CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202276Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	202276
Drug Name:	Avanafil
Indication(s):	Male erectile dysfunction
Applicant:	VIVUS, INC.
Date(s):	Submission date: June 29, 2011
	PDUFA date: April 29, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Jia Guo, Ph.D.
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Keywords: NDA review, analysis of covariance, multiple comparisons, multiple endpoints

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of Avanafil for the treatment of erectile dysfunction (ED) in men. To support this claim, the safety and efficacy data from two Phase 3, double-blind, randomized, placebo-controlled clinical trials (TA-301 and TA-302) were submitted. This review evaluates to determine from a statistical perspective if the submitted information supports this claim.

Study TA-301 was conducted in general ED population, and study TA-302 was conducted in diabetic ED population. Both studies consisted of a 4-week run-in period and a 12-week treatment period. In study TA-301, eligible subjects were randomized to receive placebo, Avanafil 50 mg, Avanafil 100 mg, or Avanafil 200 mg, and in study TA-302, subjects were randomized to receive placebo, Avanafil 100 mg, or Avanafil 200 mg.

For each sexual attempt during the run-in and treatment periods, subjects were instructed to record information pertaining to sexual experience and, if applicable, study drug administration on the diary. The IIEF questionnaire was completed at each study visit. The primary efficacy variables, based on the subject diary questions and IIEF erectile function (EF) domain score, were:

- change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to maintain an erection of sufficient duration to have successful intercourse (subject diary question 5, also referred to as SEP3);
- change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to insert his penis into his partner's vagina (subject diary question 4, also referred to as SEP2); and
- change in IIEF EF domain score from baseline to end of the 12-week treatment period.

For both studies, the Applicant analyzed each co-primary efficacy variable by an ANCOVA model, with treatment and baseline erectile dysfunction severity category as factors and baseline value as the covariate.

Two statistical issues were noted in the Applicant's data analyses:

1. For the comparisons between Avanafil dose groups with placebo, the Applicant used a step-down, multiple-comparison procedure starting from the highest Avanafil dose to the lowest one. Under this step-down procedure, all three Avanafil doses in study TA-301 are significantly better than placebo on all co-primary endpoints. The Applicant's statistical analysis plan (SAP) for TA-301 stated that "If multiple active dose groups are significantly better than placebo, then those Avanafil dose groups will be compared". But the Applicant did not pre-specify how these pair-wise comparisons between Avanafil doses would be conducted in the SAP.

2. The Applicant intended to claim that [redacted] (b) (4) but in the reviewer's opinion this claim cannot be supported by the data in the current submission.

With regards to the first issue, the reviewer applied Hochberg procedure on each co-primary endpoint for multiplicity control of overall type I error for pair-wise comparisons within Avanafil doses in study TA-301. Similar to the comparison with placebo, to claim that one Avanafil dose is more effective than another dose, this dose has to achieve statistical significance on all three primary endpoints over the other dose.

For the second issue, the reviewer found that the current submission didn't support such a claim because of the following reasons:

- [redacted] (b) (4)

The data from the two phase 3 studies demonstrated that all three Avanafil doses (50 mg, 100 mg and 200 mg) have statistically significant improvement in the three pre-specified co-primary efficacy endpoints compared with placebo. The treatment effects of Avanafil 100 mg and 200 mg are statistically significantly more effective than Avanafil 50 mg on all three co-primary endpoints. Although in both studies, Avanafil 200 mg is not more effective than Avanafil 100 mg on any co-primary endpoint, its numerical benefit was observed, especially in diabetic subjects.

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

2 INTRODUCTION

2.1 Overview

The Applicant, VIVUS, INC. seeks approval of Avanafil (50 mg, 100 mg and 200 mg) for the treatment of male erectile dysfunction (ED).

According to the Applicant, erectile dysfunction is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance. Currently, first-line therapy for erectile dysfunction consists of oral treatment with a phosphodiesterase 5 (PDE5) inhibitor, which increases penile blood flow and erection in response to sexual stimulation. The tested drug, Avanafil, is a potent and selective inhibitor of the cGMP-specific PDE5 intended for the treatment of erectile dysfunction. Avanafil is absorbed following oral administration. Sexual stimulation is required for a response to treatment.

The statistical review for this NDA is based on the two double-blind phase 3 studies, TA-301 and TA-302, which are briefly summarized in Table 1. Study TA-301 was conducted in the general ED population, and study TA-302 was in diabetic male subjects. During the development of Avanafil, the protocol for study TA-301 was submitted to FDA for special protocol assessment (SPA) on December 20, 2006 and a regulatory letter with comments from the Agency was conveyed to the Applicant on February 1, 2007. No agreement was reached by the Agency.

Table 1: Brief summary of Phase 3 clinical studies for Avanafil

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
TA-301	Phase III Randomized, Double-Blind, Placebo-Controlled	4-week run-in period 12-week treatment	Randomized: Avanafil 50 mg: 161 Avanafil 100 mg:161 Avanafil 200 mg:162 Placebo:162	≥18 yrs old males with history of mild to severe ED of at least 6 months duration.
TA-302	Phase III Randomized, Double-Blind, Placebo-Controlled	4-week run-in period 12-week treatment	Randomized: Avanafil 100 mg:129 Avanafil 200 mg:131 Placebo:130	≥18 yrs old diabetic males with history of mild to severe ED of at least 6 months duration.

