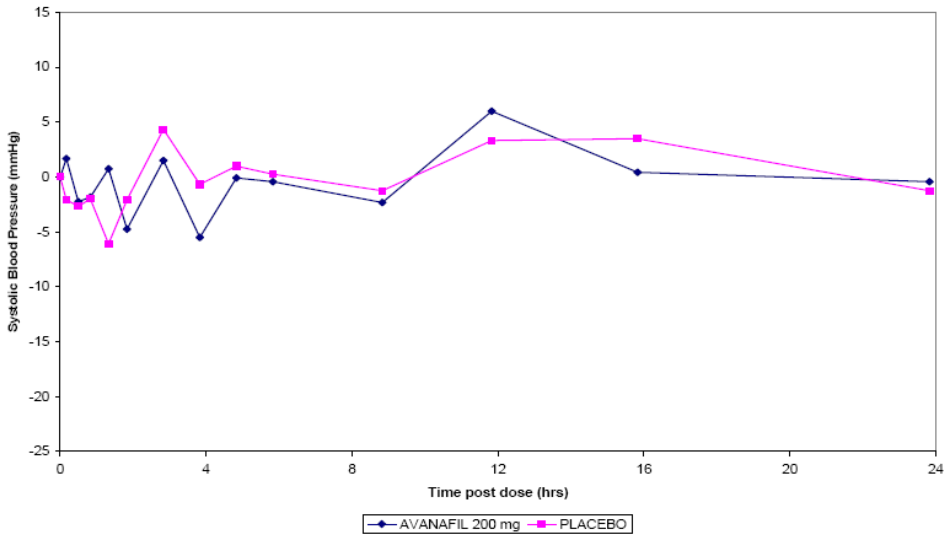

Figure 3.3.1 Mean Change in Sitting Systolic Blood Pressure From Baseline Over Time Following Administration of Avanafil 200 mg or Placebo – TA-02

However, avanafil, a PDE5 inhibitor that acts as a mild vasodilator, may potentiate the hypotensive effect of other drugs.

3.3.3.2.3.2. DDI on Vital Signs

3.3.3.2.3.2.1. With Nitrates

A single oral dose of avanafil 200 mg was shown to potentiate the hypotensive effect of glyceryl trinitrate (0.4 mg tablet administered sublingually). A statistically significant interaction between avanafil and glyceryl trinitrate was observed at the **0.5-hour time point** for blood pressure and pulse rate.

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Table 3.3.17 Number of Subjects With Clinically Significant Decreases* in Blood Pressure From Predose to Postdose at Sitting and Standing Positions After Glyceryl Trinitrate Administration

	Sitting				Standing			
Group	**A**	**B**	**C**	**P value**	**A**	**B**	**C**	**P value**
Diastolic BP Decrease > 20 mmHg								
1 (12 hour)	1 (6%)	2 (14%)	1 (8%)		3 (19%)	4 (29%)	2 (17%)	0.5853
2 (8 hour)	2 (13%)	1 (7%)	1 (7%)	0.5836	2 (13%)	3 (20%)	6 (40%)	0.1869
3 (4 hour)	4 (17%)	5 (22%)	5 (23%)	1.0000	11 (48%)	13 (57%)	9 (41%)	0.3841
4 (1 hour)	5 (22%)	4 (17%)	3 (14%)	0.6995	6 (26%)	10 (43%)	5 (24%)	0.3244
5 (0.5 hour)	8 (33%)	6 (26%)	3 (13%)	0.0561	13 (54%)	11 (48%)	6 (25%)	0.0261
1-5 combined	20 (20%)	18 (18%)	13 (14%)	0.1793	35 (35%)	41 (42%)	28 (30%)	0.1418
3-5 combined	17 (24%)	15 (22%)	11 (16%)	0.1755	30 (43%)	34 (49%)	20 (30%)	0.0175
4-5 combined	13 (28%)	10 (22%)	6 (13%)	0.0889	19 (40%)	21 (46%)	11 (24%)	0.0395
Systolic BP Decrease > 30 mmHg								
1 (12 hour)	0 (0%)	1 (7%)	2 (17%)		1 (6%)	3 (21%)	1 (8%)	
2 (8 hour)	1 (7%)	1 (7%)	0 (0%)		1 (7%)	4 (27%)	1 (7%)	0.1926
3 (4 hour)	4 (17%)	2 (9%)	2 (9%)	0.2669	5 (22%)	7 (30%)	1 (5%)	
4 (1 hour)	2 (9%)	4 (17%)	1 (5%)	0.1162	2 (9%)	8 (35%)	3 (14%)	0.0393
5 (0.5 hour)	2 (8%)	3 (13%)	0 (0%)		6 (25%)	6 (26%)	5 (21%)	0.8939
1-5 combined	9 (9%)	11 (11%)	5 (5%)	0.0893	15 (15%)	28 (29%)	11 (12%)	0.0184
3-5 combined	8 (11%)	9 (13%)	3 (4%)	0.0355	13 (19%)	21 (30%)	9 (13%)	0.0965
4-5 combined	4 (9%)	7 (15%)	1 (2%)	0.0272	8 (17%)	14 (30%)	8 (18%)	0.3359

N = 14 - 16, 15, 22 - 23, 21 - 23, and 23 - 24 for Groups 1, 2, 3, 4, and 5, respectively.
The P-value is from repeated-measures analysis on frequency data for overall treatment differences.
P-values cannot be calculated for those cases with sampling zero (subjects with missing treatments are presented but excluded from the statistical analysis).
Note: Treatment A = TA-1790 + glyceryl trinitrate,
Treatment B = Sildenafil citrate + glyceryl trinitrate,
Treatment C = Placebo + glyceryl trinitrate.
* Clinically significant decreases in blood pressure includes subjects with a decrease in systolic blood pressure of > 30 mm Hg or a decrease in diastolic blood pressure of > 20 mm Hg.

