

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202276Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA 202276 sdn1-13; sdn16; sdn 29	Submission Date(s)	6/29/11; 8/10/11; 9/15/11; 9/21/11; 9/28/11; 9/30/11; 10/5/11; 10/20/11; 10/27/11; 11/3/11; 12/21/11; 4/25/12
Brand Name	Stendra	
Generic Name	Avanafil	
Reviewer	LaiMing Lee, PhD	
Acting Team Leader	Hyunjin Kim, PharmD, MS	
OCP Division	Division of Clinical Pharmacology 3	
OND Division	Division of Reproductive and Urologic Products	
Sponsor	Vivus, Inc.	
Relevant IND	051235	
Submission Type; Code	Original; 1S	
Formulation; Strengths; Regimen	Immediate Release Oral tablet; 50 mg, 100 mg, 200 mg; 100 mg approximately 30 min before sexual activity on an as needed basis, no more than once a day	
Proposed Indication	Treatment of erectile dysfunction	

1 Executive Summary

The Clinical Pharmacology review of NDA 202276 (DARRTS, March 9, 2012) stated that NDA 202276 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement was reached on April 26, 2012 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 202276 acceptable.

13 Page(s) of Draft Labeling have been withheld in full as b4 (CCI/TS) immediately following this page

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

/s/

LAI M LEE
04/27/2012

HYUNJIN KIM
04/27/2012

REVIEW OF CLINICAL PHARMACOLOGY

NDA 202276 sdn1-13; sdn16	Submission Date(s)	6/29/11; 8/10/11; 9/15/11; 9/21/11; 9/28/11; 9/30/11; 10/5/11; 10/20/11; 10/27/11; 11/3/11; 12/21/11
Brand Name	Pending review	
Generic Name	Avanafil	
Reviewer	LaiMing Lee, Ph.D.	
Acting Team Leader	Hyunjin Kim, Pharm.D., M.S.	
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Individual Study Reviews

Study HP-01

Title: A Double-Blind, Ascending Single Oral Dose, Safety, Tolerability and Pharmacokinetic Study of TA-1790 (avanafil) in Healthy Male Volunteers

Objectives: The primary objective is to investigate the safety and tolerability of avanafil after a single oral administration of 12.5, 25, 50, 100, 200 400, 600, and 800 mg in healthy male subjects. The second objective is to assess the PK profile of avanafil and its metabolite in plasma and urine, and to preliminary assess the effect of food on its PK profiles.

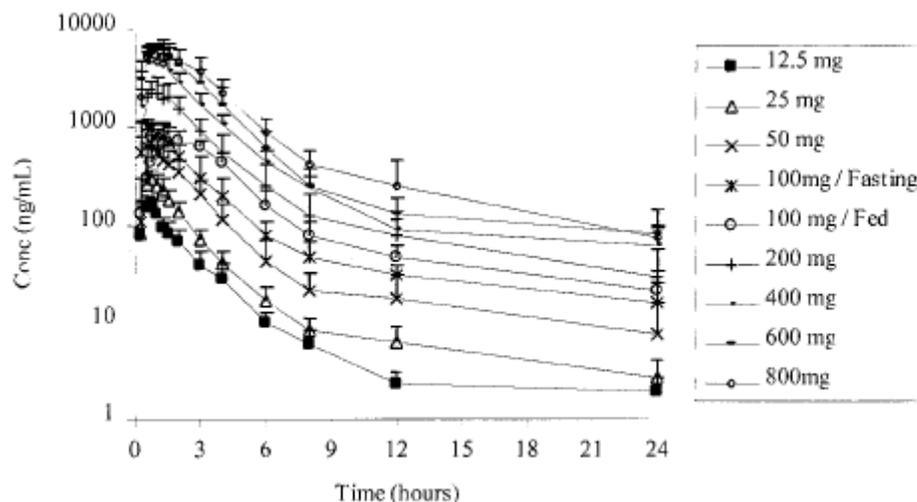
Methods: This study was a single center, randomized, double-blind, placebo-controlled, 8 single ascending doses in 8 parallel groups of healthy male subjects. Seven groups of subjects received a single dose under fasting conditions. The 100 mg group has two periods: first single dose of 100 mg under fasting conditions, followed a single dose of 100 mg after a high fat (high calorie) meal. There were 6 subjects per group. Formulation I was evaluated in this study.