Source: Statistical reviewer's summary.

2.2 Data Sources

The study reports, data and additional information were submitted electronically. These items are located in the Electronic Document Room at \\Cdsesub1\evsprod\NDA202276 under submission dates 06/29/2011.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Applicant submitted both the tabulation data and analysis data for studies TA-301 and TA-302. Data sets were complete and documented. Specific statistical SAS programs were submitted upon reviewer's request.

All statistical analyses were carried out following the pre-specified statistical analysis plan, EXCEPT the analysis of efficacy by dose timing, which was discussed in details in section 3.2.4.2.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Both studies TA-301 and TA-302 were randomized, double-blind, placebo-controlled studies which consisted of a 4-week run-in period and a 12-week treatment period. Each study contained 5 clinical visits: a screening visit; a randomization visit at the end of run-in period; and 3 follow-up visits during which the efficacy and safety of the study medication were examined over the course of a 12-week treatment period.

Both studies enrolled adult male subjects with mild to severe erectile dysfunction who were in a monogamous heterosexual relationship. Subjects with erectile dysfunction caused by spinal cord injury or radical prostatectomy were excluded. In study TA-301, subjects with diabetes were excluded as well. In study TA-302, the enrolled subjects had type 1 or type 2 diabetes.

At the screening visit, initial eligible subjects entered a 4-week, non-treatment run-in period. Subjects were instructed to record information on each of their attempts at sexual intercourse. At the end of run-in period, subjects were eligible for randomization to treatment period if they met the following criteria:

- documented at least 4 attempts at sexual intercourse during the run-in period;
- failed to maintain an erection of sufficient duration to have successful intercourse (as documented in the subject diary during the run-in period) for at least 50% of their attempts;
- had an IIEF erectile function domain score of 5 to 25, inclusive.

Randomization was stratified by disease severity as determined by IIEF erectile function domain scores (mild = IIEF score of 17 to 25; moderate = IIEF score of 11 to 16; severe = IIEF score ≤10). In study TA-301, eligible subjects were randomized in a 1:1:1:1 ratio to placebo, Avanafil 50 mg, Avanafil 100 mg, or Avanafil 200 mg. In study TA-302, eligible subjects were randomized in a 1:1:1 ratio to placebo, Avanafil 100 mg, or Avanafil 200 mg.

During the treatment period, subjects were to take one dose of study drug approximately 30 minutes prior to the initiation of sexual activity. Subjects could take up to two doses of study drug per 24-hour period provided that the doses were separated by at least 12 hours. Subjects were to make at least 4 attempts at sexual activity per month.

3.2.1.2 Primary Efficacy Endpoints

Subjects were instructed to complete a diary entry for each attempt of sexual activity during the treatment period, which included the following 7 items:

1. date and time of study drug administration;
2. date and time of sexual activity initiation;
3. were you able to achieve some erection (some enlargement of the penis)? (yes or no);
4. were you able to insert your penis into your partner's vagina? (yes or no) (Sexual Encounter Profile [SEP] question 2);
5. did your erection last long enough for you to have successful intercourse? (yes or no) (SEP3);
6. were you satisfied with your erection? (yes or no); and
7. were you satisfied overall with your sexual experience? (yes or no)

The IIEF questionnaire was completed by subjects at each study visit.

The primary efficacy variables, based on the diary questions (4 and 5) and IIEF erectile function (EF) domain score, were defined as follows:

- change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to maintain an erection of sufficient duration to have successful intercourse (subject diary question 5, also referred to as SEP3);
- change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to insert his penis into his partner's vagina (subject diary question 4, also referred to as SEP2);
- change in the IIEF EF domain score from baseline to end of the 12-week treatment period.

Each co-primary efficacy variable was analyzed by an ANCOVA model with treatment and baseline erectile dysfunction severity category as factors and baseline value as the covariate. Table 2 describes the sequential testing procedure which was applied to the co-primary efficacy variables to adjust for multiplicity in studies TA-301 and TA-302. The effectiveness can be claimed for a specific dose only if it achieves statistical significance on each of the co-primary endpoints. Hence in the step-down procedure, if a higher dose fails on one co-primary endpoint, no further testing will proceed on lower dose(s) on any endpoint.

Table 2: Step-down Procedures for Testing Efficacy Used in Studies TA-301 and TA-302

Study	Order of Step-down Procedure for Testing Efficacy (All 3 co-primary endpoints must win within a dose group to proceed)	α-level for comparison
TA-301	1. Test 200 mg group vs. placebo 2. If 200 mg vs. placebo is significant, then test 100 mg group vs. placebo 3. If 100 mg vs. placebo is significant, then test 50 mg group vs. placebo 4. If multiple active dose groups are significantly better than placebo, then those Avanafil dose groups will be compared	0.05 0.05 0.05
TA-302	1. Test 200 mg group vs. placebo 2. If 200 mg vs. placebo is significant, then test 100 mg group vs. placebo 3. If both active treatments are significantly better than placebo, then the two Avanafil dose groups will be compared	0.05 0.05

Source: Statistical reviewer's summary based on the statistical analysis plans for studies TA-301 and TA-302.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Patient Disposition

The disposition of study subjects for TA-301 and TA-302 are summarized by treatment groups in Table 3. In study TA-301, a total of 646 subjects were randomized to one of the four treatment groups and the overall study discontinuation rate is 14.9%, ranging from 12.4% to 18.6% across the treatment groups. In study TA-302, a total of 390 subjects were randomized to three treatments and the overall study discontinuation rate is 14.6%, ranging from 13.0% to 15.4% across the treatment groups. For both studies, the most common reasons for study discontinuation were protocol non-compliance (including subjects who withdrew consent), loss to follow-up and adverse events.