- Overall, 11 (12%) subjects with placebo, 15 (15%) subjects with avanafil, and 28 (29%) subjects with sildenafil had clinically significant drops in standing SBP (≥ 30 mmHg) after glyceryl trinitrate administration.

- Overall, the number (%) of subjects with symptomatic hypotension AEs after administration of glyceryl trinitrate was 11 (11%) for placebo, 24 (24%) for avanafil, and 26 (27%) for sildenafil. Thus, the occurrence of symptomatic hypotension AEs in male subjects administered avanafil coadministered with a sublingual dose of glyceryl trinitrate was more than with placebo + glyceryl trinatrate, and comparable to sildenafil citrate coadministered with glyceryl trinitrate.

Conclusions:

- Caution should be exercised when administering a sublingual dose of glyceryl trinitrate within 30 minutes of avanafil.
- The concomitant use of avanafil with any form of nitrates should be avoided.

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Reviewer's Comment: As any other PDE5 inhibitors, this statement should be included in the labeling; the concomitant use of avanafil with any forms of nitrates should be avoided.

3.3.3.2.3.2.2. With α-Blockers

With Doxazosin

Table 3.3.3.18 Statistical Comparisons of the $AUEC_{0-12}$ and Maximum Changes in Standing Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort A: Doxazosin)

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Doxazosin + Avanafil	Doxazosin + Placebo	Mean Difference		
Max decrease systolic (mmHg)	-14.46	-11.96	-2.50	-6.53 - +1.53	0.2114
Systolic AUEC0-12 (mmHg*h)	+23.54	+24.12	-0.58	-36.48 - +35.32	0.9737
Max decrease diastolic (mmHg)	-14.50	-8.08	-6.42	-9.54 - -3.30	0.0003
Diastolic AUEC0-12 (mmHg*h)	-24.23	+7.94	-32.17	-57.08 - -7.27	0.0137
Max increase pulse rate (bpm)	+19.17	+11.96	+7.21	+3.82 - +10.60	0.0002
Pulse rate AUEC0-12 (bpm*h)	+54.70	+10.16	+44.54	+21.32 - +67.76	0.0006

$AUEC_{0-12}$= area under effect-time curve from Hour 0 to Hour 12; CI= confidence interval
Cohort A: rising doses of doxazosin daily (Days 1-18) plus a single dose of 200 mg avanafil or placebo on Days 15 and 18.

Although doxazosin + avanafil decreased standing systolic BP more than doxazosin + placebo, there were no statistically significant differences observed in the maximum decrease from baseline in standing SBP (p = 0.2114) or in the $AUEC_{0-12}$ for standing SBP (p = 0.9737). The 95% CIs of differences contained zero for both comparisons.

However, statistically significant differences in the maximum decrease from baseline in standing DBP (p = 0.0003) and the $AUEC_{0-12}$ for standing DBP (p = 0.0137) were observed following doxazosin + avanafil versus doxazosin + placebo. The differences in the LSM for maximum decrease in standing DBP and $AUEC_{0-12}$ for standing DBP were -6.42 mmHg and -32.17 mmHg*h, respectively. Likewise, statistically significant differences in the maximum increase from baseline in pulse rate (p = 0.0002) and the $AUEC_{0-12}$ for standing pulse rate (p = 0.0006) were observed following avanafil versus placebo. The differences in the LSM for maximum increase in standing pulse rate and $AUEC_{0-12}$ for pulse rate were +7.21 bpm and +44.54 bpm*h, respectively.

The largest mean supine SBP decreases following avanafil occurred from Hours 0.5 to 1.75, ranging from -6.0 to -4.5 mmHg. Mean SBP changes from baseline following placebo ranged from -2.0 to +4.9 mmHg over the same period. The largest mean supine DBP decreases following avanafil occurred from Hours 0.25 to 1.25, ranging from -6.0 to -4.7 mmHg. Mean DBP changes from baseline following placebo ranged from -0.8 to +2.0 mmHg over the same period. The largest mean increases in supine pulse rate in the immediate postdose period following avanafil occurred from Hours 0.25 to 1.0, ranging from +4.4 to +7.5 bpm. Mean pulse rate changes from baseline following placebo ranged from -4.2 to -0.5 bpm over the same period.

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Table 3.3.3.19 Statistical Comparisons of the $AUEC_{0-12}$ and Maximum Changes in Supine Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort A: Doxazosin)

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
Systolic AUEC0-12 (mmHg*h)	+12.26	+45.12	-32.86	-72.15 - +6.43	0.0968
Max decrease diastolic (mmHg)	-10.58	-7.00	-3.58	-5.63 - -1.53	0.0015
Diastolic AUEC0-12 (mmHg*h)	-23.90	+7.51	-31.40	-51.22 - -11.59	0.0034
Max increase pulse rate (bpm)	+17.12	+13.37	+3.75	-2.92 - +10.42	0.2564
Pulse rate AUEC0-12 (bpm*h)	+59.48	+13.64	+45.84	+28.10 - +63.58	<0.0001

$AUEC_{0-12}$= area under effect-time curve from Hour 0 to Hour 12; CI= confidence interval
Cohort A: rising doses of doxazosin daily (Days 1-18) plus a single dose of 200 mg avanafil or placebo on Days 15 and 18.