Pharmacokinetic Sampling: Blood samples were collected for avanafil determination in plasma according to the following schedule: 0 (predose), 15, 30, 45, 60, 75 and 90 min, 2, 3, 4, 6, 8, 12, and 24 hrs post-dose. Urine samples were collected for avanafil determination according to the following schedule: 0 (predose), 0-3, 3-6, 6-12, and 12-24 hrs post-dose. Plasma and urine concentrations and its metabolite M2 were analyzed by (b) (4) using LC-MS/MS.

Results:

The median Tmax ranged from 0.63 to 1.25 hr. Mean half-life ($t_{1/2}$) ranged from 6.0 to 20 hrs and varied according the dose. AUC0-inf ranged from 381 to 24,457 ng.hr/mL after a dose of 12.5 to 800 mg and appeared to be dose proportional from 12.5 to 600 ng.hr/mL. Cmax ranged from 166 to 7249 $\mu\text{g}/\text{mL}$ after a dose of 12.5 to 800 mg and appeared dose proportional from 12.5 to 600 mg. Concomitant food intake decreased the Cmax of avanafil by 24%, increased AUC0-inf (~18% extrapolation from AUC0-t) of avanafil by 14%, and delayed Tmax by approximately 1 hr. Based on AUC0-t, the effect of food increased exposure by 24%.

The following is the mean (\pm SD) plasma concentration versus time profiles for avanafil after single oral administration of increasing doses of avanafil from 12.5 to 800 mg in healthy male volunteers (sponsor's figure 1)



The following table is a summary of geometric mean pharmacokinetic parameters of avanafil in plasma following a single dose of avanafil in healthy male subjects (sponsor's table 10).

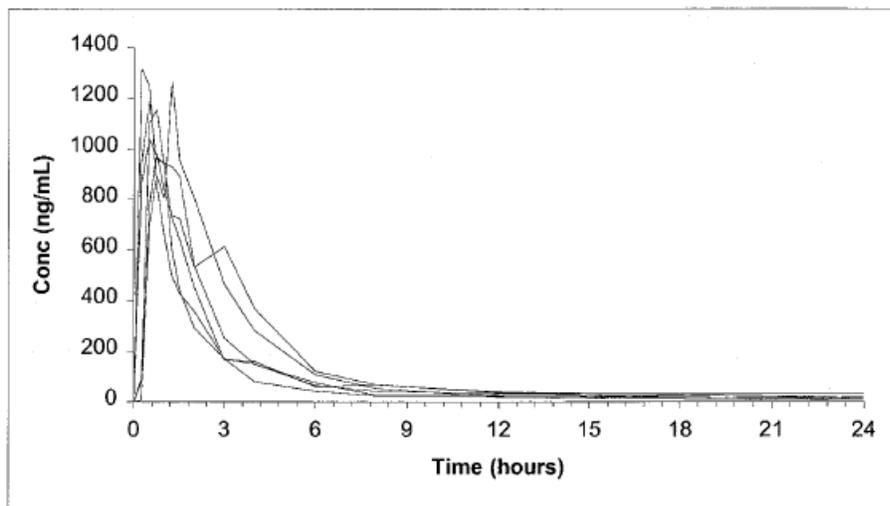
Dose (mg)		C_{max} (ng/mL)	t_{max}^* (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	Ae (μ g)	Clr (mL/min)
12.5	Mean	165.50	0.63	6.02	364.21	380.55	-	-
	SD	38.96	0.25-0.75	5.68	109.99	116.09	-	-
25	Mean	311.75	0.75	9.71	694.08	741.43	-	-
	SD	55.44	0.50-1.00	7.92	134.90	187.48	-	-
50	Mean	732.28	0.75	9.41	1736.39	1885.90	-	-
	SD	383.07	0.50-1.50	5.06	736.06	974.58	-	-
100 (Fasted)	Mean	1156.73	0.63	16.69	2909.93	3451.09	6.0	0.037
	SD	128.24	0.25-1.25	16.51	480.60	844.74	4.7	0.035
200	Mean	2593.67	0.88	8.91	7688.58	8165.07	21.0	0.039
	SD	727.81	0.50-1.00	4.60	2606.78	3104.47	19.2	0.034
400	Mean	5993.67	0.75	19.84	14868.97	17363.12	33.1	0.037
	SD	1380.01	0.75-1.00	28.04	2924.20	6510.88	29.4	0.031
600	Mean	7248.50	0.75	11.78	20715.60	22388.05	62.8	0.051
	SD	987.87	0.50-1.25	5.34	6115.30	6695.51	40.7	0.034
800	Mean	6301.67	1.25	8.29	23481.27	24456.62	67.6	0.046
	SD	1211.59	0.50-1.50	4.78	3940.42	3778.23	70.3	0.048