Table 3: Summary of subject disposition for studies TA-301 and 302

	Placebo n (%)	Avanafil 50 mg n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Study TA-301					
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	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)
Study TA-302					
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	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 restricted medication	1 (0.8)		1 (0.8)	0 (0.0)	2 (0.5)

Source: Table 4 in Applicant's TA-301 study report and Table 4 in Applicant's TA-302 study report.

For statistical analyses, the Applicant pre-defined the following populations in both studies

- Safety Population - all subjects who took at least one dose of study drug and had safety data available;
- ITT Population - all subjects who were randomized, took at least one dose of study drug (as reported in the subject diary), and had at least one post-dose efficacy assessment;
- Evaluable Population - as all subjects in the ITT Population who reported using at least 6 doses of study drug during the treatment period and had at least 4 attempts at sexual intercourse during the non-treatment run-in period.

The numbers of subjects in each defined analysis populations were presented in Table 4. A total of 622 out of 646 (96.3%) subjects were included in ITT population in study TA-301, and 379 out of 390 (97.2%) subjects were included in ITT population in study TA-302.

Table 4: Summary of analysis populations in studies TA-301 and TA-302

Analysis Population	Placebo n (%)	Avanafil 50 mg n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Study TA-301 (N)	162 (100.0)	161 (100.0)	161 (100.0)	162 (100.0)	646 (100.0)
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)
Study TA-302 (N)	130 (100.0)		129 (100.0)	131 (100.0)	390 (100.0)
Safety Population	130 (100.0)		127 (98.4)	131 (100.0)	388 (99.5)
Intent-to-Treat Population	127 (97.7)		126 (97.7)	126 (96.2)	379 (97.2)
Evaluable Population	121 (93.1)		119 (92.2)	122 (93.1)	362 (92.8)

Source: Table 4 in the Applicant's study TA-301 report/Table 4 in the Applicant's study TA-302 report.
The denominators are the numbers of randomized subjects (N).

3.2.2.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of the treatment groups are summarized in the Appendix (Table 10 and Table 11) for study TA-301 and TA-302 respectively. In both studies, more than 80% of the subjects were white (85.6% for TA-301; 80.5% for TA-302). The mean age of subjects was 55.7 years in study TA-301 and 58.0 years in TA-302. At baseline, mean duration of erectile dysfunction was 77.4 months in TA-301 and 72.3 months in TA-302. In TA-302, 89.5% of subjects had type 2 diabetes and 10.5% of subjects had type 1 diabetes. The mean duration of diabetes was 11.3 years.

3.2.3 Statistical Methodologies

3.2.3.1 Analysis of Primary Efficacy Endpoints

For both studies, the Applicant analyzed each co-primary efficacy variable by an ANCOVA model with treatment and baseline erectile dysfunction severity category as factors and baseline value as the covariate. Least-squares (LS) means, corresponding standard errors, and p-values for the change in each primary efficacy variable were presented by treatment group. For each treatment comparison of interest, the difference in LS means, corresponding standard error, two-sided 95% confidence interval, and two-sided p-value were derived from the ANCOVA model.

All three co-primary endpoints must be significant at the $p < 0.05$ level for treatment at a dose level to be considered effective. A step-down, multiple-comparison procedure was used to compare the efficacy of each Avanafil dose group with placebo as described in section 3.2.1.

3.2.3.2 Analysis of Efficacy by Dose Timing

In addition to the co-primary efficacy endpoints, the Applicant also pre-specified descriptive analyses of the diary question responses by the time between dose administration and sexual attempts, which was categorized in the SAP as follows: less than or equal 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; and greater than 120 minutes.

The counts and percentage of successful or satisfied responses were presented by treatment group for each time interval.

3.2.3.3 Missing Data Handling

In the analysis of co-primary endpoints derived from the subject diaries, only the observed data were employed. For the co-primary endpoint based on IIEF data, the last observation carried forward (LOCF) algorithm was used. When needed for calculation, partial dates were handled by using the first for missing day and January for missing month.

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Endpoints

The Applicant's analysis results on the co-primary efficacy endpoints are summarized in Table 5 and Table 6. In studies TA-301 and TA-302, all Avanafil doses demonstrated statistically significant improvement on all three co-primary endpoints compared with placebo using the pre-specified hierarchal testing procedure.

In study TA-301, relative to placebo, the treatment effect of Avanafil 50 mg, 100 mg and 200 mg was 13.8%, 29.3% and 30.2% on the change in percentage of sexual attempts having successful intercourse (SEP3) respectively; 11.1%, 20.1% and 22.7% on the change in percentage of sexual attempts having successful vaginal penetration (SEP2); 2.6, 5.5 and 6.7 on the change in IIEF EF domain score. In study TA-302, relative to placebo, the treatment effect of Avanafil 100 mg and 200 mg was 15.6% and 16.4% in change in percentage of sexual attempts having successful intercourse respectively; 9.0% and 11.7% in the change in percentage of sexual attempts having successful vaginal penetration; 2.9 and 4.1 on the change in IIEF EF domain score. Detailed analyses results are presented in Table 12 to Table 17 to in Appendix.