A statistically significant difference in the maximum decrease from baseline in supine SBP (p = 0.0005) was observed following avanafil versus placebo. The difference in the LSM was -6.00 mmHg. No statistically significant difference was observed in the AUEC0-12 for supine SBP (p = 0.0968) following avanafil versus placebo; the 95% CI of the difference contained zero for this comparison.

Table 3.3.3.20 Incidence of Potentially Clinically Important Hemodynamic Results (Cohort A: Doxazosin)

Parameter	Number of Subjects	
	Doxazosin + Avanafil (N = 24)	Doxazosin + Placebo (N = 24)
Standing SBP < 85 mmHg	3	0
Standing SBP decrease > 30 mmHg	1	0
Standing DBP < 45 mmHg	2	0
Standing DBP decrease > 20 mmHg	4	1
Supine SBP < 85 mmHg	0	0
Supine SBP decrease > 30 mmHg	0	0
Supine DBP < 45 mmHg	0	0
Supine DBP decrease > 20 mmHg	0	0

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.

Reviewer's Comment: There appears to be a pharmacodynamic reaction between avanafil and doxazosin, occurring soon after concomitant dosing, and resolving fairly soon thereafter. This will need to be shown in labeling, with an appropriate precaution. This will be a review issue.

With Tamsulosin

Table 3.3.3.21 Statistical Comparisons of the $AUEC_{0-12}$ and Maximum Changes in Standing Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort B: Tamsulosin)

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Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Tamsulosin + Avanafil	Tamsulosin + Placebo	Mean Difference		
Max decrease systolic (mmHg)	-14.50	-10.88	-3.63	-8.14 - +0.89	0.1101
Systolic AUEC0-12 (mmHg*h)	+11.71	+15.41	-3.70	-34.37 - +26.97	0.8047
Max decrease diastolic (mmHg)	-13.13	-9.46	-3.67	-7.86 - +0.53	0.0835
Diastolic AUEC0-12 (mmHg*h)	-24.40	-3.69	-20.71	-46.46 - +5.03	0.1094
Max increase pulse rate (bpm)	+22.25	+19.79	+2.46	-1.32 - +6.24	0.1913
Pulse rate AUEC0-12 (bpm*h)	+97.82	+66.26	+31.56	+0.44 - +62.68	0.0471

AUEC0-12= area under effect-time curve from Hour 0 to Hour 12; CI= confidence interval
Cohort B: tamsulosin 0.4 mg daily (Days 1-11) plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.

Although tamsulosin + avanafil decreased standing systolic and diastolic BP more than tamsulosin + placebo, and the active combination increased standing pulse rate considerably compared to tamsulosin + placebo, there were no statistically significant differences observed in the maximum decrease from baseline in standing SBP (p = 0.1101) or DBP (p = 0.0835), the $AUEC_{0-12}$ for standing SBP (p = 0.8047) or DBP (p = 0.1094), or the maximum increase from baseline in standing pulse rate (p = 0.1913) following avanafil versus placebo. The 95% CIs of differences contained zero for all of these comparisons.

Differences in the $AUEC_{0-12}$ for standing pulse rate following avanafil versus placebo were marginally statistically significant (p = 0.0471). The difference in the LSM for this parameter was +31.56 bpm*h, with a 95% CI of 0.44 – 62.68 bpm*h.

The largest mean supine SBP decreases following avanafil occurred from Hours 0.25 to 1.5, ranging from -4.9 to -3.3 mmHg. Mean supine SBP changes from baseline following placebo ranged from -0.2 to +1.8 mmHg over the same period. The largest mean supine DBP decreases following avanafil occurred from Hours 0.25 to 1.5, ranging from -4.5 to -3.2 mmHg. Mean supine DBP changes from baseline following placebo ranged from 0 to +1.9 mmHg over the same period. The largest mean increases in supine pulse rate in the immediate postdose period following avanafil occurred from Hours 0.25 to 1.0, ranging from +4.9 to +8.4 bpm. Mean pulse rate changes from baseline following placebo ranged from -1.8 to -0.2 bpm over the same period.

Table 3.3.3.22 Statistical Comparisons of the $AUEC_{0-12}$ and Maximum Changes in Supine Blood Pressure and Pulse Rate: Doxazosin with Avanafil or Placebo (Cohort B: Tamsulosin)

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
Systolic AUEC0-12 (mmHg*h)	+20.86	+28.87	-8.01	-39.41 - +23.40	0.6023
Max decrease diastolic (mmHg)	-10.04	-6.71	-3.33	-6.49 - -0.18	0.0392
Diastolic AUEC0-12 (mmHg*h)	-16.52	-1.50	-15.02	-47.21 - +17.18	0.3439
Max increase pulse rate (bpm)	+20.75	+16.08	+4.67	+0.37 - +8.96	0.0344
Pulse rate AUEC0-12 (bpm*h)	+92.65	+51.89	+40.76	+17.85 - +63.66	0.0013

$AUEC_{0-12}$= area under effect-time curve from Hour 0 to Hour 12; CI= confidence interval
Cohort B: tamsulosin 0.4 mg daily (Days 1-11) plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.

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No statistically significant differences were observed in the maximum decrease from baseline in supine SBP (p = 0.0580), $AUEC_{0-12}$ for supine SBP (p = 0.6023), or AUEC0-12 for supine DBP (p = 0.3439). The 95% CIs of differences contained zero for all of these comparisons. However, a statistically significant difference in the maximum decrease from baseline in supine DBP (p = 0.0392) was observed following avanafil versus placebo. The difference in the LSM was -3.33 mmHg.