* median and range

The following table is a summary of geometric mean pharmacokinetic parameters of avanafil in plasma following a single dose of 100 mg avanafil in healthy male subjects under fasted and fed conditions (sponsor's table 12)

Dose (mg)		C_{max} (ng/mL)	t_{max}^* (h)	$t_{1/2}$ (h)	AUC_{0-1} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	Ae (μ g)	Clr (mL/min)
100 (Fasted)	Mean	1156.73	0.63	16.69	2909.93	3451.09	6.0	0.037
	SD	128.24	0.25-1.25	16.51	480.60	844.74	4.7	0.035
100 (Fed)	Mean	876.28	1.75	9.15	3632.10	3942.83	9.8	0.048
	SD	236.20	1.25-4.00	3.43	845.17	1016.58	8.5	0.048
ANOVA		NS	NS ⁽¹⁾	NS	P<0.05	NS	-	-
90% CI		0.56-0.97	-	-	1.10-1.39	0.90-1.45	-	-

The following figure is the plasma concentration versus time profile for avanafil after a single oral administration of 100 mg avanafil under fasted condition (sponsor's table 14.4.4)



The following figure is the plasma concentration versus time profile for avanafil after a single oral administration of 100 mg avanafil under fed condition (sponsor's table 14.4.5)

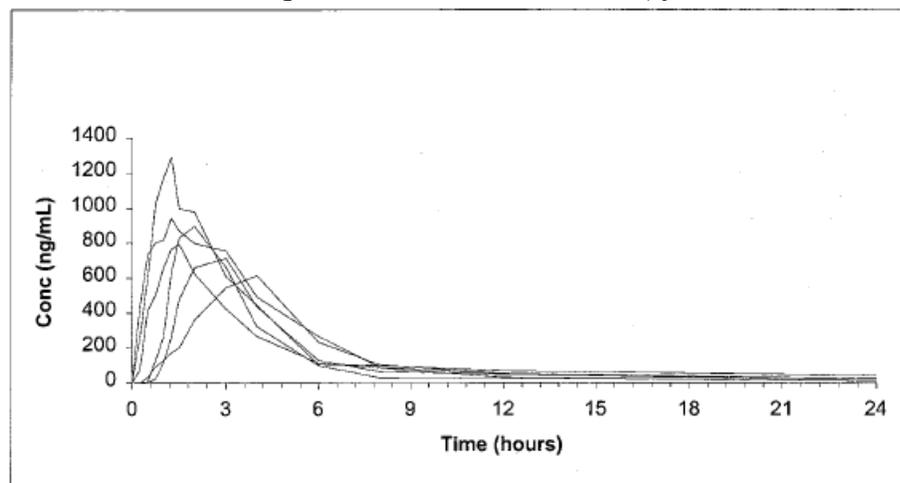


Table 17: Number of Adverse Events per Treatment by Preferred Term

System organ class	Preferred term	TA-1790 25 mg (Fasting) (N=6)		TA-1790 50 mg (Fasting) (N=6)		TA-1790 100 mg (Fasting) (N=7)		TA-1790 100 mg (Fed) (N=6)		TA-1790 200 mg (Fasting) (N=6)		TA-1790 400 mg (Fasting) (N=6)		TA-1790 600 mg (Fasting) (N=6)		TA-1790 800 mg (Fasting) (N=6)		TA-1790 TOTAL (N=65)	
		n	AE	n	AE	n	AE	n	AE	n	AE	n	AE	n	AE	n	AE	n	AE
		ALL CLASSES	ALL EVENTS	1	1	1	1	2	2	1	1	1	1	3	5	5	12	6	8
Nervous system disorders	ALL EVENTS	1	1			1	1	1	1	1	1	3	3	5	6	4	4	16	17
	Vasovagal attack	1	1															1	1
	Headache NOS					1	1	1	1	1	1	3	3	5	6	4	4	15	16
Infections and infestations	ALL EVENTS			1	1													1	1
	Bronchitis NOS			1	1													1	1
Vascular disorders	ALL EVENTS					1	1					1	1			2	2	4	4
	Postural hypotension					1	1					1	1			2	2	4	4
Gastrointestinal disorders	ALL EVENTS											1	1	3	4	2	2	6	7
	Nausea											1	1	3	4	2	2	6	7
General disorders and administration site conditions	ALL EVENTS													2	2			2	2
	Fatigue													2	2			2	2

n = Number of subjects
 AE = Number of treatment emergent adverse events
 N = Number of subjects per group

The Sponsor states the following:

- Concomitant food intake decreased the C_{max} of avanafil by 24% and increased AUC_{0-inf} of avanafil by 14%.