Table 5: Mean Change in the Primary Efficacy Variables from Baseline to the End of Treatment Period - Study TA-301 Intent-to-Treat Population (LOCF)

	Placebo (N=155)	Avanafil 50 mg (N=154)	Avanafil 100 mg (N=157)	Avanafil 200 mg (N=156)
IIEF EF Domain Score				
Endpoint	15.3	18.1	20.9	22.2
Change from baseline*	2.9	5.4	8.3	9.5
Difference vs. placebo (p-value)	-	2.6 (0.0014)	5.5 (<0.0001)	6.7 (<0.0001)
Difference vs. Avanafil 50 mg (p-value)	-	-	2.9 (0.0003)	4.1 (<0.0001)
Difference vs. Avanafil 100 mg (p-value)			-	1.2 (0.1366)
Vaginal Penetration (SEP2)				
Endpoint	53.8%	64.3%	73.9%	77.3%
Change from baseline*	7.1%	18.2%	27.2%	29.8%
Difference vs. placebo (p-value)	-	11.1%(0.0009)	20.1%(<0.0001)	22.7%(<0.0001)
Difference vs. Avanafil 50 mg (p-value)	-	-	9.0% (0.0064)	11.7% (0.0004)
Difference vs. Avanafil 100 mg (p-value)			-	2.6% (0.4221)
Successful Intercourse (SEP3)				
Endpoint	27.0%	41.3%	57.1%	57.0%
Change from baseline*	14.1%	27.8%	43.4%	44.2%
Difference vs. placebo (p-value)	-	13.8% (0.0002)	29.3%(<0.0001)	30.2%(<0.0001)
Difference vs. Avanafil 50 mg (p-value)	-	-	15.6%(<0.0001)	16.4%(<0.0001)
Difference vs. Avanafil 100 mg (p-value)			-	0.8% (0.8198)

* Least-square estimate from ANCOVA model.
Source: Table 9-11, page 52-54 TA-301 study report.

Table 6: Mean Change in the Primary Efficacy Variables from Baseline to the End of Treatment Period - Study TA-302 Intent-to-Treat Population (LOCF)

	Placebo (N=127)	Avanafil 100 mg (N=126)	Avanafil 200 mg (N=126)
IIEF EF Domain Score			
Endpoint	13.2	15.8	17.3
Change from baseline*	1.8	4.5	5.4
Difference vs. placebo (p-value)	-	2.8 (0.0017)	3.6 (<0.0001)
Difference vs. Avanafil 100 mg (p-value)	-	-	0.8 (0.3387)
Vaginal Penetration (SEP2)			
Endpoint	42.0%	54.0%	63.5%
Change from baseline*	7.5%	21.5%	25.9%
Difference vs. placebo (p-value)		14.0% (0.0004)	18.4% (<0.0001)
Difference vs. Avanafil 100 mg (p-value)	-	-	4.4% (0.2719)
Successful Intercourse (SEP3)			
Endpoint	20.5%	34.4%	40.0%
Change from baseline*	13.6%	28.7%	34.0%
Difference vs. placebo (p-value)	-	15.2% (<0.0001)	20.4% (<0.0001)
Difference vs. Avanafil 100 mg (p-value)	-	-	5.3% (0.1724)

* Least-square estimate from ANCOVA model.
Source: Table 9-11, page 52-54 TA-302 study report.

For the primary efficacy endpoints, the reviewer is able to replicate the Applicant's results shown in Table 5, Table 6 and Table 12 to Table 17 in Appendix.

Reviewer's comments:

The results in Table 5 showed that in study TA-301 all three Avanafil doses are statistically significantly better than placebo with regards to primary efficacy endpoints. The Applicant's multiplicity control approach stated that "if multiple active dose groups are significantly better than placebo, then those Avanafil dose groups will be compared" in study TA-301 without pre-specifying how these comparisons would be conducted in the SAP. With regards of this issue, the reviewer used Hochberg procedure on each co-primary endpoint to compare three Avanafil doses in TA-301. To claim that one Avanafil dose is statistically different from another dose, it has to achieve statistical significance on all three co-primary endpoints vs. the other.

Using Hochberg procedure, this review concluded that in study TA-301, Avanafil 100 mg and 200 mg are statistically significantly better than 50 mg and they are not different from each other. In both studies, numerical benefit is seen in Avanafil 200 mg over 100 mg, especially in the diabetic subjects.

3.2.4.2 Efficacy by Dose Timing

Applicant's analysis results

The Applicant provided descriptive analysis in support of their claim that (b) (4) The descriptive statistics of the responses to subject diary questions 3 to 7 according to time between dose and attempt for all diaries during the treatment period were presented in the study reports respectively. In the Applicant's study reports, instead of using pre-defined categories as in section 3.2.3.2, time between dose administration and sexual attempts were re-categorized 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 7 is shown as an example of the Applicant's analysis results.

Table 7: Summary of Attempts in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse by Time Interval (SEP3) – Study TA-301 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.