Statistically significant differences in the maximum increase from baseline in supine pulse rate (p = 0.0344) and $AUEC_{0-12}$ for supine pulse rate (p = 0.0013) were also observed following tamsulosin + avanafil compared to tamsulosin + placebo. The differences in the LSMs for these parameters were +4.67 bpm and +40.76 bpm*h, respectively.

Table 3.3.3.23 Incidence of Potentially Clinically Important Hemodynamic Results (Cohort B: Tamsulosin)

Parameter	Number of Subjects	
	Tamsulosin + Avanafil (N = 24)	Tamsulosin + Placebo (N = 24)
Standing SBP < 85 mmHg	2	0
Standing SBP decrease > 30 mmHg	1	0
Standing DBP < 45 mmHg	2	0
Standing DBP decrease > 20 mmHg	4	1
Supine SBP < 85 mmHg	0	0
Supine SBP decrease > 30 mmHg	0	0
Supine DBP < 45 mmHg	0	1
Supine DBP decrease > 20 mmHg	1	1

SBP= systolic blood pressure; DBP= diastolic blood pressure
Cohort B: tamsulosin 0.4 mg daily (Days 1-11) plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.

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 postdose 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 those farther removed from the time of dosing (Hours 7.0, 8.0, and 24.0).

Two subjects experienced potentially clinically important supine hemodynamic events. One subject had a single isolated potentially clinically important supine DBP event at Hour 24.0 following placebo and one subject experienced decreases in supine DBP at multiple time points following avanafil from Hours 0.25 to 3.5 and Hours 6.0 to 12.0.

Reviewer's Comments: There appears to be a pharmacodynamic interaction between avanafil and tamsulosin, which may be somewhat less than the interaction between doxazosin and avanafil.

Based on these results, and the known class effect, the Sponsor advises caution when avanafil is co-administered with alpha-blockers. Subjects should be stable on alpha-

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blocker therapy prior to initiating treatment with avanafil, and avanafil should be initiated at the 50 mg dose.

The potential risk of co-administration of avanafil and alpha-blockers should be included in the Precautions section, and the lower starting dose of avanafil for alpha-blocker user at initiating stage should be inserted in labeling. This will be a review issue.

3.3.3.2.3.2.3. With Alcohol (Study TA-15)

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

An analysis of variance (ANOVA) model corresponding to a crossover study design with sequence, period, and treatment as fixed effects and subject within sequence as the random effect was used to compare the mean differences between treatments as follows:

Treatment A – Treatment B
Treatment A – Treatment C
Treatment B – Treatment C

The dependent variables to be analyzed using ANOVA were maximum decrease in SBP and DBP, and maximum increase in pulse rate as well as $AUEC_{0-t}$ of SBP, DBP, and pulse rate. All statistical tests were carried out using two-sided tests. Ninety-five percent (95%) confidence interval (CI) for mean difference was also calculated.

Mean maximum percent blood alcohol levels occurred at Hour 0.5 for Treatments A and B, with values of 0.0569% and 0.0547%, respectively. At Hour 2, mean levels had decreased to 0.0259% and 0.0245% for Treatments A and B, respectively. By Hour 6, mean alcohol levels had returned to baseline (0.0000%).

Table 3.3.3.24 Mean Hemodynamic Parameters

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
Systolic $AUEC_{0-t}$ (mmHg*h)	-15.4 ± 31.93	-2.8 ± 15.17	-10.0 ± 23.42
Max decrease diastolic (mmHg)	-14.6 ± 7.93	-9.6 ± 6.97	-11.4 ± 5.57
Diastolic $AUEC_{0-t}$ (mmHg*h)	-21.4 ± 29.88	-3.8 ± 18.63	-8.6 ± 21.53
Max increase pulse rate (bpm)	+19.3 ± 9.38	+10.2 ± 10.82	+15.4 ± 7.20
Pulse rate $AUEC_{0-t}$ (bpm*h)	+30.7 ± 24.95	+6.2 ± 28.73	+13.7 ± 15.30

$AUEC_{0-t}$ =Area under effect-time curve from Hour 0 to Hour t

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

At most postdose time points through Hour 2, 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 B (alcohol + placebo). Treatment B (alcohol alone) actually showed the least change from baseline for BP and pulse across time points. By Hour 4, mean BP and pulse measurements were near baseline values for all treatments.

Table 3.3.3.25 Statistical Comparisons of the $AUEC_{0-t}$ and Maximum Changes in Supine Blood Pressure and Pulse Rate: Treatment A versus B

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Treatment A	Treatment B	Mean Difference		
Max decrease systolic (mmHg)	-14.46	-10.93	-3.53	-9.68 - 2.63	0.2483
Systolic $AUEC_{0-12}$ (mmHg*h)	-15.27	-2.79	-12.48	-30.92 - 5.96	0.1752
Max decrease diastolic (mmHg)	-14.14	-9.60	-4.54	-8.98 - -0.10	0.0454
Diastolic $AUEC_{0-12}$ (mmHg*h)	-20.07	-3.75	-16.32	-30.19 - -2.46	0.0230
Max increase pulse rate (bpm)	+19.53	+10.20	+9.33	3.35 - 15.31	0.0037
Pulse rate $AUEC_{0-12}$ (bpm*h)	+31.23	+6.16	+25.07	8.58 - 41.56	0.0045

There were also statistically significant differences in diastolic pressure maximum decrease ($p < 0.05$) and pulse rate maximum increase ($p < 0.005$) when comparing Treatments A and B.