- Absorption of avanafil was rapid and plasma concentrations decline was biexponential with a terminal half-life ranging from 6 to 12 hrs, which was not statistically different across dose groups
- Concentrations of avanafil metabolite M2 were very low thus preventing any further analysis
- Maximum concentrations of avanafil increased proportionally with the dose between 12.5 and 600 mg
- Extent of avanafil absorption increased proportionally with the dose across the entire range of 12.5 to 800 mg dose tested.

Reviewer's Comment:

- Concomitant food intake decreased the C_{max} of avanafil by 24%, increased AUC_{0-inf} (~18% extrapolation from AUC_{0-t}) of avanafil by 14%, and delayed T_{max} by approximately 1 hr. Based on AUC_{0-t}, the effect of food increased exposure by 24%.
- The most common adverse event was headache and was not reported in the placebo group.
- Urinary excretion of avanafil were all very with the highest measurable amount of 170.3 µg in the 0-3 hr sample in subject #58 given 800 mg, representing 2.5 % of the administered dose. LLOQ in urine was 10 ng/mL and most urine samples were below the LLOQ.
- Metabolite M2 were below the LLOQ of 2.00 ng/mL.
- Noted in the PK profile, at doses of 50 mg and higher, return to baseline was not achieved by the last blood draw at 24 hrs post-dose.
- Estimation of terminal half-life was conducted with only 3 to 4 time points (6, 8, 12, and 24 hrs) after the initial elimination phase from 0-6 hrs and is therefore inaccurate estimation of the true terminal half-life.
- Additionally, subject #26 from the 100 mg dose group had an estimated half-life significantly longer than others at 49.4 hrs, while subject #48 from the 400 mg dose group had an estimated half-life of 76.9 hrs.
- Dose proportionality for C_{max}, AUC_{0-t}, and AUC_{0-inf} appeared to be linear for up to 600 mg. The sponsor claims a linear increase in AUC_{0-inf} for doses 12.5 to 800 mg; however, there was a small increase in exposure (2068 ng.hr/mL) going from 600 to 800 mg representing less than a linear increase from 600 to 800 mg as seen with the lower doses.

Study TA-02

Title: A Double-Blind, Randomized, Parallel Evaluation of the Pharmacokinetics and Safety of Single and Multiple Doses of TA-1790

Objectives: The objective of the study was to evaluate the PK effects of TA-1790 following single and multiple tablet dosing and to assess the safety and tolerance of multiple doses of TA-1790 (avanafil).