(b) (4)

Reviewer's Analysis results

To evaluate the validity of the Applicant's analysis results as evidence to support the claim, the reviewer first checked the size of the data for the time between dose administration and sexual attempts by intervals. Table 8 shows that more than 80% of the study subjects had sexual attempts within 15 to 30 minutes after the dose administration in studies TA-301 and TA-302. But only about 20% - 30% of the study subjects had sexual attempts within 15 to 25 minutes among each treatment group. Table 9 shows that among all the sexual attempts occurred during 15 to 30 minutes after the dose administration, about 10% attempts occurred within 15 to 25 minutes after the dose administration.

Also in both studies, about 20% - 30% of the study subjects had sexual attempts after 120 minutes of the dose administration and the total number of sexual attempts after 120 minutes was ranged from 79 to 155 across all treatment groups in two studies.

(b) (4)

Table 8: Number of subjects who had sexual attempts by time intervals – ITT population

Time Interval From Dose to Attempt	Placebo	Avanafil 50 mg	Avanafil 100 mg	Avanafil 200 mg
TA-301 (N)	155(100%)	154(100%)	157(100%)	156(100%)
>15 minutes and ≤30 minutes	129(83.2%)	127(82.5%)	135(86.0%)	133(85.3%)
>15 minutes and ≤25 minutes	38 (24.5%)	38(24.7%)	49(31.2%)	51 (32.7%)
>25 minutes and ≤30 minutes	120(77.4%)	123(79.9%)	130(82.8%)	126(80.8%)
>120 minutes	33(21.3%)	36(23.4%)	54(34.4%)	44(28.2%)
>120 minutes and <=360 minutes	32(20.6%)	30(19.5%)	50(31.8%)	41(26.3%)
>360 minutes	6(3.9%)	12(7.8%)	11(7.0%)	13(8.3%)
TA-302 (N)	127(100%)		126(100%)	126(100%)
>15 minutes and ≤30 minutes	107(84.3%)		107(84.9%)	110(87.3%)
>15 minutes and ≤25 minutes	35(27.6%)		30(23.8%	31(24.6%)
>25 minutes and ≤30 minutes	103(81.1%)		105(83.3%)	106(84.1%)
>120 minutes	28(22.0%)		24(19.0%)	37(29.4%)
>120 minutes and <=360 minutes	26(20.5%)		20(15.9%)	33(26.2%)
>360 minutes	7(5.5%)		7(5.6%)	16(12.7%)

Source: Statistical reviewer's calculation.
N is the number of subjects in ITT population

Table 9: Number of sexual attempts by time intervals – ITT population

Time Interval From Dose to Attempt	Placebo	Avanafil 50 mg	Avanafil 100 mg	Avanafil 200 mg
TA-301				
>15 minutes and ≤30 minutes	973(100%)	1014(100%)	894(100%)	1071(100%)
>15 minutes and ≤25 minutes	87 (8.9%)	100(9.9%)	163(18.2%)	170(15.9%)
>25 minutes and ≤30 minutes	886(91.1%)	914(90.1%)	845(81.8%)	901(84.1%)
>120 minutes	93(100%)	128(100%)	142(100%)	135(100%)
>120 minutes and <=360 minutes	81(87.1%)	106(82.8%)	119(83.8%)	123(91.1%)
>360 minutes	12(12.9%)	22(17.2%)	23(16.2%)	12(8.9%)
TA-302				
>15 minutes and ≤30 minutes	719(100%)		749(100%)	797(100%)
>15 minutes and ≤25 minutes	119(16.6%)		67(8.9%)	95(11.9%)
>25 minutes and ≤30 minutes	600(63.4%)		682(91.1%)	702(88.1%)
>120 minutes	96(100%)		79(100%)	155(100%)
>120 minutes and <=360 minutes	75(78.1%)		67(84.8%)	124(80.0%)
>360 minutes	21(21.9%)		12(15.2%)	31(20.0%)

Source: Reviewer's analysis results

Reviewer's comments

In addition to the issues related to findings based on limited data, it is the opinion of this reviewer that the Applicant's claim (b) (4)

(1) (b) (4)

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(2) (b) (4)

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy of Avanafil was also explored by subgroups defined by age (<50 years, ≥50 years and <65 years, and ≥65 years), race (White and non-White), baseline erectile dysfunction severity (mild, moderate, and severe), and duration of erectile dysfunction (<24 months, ≥24 months and <60 months, and ≥60 months).

In both studies, analyses of each co-primary efficacy endpoint by subgroups were performed using the same ANCOVA model described previously in section 3.2.3.1 with additional terms for subgroup and treatment by subgroup interaction as appropriate.

4.1 Gender, Race, Age, and Geographic Region

Both phase 3 studies were conducted in the U.S. and enrolled male subjects only; therefore, analysis by gender and geographical region was not performed.

The efficacy results by race groups are shown in Table 18 to Table 23. In study TA-301, the treatment effect relative to placebo was observed for each Avanafil dose in white subjects and non-white subjects. And the treatment effect of Avanafil doses was greater in non-white subjects compared to white subjects. In study TA-302, the treatment by race group interaction for each co-primary endpoint was statistically significant at the 0.05 level. The treatment effect was only seen in the white subjects. Minimal or no treatment effect was seen for each Avanafil dose in non-white subjects. Due to the small sample size of non-white subjects, no definitive conclusion can be drawn.

The efficacy results of co-primary endpoints by age subgroups are presented in
Table 24 to Table 29. No treatment by age subgroup interaction was found statistically significant.