Table 3.3.3.26 Statistical Comparisons of the $AUEC_{0-t}$ and Maximum Changes in Supine Blood Pressure and Pulse Rate: Treatment A versus C

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Treatment A	Treatment C	Mean Difference		
Max decrease systolic (mmHg)	-14.46	-11.58	-2.88	-9.13 - 3.38	0.3520
Systolic $AUEC_{0-12}$ (mmHg*h)	-15.27	-9.36	-5.91	-24.67 - 12.84	0.5216
Max decrease diastolic (mmHg)	-14.14	-11.20	-2.94	-7.44 - 1.56	0.1902
Diastolic $AUEC_{0-12}$ (mmHg*h)	-20.07	-7.64	-12.43	-26.44 - 1.58	0.0794
Max increase pulse rate (bpm)	+19.53	+15.86	+3.67	-2.38 - 9.72	0.2231
Pulse rate $AUEC_{0-12}$ (bpm*h)	+19.53	+15.86	+3.67	-2.38 - 9.72	0.2231

While the decreases in standing systolic and diastolic BP, and increases in standing pulse rate were greater for Treatment A (avanafil + alcohol) compared to Treatment C (avanafil alone), there were no statistically significant differences in blood pressure maximum decreases ($p > 0.05$) and pulse rate maximum increases ($p > 0.05$) when comparing Treatments A and C.

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Table 3.3.3.26 Statistical Comparisons of the $AUEC_{0-t}$ and Maximum Changes in Supine Blood Pressure and Pulse Rate: Treatment B versus C

Hemodynamic Parameter	Least-Squares Means			95% CI	P-Value
	Treatment B	Treatment C	Mean Difference		
Max decrease systolic (mmHg)	-10.93	-11.58	0.65	-5.50 - 6.80	0.8291
Systolic $AUEC_{0-12}$ (mmHg*h)	-2.79	-9.36	6.57	-11.87 - 25.01	0.4693
Max decrease diastolic (mmHg)	-9.60	-11.20	1.60	-2.84 - 6.04	0.4636
Diastolic $AUEC_{0-12}$ (mmHg*h)	-3.75	-7.64	3.89	-9.97 - 17.76	0.5679
Max increase pulse rate (bpm)	+10.20	+15.86	-5.66	-11.64 - 0.32	0.0625
Pulse rate $AUEC_{0-12}$ (bpm*h)	+10.20	+15.86	-5.66	-11.64 - 0.32	0.0625

There did not appear to be numeric nor statistically significant differences in blood pressure maximum decreases ($p > 0.05$) and pulse rate maximum increases ($p > 0.05$) when comparing Treatments B (alcohol alone) and C (avanafil alone).

The Sponsor concludes that alcohol (a single dose of 0.5 g/kg) did not potentiate the hypotensive effects of avanafil over the 4-hour observation period in healthy volunteers when administered with a 200 mg dose of avanafil (comparison A vs. C). However, the Sponsor concludes that avanafil produced a "*small*" but statistically significant change in maximum diastolic pressure decrease ($p <0.05$) and maximum pulse rate increase ($p < 0.005$) when administered with alcohol compared to alcohol administered alone (comparison A vs. B). They note that this did not appear to correspond to an increase in hemodynamic-related adverse events. They also note that there were no reports of orthostatic hypotension or dizziness. They conclude that the hypotensive effects of alcohol were not potentiated when a single oral dose of avanafil 200 mg was given with 0.5 g/kg alcohol.

While the Sponsor believes that a single oral 100 mg dose of avanafil administered with an alcohol drink appears to be safe and generally well tolerated by the heathy male subjects in this study, they nonetheless state that subjects should be made aware that both alcohol and avanafil act as mild vasodilators. Substantial consumption of alcohol (e.g., 3 units or greater) in combination with avanafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Reviewer's Comments: A Precaution in labeling appears necessary for consumption of alcohol and avanafil, similar to the Precaution which exists for the currently approved PDE5 inhibitors. This will be a review issue.

With Antihypertensives (TA-019)

With Amlodipine (5 mg, QD)

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Table 3.3.3.28: Incidence of Potentially Clinically Important Blood Pressure-Related Events Following Co-Administration of Avanafil + Amlodipine versus Placebo + Amlodipine – TA-019

Parameter	Number of Subjects	
	Avanafil + Amlodipine (N = 23)	Placebo + Amlodipine (N=23)
Standing SBP <85 mmHg	0	0
Standing SBP decrease >30 mmHg	0	0
Standing DBP <45 mmHg	0	0
Standing DBP decrease >20 mmHg	0	1
Supine SBP <85 mmHg	0	1
Supine SBP decrease >30 mmHg	0	1
Supine DBP <45 mmHg	0	3
Supine DBP decrease >20 mmHg	1	3

Treatment consisted of amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil or placebo on Days 12 and 19.
DBP= diastolic blood pressure; SBP= systolic blood pressure.

- A single oral dose of avanafil 200 mg co-administered with amlodipine (5 mg once daily) resulted in a mean maximum change in supine SBP/DBP of 1/-1 mmHg compared to placebo. No statistically significant difference in the maximum decrease from baseline in standing SBP was observed following co-administration of avanafil with amlodipine compared to placebo.
- A statistically significant difference in the maximum increase from baseline in standing pulse rate (secondary endpoint) was observed following co-administration of avanafil with amlodipine versus placebo with amlodipine (not shown in Table 3.3.3.28) Treatment differences were most notable in the first 4 hours postdose, and remained slightly higher than placebo from Hours 5.0 to 10.

With Enalapril (10 mg BID)

Table 3.3.3.29: Incidence of Potentially Clinically Important Blood Pressure-Related Events Following Co-Administration Avanafil + Enalapril Versus Placebo + Enalapril – TA-019

Parameter	Number of Subjects	
	Avanafil + Enalapril (N = 24)	Placebo + Enalapril (N=24)
Standing SBP <85 mmHg	0	0
Standing SBP decrease >30 mmHg	0	0
Standing DBP <45 mmHg	0	0
Standing DBP decrease >20 mmHg	0	1
Supine SBP <85 mmHg	0	0
Supine SBP decrease >30 mmHg	1	0
Supine DBP <45 mmHg	1	0
Supine DBP decrease >20 mmHg	1	0

Treatment consisted of enalapril 10 mg BID on Days 1-11 plus a single dose of 200 mg avanafil or placebo on Days 8 and 11. BID = twice daily;
DBP= diastolic blood pressure; SBP= systolic blood pressure.

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- A single oral dose of avanafil 200 mg co-administered with enalapril (10 mg twice daily) resulted in a mean maximum decrease in supine SBP/DBP of -1.75/-3.46 mmHg compared to placebo, accompanied by a mean maximum increase in pulse rate of 0.96 bpm. No statistically significant difference in the maximum decrease from baseline in standing SBP was observed following co-administration of avanafil with enalapril compared to placebo.
- A statistically significant difference in the maximum decrease from baseline in supine DBP (a secondary endpoint) was observed following co-administration of avanafil with enalapril versus placebo with enalapril (not shown in Table 3.3.3.29). Supine DBP returned to baseline by 4 hours post-avanafil dosing.

Amlodipine+placebo / Enalopril+Placebo: One subject in each cohort experienced potentially clinically important decreases in BP following co-administration of enalapril or amlodipine with placebo. In both cases, the events resolved within 1 hour after onset and were not accompanied by concurrent symptoms of hypotension

The Sponsor concludes that a single oral 200 mg dose of avanafil, administered with 10 mg enalapril or 5 mg amlodipine, appeared to be safe and generally well tolerated by the healthy male subjects in this study. The Sponsor states that small reductions in blood pressure occurred following co-administration of avanafil with these blood pressure-lowering agents compared with placebo, but no clinically significant hemodynamic events or changes. The Sponsor concludes that physicians should discuss the potential for avanafil to enhance the blood pressure-lowering effect of antihypertensive medications with subjects.

Reviewer's comment: The interaction potential of avanafil with anti-hypertensive agents amlodipine and enalapril appears small, but nonetheless is a review issue. Specific labeling will be crafted as needed after the NDA review is completed.

3.3.3.2.4. Other Related Safety Studies

3.3.3.2.4.1. TQT Study (TA-140)

- In this TQT study, it appears that the QTcI interval data did not show a signal of any effect except for the 3 hour time point for the 800 mg dose which had an upper CI of 10.2 msec.
- This appears to have been a well conducted and valid thorough QT study.
- In addition to the QT interval, the study assessed other ECG intervals. According to the Sponsor, avanafil had no effects on PR and QRS interval duration or cardiac morphology. Further, there appeared to be no effect of the clinical dose of avanafil on heart rate, but a marked effect on heart rate at the 8 fold increased dose (800mg) which was used as the supratherapeutic dose.
- The Sponsor provides a cardiologist's opinion, from the preponderance of data including a PD-PK analysis, that avanafil does not affect cardiac repolarization.

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Reviewer's Comment: From a cursory review of the data, it appears that the Sponsor is correct, and that avanafil does not affect cardiac repolarization. However, a complete review by Clinical Pharmacology and also the Interdisciplinary Review Team –QT (IRT-QT) is needed.

3.3.3.2.4.2. Safety for Sperm (Studies TA-014 and TA-021)

Study TA-014: A single-center, open-label, pharmacokinetic study that evaluated avanafil semen exposure and the acute effect of avanafil 200 mg on sperm function in 6 healthy young male subjects.

- Overall, the Sponsor reports that mean sperm motility remained within the reference range and was not considered to be significantly affected by a single dose of avanafil 200 mg.
- Overall, the Sponsor reports that no acute effects on morphological normal forms, sperm count, sperm concentrations, or forward progress were noted (in this single dose study).
- Two subjects showed notable decreased sperm motility and decreased 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. These sperm motility values were still higher than the 20% abnormality criterion. The Sponsor believes that it is possible that these 2 subjects had a pre-existing condition (e.g., leukocytospermia) that could have affected such sperm motility and that the low sperm motility values were not related to study drug.

Study TA-021: A double-blind, placebo-controlled, randomized, crossover study to determine the acute effect of a single oral dose of avanafil 200 mg on sperm function in 17 healthy young male subjects.

- While a very small percent of the avanafil dose (~0.0002%) was detected in seminal fluid, 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 both the avanafil and placebo treatment groups.
- 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.

Reviewer's Comments: Both were single-dose studies, and the efforts from longer term use are unknown at this moment. As discussed with Sponsor at the Pre-NDA meeting, a

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longer-term sperm study (e.g., 12 weeks treatment) may be requested as a Post-Marketing Requirement.

3.3.3.2.4.3. Safety in Special Population and Situations

3.3.3.2.4.3.1. In Hepatic Impairment Status

The Sponsor states that a single dose of avanafil 200 mg appeared to be safe and well tolerated by subjects with normal hepatic function and subjects with hepatic impairment. They further state that no dose adjustment is required for subjects with mild or moderate hepatic insufficiency. Patients with severe hepatic impairment were not studied.

3.3.3.2.4.3.2. In Renal Impairment Status

The Sponsor states that a single dose of avanafil 200 mg appeared to be safe and well tolerated by subjects with normal renal function and subjects with renal impairment. They further state that no dose adjustment is required for subjects with mild or moderate renal insufficiency. Patients with severe renal impairment were not studied.