4.2 Other Special/Subgroup Populations

In both studies, analyses of each co-primary efficacy endpoint were also performed for subgroups of subjects based baseline erectile dysfunction severity (mild, moderate, and severe), and duration of erectile dysfunction (<24 months, ≥24 months and <60 months, and ≥60 months).

The results by ED severity are presented in Table 30 to Table 35. No treatment by ED severity subgroup interaction is statistically significant in the analysis of each co-primary efficacy endpoint. Table 36 to Table 41 presented the efficacy results by ED duration subgroups. In TA-301, the treatment effect of Avanafil 50 mg was much larger compared to Avanafil 100 mg and 200 mg in subjects who had ED <24 months, but in subjects who had ED >= 24 months, the treatment effect of Avanafil 50 mg is smaller compared to Avanafil 100 mg and 200 mg.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Applicant submitted two double-blind phase 3 studies (TA-301 and TA-302) to demonstrate superiority of Avanafil compared to placebo. In study TA-301, three Avanafil doses (50 mg, 100 mg and 200 mg) were administered in general ED population while in study T-302, two doses (100 mg and 200mg) were administered in diabetic subjects. Both studies were designed to demonstrate efficacy with respect to three co-primary endpoints.

In study TA-301, under a step-down, multiple comparison procedure, all three Avanafil doses are significantly better than placebo on all co-primary endpoints. The Applicant's statistical analysis plan for TA-301 stated that "If multiple active dose groups are significantly better than placebo, then those Avanafil dose groups will be compared". However, the applicant did not pre-specify how these pair-wise comparisons within Avanafil doses would be conducted. To address this issue, the reviewer applied Hochberg procedure on each co-primary endpoint for multiplicity control of overall type I error for pair-wise comparisons within Avanafil doses in study TA-301. Similar to the comparison with placebo, one Avanafil dose can be claimed more effective than another dose, unless this dose achieves statistical significance on all three primary endpoints over the other dose.

In this NDA submission, the Applicant intended to claim (b) (4) but the reviewer found that the current submission didn't support such a claim because of the following reasons:

- (b) (4)

5.2 Conclusions and Recommendations

The purpose of this review was to evaluate the efficacy data in support of Avanafil in the treatment of erectile dysfunction in men. Based on reviewer's analyses, the results support the efficacy of Avanafil 50 mg, 100 mg and 200 mg in the improvement of all three protocol specified co-primary endpoints. The treatment effects of Avanafil 100 mg and 200 mg on all three co-primary endpoints are statistically significantly better than Avanafil 50 mg. Although Avanafil 200 mg is not statistically more effective than Avanafil 100 mg, numerical improvement was seen in diabetic subjects.

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

APPENDICES

Demographics and Baseline Characteristics

Table 10 Patient demographics and baseline characteristics – Study TA-301 Randomized population

	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 and <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 months and <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)

Baseline was defined as the last measurement prior to the first dose of study drug.
1. Age and duration of erectile dysfunction were calculated according to the date of informed consent.
SD = standard deviation.
Source: Post-text Table 14.1.4.4

Source: Table 5 in the Applicant's TA-301 study report.

Table 11: Patient demographics and baseline characteristics – Study TA-302 Randomized population

	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)

Baseline was defined as the last measurement prior to the first dose of study drug.
1. Age, duration of erectile dysfunction, and duration of diabetes were calculated at informed consent.
SD = standard deviation.
Source: Post-text Table 14.1.4.4

Source: Table 5 in the Applicant's TA-302 study report.

Applicant's efficacy results

Table 12: Change in the Percentage of Sexual Attempts between the Run-in Period and the Treatment Period in Which the Subject Was Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) – Study TA-301 Intent-to-Treat 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
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
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				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

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 and erectile dysfunction severity 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; vs. = versus.
Source: Post-text Table 14.2.1.1.1

Source: Table 9 in the Applicant's TA-301 study report.

Table 13: Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which the Subject Was Able to Insert His Penis Into His Partner's Vagina (SEP2) – Study TA-301 Intent-to-Treat 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
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
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				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

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 and erectile dysfunction severity 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; vs. = versus.
Source: Post-text Table 14.2.1.2.1

Source: Table 10 in the Applicant's TA-301 study report.

Table 14: Change in IIEF Erectile Function Domain Score from Baseline to End of Treatment – Study TA-301 Intent-to-Treat 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
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
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				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

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.

CI = confidence interval; IIEF = International Index of Erectile Function; LS = least squares; SD = standard deviation; SE = standard error; Tmt = treatment; vs. = versus.
Source: Post-text Table 14.2.1.3.1

Source: Table 11 in the Applicant's TA-301 study report.

Table 15 : Change in the Percentage of Sexual Attempts between the Run-in Period and the Treatment Period in Which the Subject Was Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) – Study TA-302 Intent-to-Treat 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
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
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				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.
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.

CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; Tmt = treatment; vs. = versus.
Source: Post-text Table 14.2.1.1.1

Source: Table 9 in the Applicant's TA-302 study report.

Table 16: Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which the Subject Was able to Insert His Penis Into His Partner's Vagina (SEP2) – Study TA-302 Intent-to-Treat 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
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 and erectile dysfunction severity 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; vs. = versus.
Source: Post-text Table 14.2.1.2.1

Source: Table 10 in the Applicant's TA-302 study report.