3.3.3.2.4.3.3. Drug Interaction

The known pharmacodynamic interactions have been studied appropriately (see previous sections of this memo) and these will be review issues. Any additional concerns from Clinical Pharmacology will be addressed as they are raised by our Clinical Pharmacology colleagues.

3.3.3.3. Preliminary safety and tolerability conclusions:

At this time, the Reviewer concludes:

1. The exposure of avanafil to patients and other subjects including the long-term exposure complied with ICH standards is adequate for filing.
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.

3.3.4. Other considerations of Filing Review:

3.3.4.1. Pediatric Waiver:

The sponsor has requested a pediatric waiver under 21 CFR 314.55(c)(2)(iii).

Reviewer's Comment: (b) (4) . *Therefore, it*

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is not clear that a waiver will be accepted. The waiver request will be be presented to the Pediatric Review Committee (PeRC).

3.3.4.2. Recommendation for a Division of Scientific Investigations (DSI) Audit:

Since avanafil is a new molecular entity, routine DSI audit of several U.S. study sites will be requested. One of the key variables for picking sites is number of subjects enrolled. The largest sites in Studies TA-301 and TA-302 are shown below.

Table 3.3.4.1 Centers with most Enrollment of Subjects in Phase 3 Studies

Principle Investigator	Investigator Location	TA-301		TA-302		TA-314	
		Site ID	# of Ran-domized	Site ID	# of Ran-domized	Site ID	# with Avanafil
Ronald Surowitz	Jupiter, FL	140	38	221	33	440	56
Douglas Young	Sacramento, CA	135	37	231	31	435	42
Jeffrey Rosen	Coral Gables, FL	127	36	222	20	427	51
David Cook	Winston-Salem, NC	116	28	233	19	416	36
Dario Altamirano	Hialeah, FL	115	31	220	14	415	28
Brian Goldman	Raleigh, NC	110	20	219	22	410	29
Gary Karlin	Lawrenceville, NJ	111	31	208	11	411	31
Sidney Clevinger	Ocala, FL	136	16	236	19	436	25
Larry Gilderman	Pembroke Pines, FL	119	26	215	14	419	12
Jonathan Staub	Wilmington, NC	121	19	238	16	421	24
Gerard Henry	Shreveport, LA	104	16	203	13	404	21
Joseph Soufer	Waterbury, CT	134	13	228	13	434	22
LeRoy Jones	San Antonio, TX			234	19		

Reviewer's comment: The sites for DSI audit will be further discussed with the Office of Compliance as part of the filing review.

3.3.4.3. Review of Financial Disclosure Documents:

Form FDA 3454 (10/09) ("Certification: Financial Interests and Arrangements of Clinical Investigators"), dated May 30, 2011, and signed by Malcolm McKay, V.P. Regulatory Affairs and Compliance Officer, Vivus, Inc., was included in this submission. Financial disclosure documents were submitted for clinical investigators (principal and sub-investigators) for clinical studies under IND 51,235 (for the three Phase 3 studies).

Form FDA 3455 (10/09) ("Disclosure: Financial Interests and Arrangements of Clinical Investigators"), dated May 30, 2011, signed by Malcolm McKay, V.P. Regulatory Affairs and Compliance Officer, Vivus, Inc., was submitted. In accordance with 21 CFR Part 54.4, certification and disclosure requirements, forms of clinical investigator certification and financial disclosure provided by Vivus, Inc., were signed by individual investigators and submitted. To the extent investigators have provided financial disclosure information via questionnaires, they were asked to do so based on site-specific (or if shorter, their

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individual) study start and completion dates. A total of 226 investigators (43 PI's and 183 sub-PI's) from study sites all over the United States had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54.4(a)(3)(i), 54.2 (a)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4 (a)(3)(ii), 54.2(f)], proprietary interest in the tested product [21 CFR 54.4(a)(3)(iii), 54.2(c)], or significant equity interest in the sponsor of the covered study product [21 CFR 54.4(a)(3)(iv), 54.2(b)].

Reviewer's Comment: The financial disclosure information is acceptable.

3.3.4.4. Labeling:

The proposed label complies with the basic requirements of the Physician Labeling Rule (PLR). Some highlights of the proposed label include:

- INDICATIONS AND USAGE (HIGHLIGHTS and Full Prescribing Information): "Avanafil is indicated for the treatment of male erectile dysfunction."
- ADVERSE REACTIONS, Clinical Studies Experience: (b) (4)
- CLINICAL STUDIES (b) (4)

Reviewer's Comments: Time to onset and duration of effect claims will be a review issue. No efficacy claims will be allowed from open-label studies.

3.3.4.5. Trade Name:

The included submission of proposed trade name has been determined by the Division of Medication Errors Prevention and Analysis (DMEPA) to be not acceptable due to similarity to the other current approved names. The reader is referred to the DMEPA review.

Reviewer's Comment: The Sponsor will be informed that a new trade name needs to be designed and submitted for review.

3.3.5. Clinically relevant issues from filing reviews by other disciplines:

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Filing reviews form the other disciplines are pending. When those reviews become available, all clinically relevant issues from those filing reviews will be evaluated by this reviewer.

3.4. Summary of Initial Clinical Review

3.4.1. Efficacy:

1. Treatment with avanafil appears to be statistical superior to placebo with regards to the three co-primary efficacy endpoints (SEP #3 and SEP #2, and EF domain score of IIEF,),
2. [redacted] (b) (4)
3. The efficacy results from the long term (6 month) study are not suitable to be counted into the efficacy database to support the NDA based on the open label nature;
4. Sub-population analyses for efficacy will be reviewed but labeling claims for these sub-populations are unlikely.

3.4.2. Safety:

1. The extent of whole patient population exposure complied with ICH standards and is adequate for filing, including long term exposure.
2. Overall, the safety and tolerability profile of avanafil appears consistent with known effects of other PDE5 inhibitors. The most frequently reported adverse events were headache, flushing, nasopharyngitis, and nasal congestion. Most of the adverse events were mild or moderate in severity.
3. Some of special safety studies were conducted with single dose of avanafil (e.g. sperm studies). It will be a review issues to determine whether a multi-dose sperm study is needed.

3.4.3. Others:

1) Clincial site audits by the Division of Scientific Investigation (DSI) will be discussed at the filing meeting.
2) The submitted trade name has been determined by DMEPA to be not acceptable. This issue needs to be conveyed to Sponsor

4. Recommended Regulatory Action:

From a clinical perspective, NDA 202,276 is fileable. The following are Clinical comments to be conveyed to the sponsor in the 74-Day letter:

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

2. The support provided for (b) (4) will be a review issue.

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

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

5. As previously conveyed to you, your proposed trade name is not acceptable based upon the potential for look-alike medication errors. You should submit an alternative trade name.

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Appendix I

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202276 **Applicant: Vivus** **Stamp Date: June 29, 2011**

Drug Name: Avanafil **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?			X	
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	X			

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	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		All pivotal studies were conducted in the U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.
[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	All pivotal studies were conducted in the U.S.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X		
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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

2. The support provided for [redacted] (b) (4) will be a review issue.

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

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

5. As previously conveyed to you, your proposed trade name is not acceptable based upon the potential for look-alike medication errors. You should submit an alternative trade name.

Guodong Fang	August 9, 2011
Reviewing Medical Officer	Date
Mark Hirsch	August 9, 2011
Clinical Team Leader	Date

Reference ID: 2997438

Appendix II

NDA 202276: Total Enrollment by Centers and PIs For Phase 3 Studies

	Principle Investigator	Investigator Location	TA-301		TA-302		TA-314	
			Site ID	# of Ran-domized	Site ID	# of Ran-domized	Site ID	# with Avanafil
01	Morris Brown	Atlanta, GA	101	0	–	–	401	–
02	James Clower	Jacksonville, FL	102	18	202	6	402	18
03	Irwin Goldstein	San Diego, CA	103	8	218	9	403	9
04	Gerard Henry	Shreveport, LA	104	16	203	13	404	21
05	Gladstone Sellers	Sandy Springs, GA	105	13	227	3	405	16
06	Selwyn Spangenthal	Charlotte, NC	106	11	205	14	406	11
07	Laurence Belkoff	Bala Cynwyd, PA	107	9	207	18	407	17
08	Steven Bowman	Clearwater, FL	108	10	216	8	408	8
09	Richard Egelhof	Wichita, KS	109	7	211	5	409	7
10	Brian Goldman	Raleigh, NC	110	20	219	22	410	29
11	Gary Karlin	Lawrenceville, NJ	111	31	208	11	411	31
12	Robert Kaufmann	Austell, GA	112	0	–		–	–
13	David Miller	Harrisburg, NC	113	11	229	3	413	9
14	Miguel Trevino	Clearwater, FL	114	20	201	9	414	23
15	Dario Altamirano	Hialeah, FL	115	31	220	14	415	28
16	David Cook	Winston-Salem, NC	116	28	233	19	416	36
17	Michael Cromer	Tampa, FL	117	14	213	7	417	14
18	Garth Denyer	Spring, TX	118	7	223	–	418	6
19	Larry Gilderman	Pembroke Pines, FL	119	26	215	14	419	12
20	John McGettigan	Tucson, AZ	120	15	237	6	420	15
21	Jonathan Staub	Wilmington, NC	121	19	238	16	421	24
22	Bret Wittmer	Madisonville, KY	122	17	212	4	422	18
23	John Earl	Hickory, NC	123	18	–	–	423	17
24	George Adams	Homewood, AL	124	10	204	–	424	8
25	James Barada	Albany, NY	125	5	206	1	425	4
26	Wayne Cline	Salisbury, NC	126	11	226	6	426	14
27	Jeffrey Rosen	Coral Gables, FL	127	36	222	20	427	51
28	Sergio Rovner	El Paso, TX	128	2	230	10	428	6
29	Martin van Cleeff	Cary, NC	129	24	209	5	429	21
30	Michael Warren	Lancaster, PA	130	16	239	3	430	15
31	Wilbur Wells, Jr.	Birmingham, AL	131	10	210	0	431	8
32	Mira Baron	Cleveland, OH	132	15	224	8	432	15
33	George Raad	Charlotte, NC	133	16	225	11	433	13
34	Joseph Soufer	Waterbury, CT	134	13	228	13	434	22
35	Douglas Young	Sacramento, CA	135	37	231	31	435	42
36	Sidney Clevinger	Ocala, FL	136	16	236	19	436	25
37	John Ervin	Kansas City, MO	137	20	214	8	437	25
38	Andrew McCullough	New York, NY	138	4	–	–	438	2
39	Richard Townsend	Jacksonville, FL	139	5	217	0	439	2
40	Ronald Surowitz	Jupiter, FL	140	38	221	33	440	56
41	Maxwell Axler	Houston, TX	141	11	235	3	441	10
42	Michael Bennett	San Diego, CA	142	8	232	4	442	4
43	LeRoy Jones	San Antonio, TX	–	–	234	14	–	–

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/s/

GUODONG FANG
08/08/2011

MARK S HIRSCH
08/09/2011
I concur.