Table 17: Change in IIEF Erectile Function Domain Score from Baseline to End of Treatment – Study TA-302 Intent-to-Treat 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
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 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.

CI = confidence interval; IIEF = International Index of Erectile Function; LS = least squares; SD = standard deviation; SE = standard error; Tmt = treatment; vs. = versus.
Source: Post-text Table 14.2.1.3.1

Source: Table 11 in the Applicant's TA-302 study report.

Subgroup analysis results

Table 18: Change between run-in period and treatment period in SEP3 (%) by race group – Study TA-301 Intent-to-treat population

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
White						
Placebo	126	13.0 (17.84)	27.6 (31.76)	14.6 (27.66)		
Avanafil 50 mg	129	12.9 (18.62)	39.6 (35.20)	26.8 (32.13)	12.3 (4.02)	0.0024
Avanafil 100 mg	133	14.0 (18.89)	55.7 (35.74)	41.8 (33.25)	27.2 (3.99)	<0.0001
Avanafil 200 mg	144	12.4 (18.52)	57.1 (37.92)	44.7 (35.60)	29.5 (3.91)	<0.0001
Non-White						
Placebo	29	11.0 (17.96)	24.2 (30.23)	13.4 (27.97)		
Avanafil 50 mg	25	16.7 (18.41)	49.7 (39.17)	22.1 (42.06)	20.9 (8.78)	0.0175
Avanafil 100 mg	24	13.4 (19.14)	64.3 (37.65)	50.9 (36.89)	40.5 (8.87)	<0.0001
Avanafil 200 mg	12	13.3 (19.34)	56.2 (37.63)	43.0 (38.01)	32.3 (11.01)	0.0034
P-value for treatment by race group interaction term: 0.5466						

Source: Statistical reviewer's analysis results

Table 19: Change between run-in period and treatment period in SEP3 (%) by race group – Study TA-302 Intent-to-treat population

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
White						
Placebo	102	9.1 (15.58)	17.7 (26.94)	8.6 (26.70)		
Avanafil 100 mg	109	8.9 (18.35)	36.8 (37.22)	27.9 (34.36)	19.6 (4.17)	<0.0001
Avanafil 200 mg	96	7.2 (14.35)	39.8 (37.25)	32.6 (33.63)	23.0 (4.30)	<0.0001
Non-White						
Placebo	25	13.4 (19.41)	31.9 (34.96)	18.5 (30.88)		
Avanafil 100 mg	17	3.7 (8.57)	18.8 (26.11)	15.1 (27.47)	-9.6 (9.60)	0.3201
Avanafil 200 mg	30	10.3 (16.65)	40.8 (33.86)	30.5 (31.14)	10.3 (8.21)	0.2122
P-value for treatment by race group interaction term: 0.0213						

Source: Statistical reviewer's analysis results

Table 20: Change between run-in period and treatment period in SEP2 (%) by race group – Study TA-301 Intent-to-treat population

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
White						
Placebo	126	46.0 (35.81)	54.3 (37.76)	8.3 (30.03)		
Avanafil 50 mg	129	41.4 (36.10)	61.2 (37.42)	19.9 (36.36)	8.9(3.65)	0.0154
Avanafil 100 mg	133	45.2 (38.55)	72.9 (32.19)	27.8 (35.00)	18.6(3.62)	<0.0001
Avanafil 200 mg	144	47.5 (38.72)	77.5 (31.55)	29.9 (34.94)	22.1(3.55)	<0.0001
Black						
Placebo	29	46.7 (39.11)	51.8 (38.99)	2.2 (39.99)		
Avanafil 50 mg	25	66.3 (33.21)	80.3 (32.20)	14.0 (30.97)	21.5(7.98)	0.0071
Avanafil 100 mg	24	54.5 (37.42)	78.9 (32.83)	24.5 (36.75)	27.0 (8.04)	0.0009
Avanafil 200 mg	12	57.1 (31.52)	74.9 (31.31)	17.8 (46.33)	21.2 (9.99)	0.0341
P-value for treatment by race group interaction term: 0.4208						

Source: Statistical reviewer's analysis results

Table 21: Change between run-in period and treatment period in SEP2 (%) by race group – Study TA-302 Intent-to-treat population

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
White						
Placebo	102	31.9 (36.10)	36.4 (38.69)	4.6 (30.85)		
Avanafil 100 mg	109	31.6 (34.29)	55.2 (39.76)	23.6 (36.53)	19.3(4.25)	<0.0001
Avanafil 200 mg	96	36.8 (37.29)	63.7 (39.00)	26.9 (32.62)	24.6(4.40)	<0.0001
Non-White						
Placebo	25	53.1 (34.34)	64.5 (34.12)	11.4 (32.47)		
Avanafil 100 mg	17	38.1 (41.25)	45.9 (37.14)	7.8 (39.53)	-13.0(9.78)	0.1854
Avanafil 200 mg	30	56.5 (35.40)	62.8 (38.22)	6.3 (38.22)	-4.0(8.37)	0.6345
P-value for treatment by race group interaction term: 0.0023						

Source: Statistical reviewer's analysis results

Table 22: Change between run-in period and treatment period in IIEF EF domain score (%) by race group – Study TA-301 Intent-to-treat population

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
White						
Placebo	123	12.4 (5.21)	15.5 (7.83)	3.1 (6.46)		
Avanafil 50 mg	127	12.3 (5.18)	17.7 (8.07)	5.4 (7.32)	2.2(0.89)	0.0116
Avanafil 100 mg	132	12.7 (5.41)	20.7 (7.97)	8.0 (7.74)	5.0(0.88)	<0.0001
Avanafil 200 mg	143	12.9 (5.08)	22.3 (7.78)	9.4 (7.01)	6.4(0.86)	<0.0001
Non-White						
Placebo	29	12.5 (4.79)	14.6 (7.72)	2.1 (6.10)		
Avanafil 50 mg	25	14.4 (5.01)	19.8 (7.15)	5.4 (8.73)	4.1(1.92)	0.0326
Avanafil 100 mg	24	12.1 (5.36)	22.1 (7.59)	10.0 (7.26)	8.0(1.94)	<0.0001
Avanafil 200 mg	12	11.4 (3.68)	21.2 (7.36)	8.0 (7.74)	7.4(2.40)	0.0021
P-value for treatment by race group interaction term: 0.5400						

Source: Statistical reviewer's analysis results

Table 23: Change between run-in period and treatment period in IIEF EF domain score (%) by race group – Study TA-302 Intent-to-treat population

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
White						
Placebo	100	10.9(5.04)	12.3(7.45)	1.4(6.29)		
Avanafil 100 mg	108	11.0(4.87)	16.2(8.65)	5.2(7.14)	3.9(0.95)	<0.0001
Avanafil 200 mg	95	11.7(5.11)	17.4(8.76)	5.7(7.80)	4.4(0.98)	<0.0001
Non-white						
Placebo	25	13.4(4.47)	16.8(7.82)	3.4(5.89)		
Avanafil 100 mg	17	12.5(4.02)	12.8(4.20)	0.4(4.17)	-3.6(2.15)	0.0951
Avanafil 200 mg	30	12.9(5.04)	17.1(8.43)	4.2(6.43)	0.6 (1.85)	0.7581
P-value for treatment by race group interaction term: 0.0060						

Source: Statistical reviewer's analysis results

Table 24: Change between run-in period and treatment period in SEP3 (%) by age group – Study TA-301 Intent-to-treat population

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

Table 25: Change between run-in period and treatment period in SEP3 (%) by age group – Study TA-302 Intent-to-treat population

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

Table 26: Change between run-in period and treatment period in SEP2 (%) by age group – Study TA-301 Intent-to-treat population

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

Table 27: Change between run-in period and treatment period in SEP2 (%) by age group – Study TA-302 Intent-to-treat population

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

Table 28: Change between run-in period and treatment period in IIEF EF domain score (%) by age group – Study TA-301 Intent-to-treat population

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

Table 29: Change between run-in period and treatment period in IIEF EF domain score (%) by age group – Study TA-302 Intent-to-treat population

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

Table 30: Change between run-in period and treatment period in SEP3 (%) by ED severity – Study TA-301 Intent-to-treat population

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

Table 31: Change between run-in period and treatment period in SEP3 (%) by ED severity – Study TA-302 Intent-to-treat population

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

Table 32: Change between run-in period and treatment period in SEP2 (%) by ED severity – Study TA-301 Intent-to-treat population

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

Table 33: Change between run-in period and treatment period in SEP2 (%) by ED severity – Study TA-302 Intent-to-treat population

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

Table 34: Change between run-in period and treatment period in IIEF EF domain score (%) by ED severity – Study TA-301 Intent-to-treat population

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

Table 35: Change between run-in period and treatment period in IIEF EF domain score (%) by ED severity – Study TA-302 Intent-to-treat population

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

Table 36: Change between run-in period and treatment period in SEP3 (%) by ED duration – Study TA-301 Intent-to-treat population

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

Table 37: Change between run-in period and treatment period in SEP3 (%) by ED duration – Study TA-302 Intent-to-treat population

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

Table 38: Change between run-in period and treatment period in SEP2 (%) by ED duration – Study TA-301 Intent-to-treat population

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

Table 39: Change between run-in period and treatment period in SEP2 (%) by ED duration – Study TA-302 Intent-to-treat population

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

Table 40: Change between run-in period and treatment period in IIEF EF domain score by ED duration – Study TA-301 Intent-to-treat population

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

Table 41: Change between run-in period and treatment period in IIEF EF domain score by ED duration – Study TA-302 Intent-to-treat population

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

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/s/

JIA GUO
03/22/2012

MAHBOOB SOBHAN
04/09/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 20-2276 **Applicant:** VIVUS INC **Stamp Date: Jun 29, 2011**

Drug Name: (b) (4) (AVANAFIL) **NDA/BLA Type: New**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	√			Subjects are male only
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		√		The analysis on primary endpoint based IIEF used LOCF imputation. All other efficacy analyses only use observed data.

File name: 5_Statistics Filing Checklist for a New NDA_202276

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

There is no review issue noted at this time.

Requests to the Applicant on 74-day letter:

1. To assess the sensitivity of missing data, the Applicant should analyze the observed data for the EFS of the IIEF questionnaire without LOCF imputation using ANCOVA model specified in the study protocol.

Jia Guo, Ph.D.	08/09/2011
Reviewing Statistician	Date
Mahboob Sobhan, Ph.D.	08/09/ 2011
Supervisor/Team Leader	Date

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/s/

JIA GUO
08/18/2011

MAHBOOB SOBHAN
08/26/2011