Methods: This was a randomized, double-blind, single- and multiple-doses, parallel design study. Subjects were randomly assigned to one of three treatment groups (A, B, or C) with the drug: placebo ratio of 12:4 per group. The study consisted of a single dose PK evaluation over a 72-hr period, followed by a multiple dose PK evaluation over a 17-day period. Formulation I was evaluated in this study.

The single dose PK evaluation consisted of subjects receiving a single dose of avanafil on Day 1. During Days 1-3, blood samples for avanafil PK were collected, physical exams and vital signs were collected. An ECG was performed immediately prior to dosing and 1, 2, 4, 8 and 24 hrs postdose to evaluate QT interval. Subjects were in the study clinic for the first 72 hrs (Days 1-3) and then were discharged on Day 4 with instructions to return in morning to begin the multiple dose PK portion of the study.

On Days 4-17, subjects returned to the study site each morning to receive their daily dose and was observed for 2 hrs postdose before being discharged. On the last QD dosing day, subjects returned to the clinic for 72 hrs (Days 17-20) of follow-up that consisted of blood collection, physical examination and vital signs, including ECG.

The following is a summary of scheduled events for the single and multiple dose study (sponsor's table 9.1:1)

A total of 48 male subjects were enrolled in the study with 46 subjects completing the study. Subject 6 was dropped from the study by the Investigator due to failure to return to Day 16 events. Subject 16 was dropped from the study by the Investigator due to a serious adverse event – pharyngolaryngeal pain. PK analysis were conducted on 36 subjects treated with avanafil (N=12 in each group). Of the enrolled subjects, the mean age was 41.2 yrs (range: 30-54 yrs), mean height was 69.2 in (range: 61.5-75.0 in), and mean weight was 178.9 lbs (range: 134-226 lbs). Of the 46 subjects who completed the study, 28 were Caucasian, 14 were Hispanic and 4 were Black.

Treatment A: avanafil 50 mg QD (1 x 50 mg tablet) or placebo
Treatment B: avanafil 100 mg QD (1x 100 mg tablet) or placebo
Treatment C: avanafil 200 mg QD (2 x 100 mg tablet) or placebo

Avanafil or placebo-matched tablets were given with 240 mL room temperature tap water.

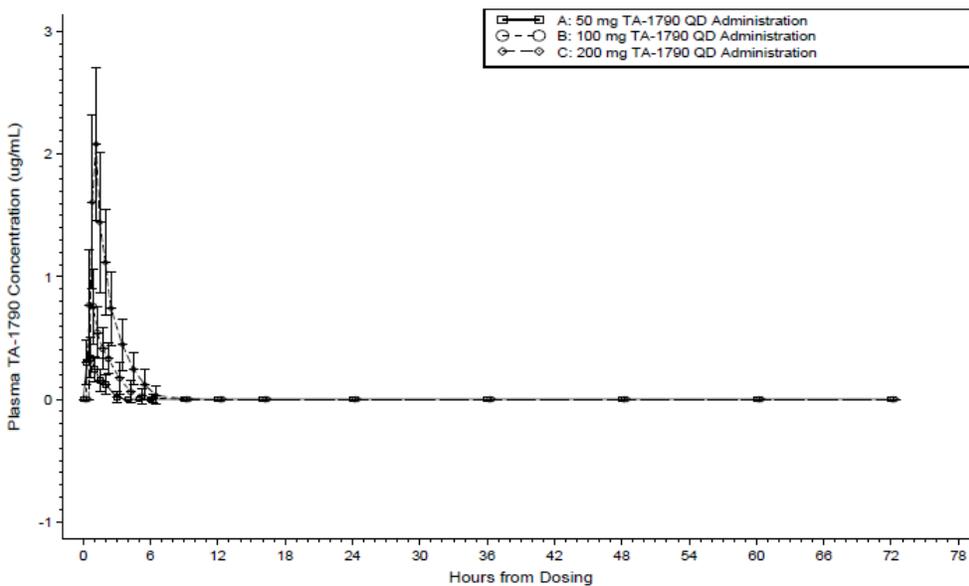
Pharmacokinetic Sampling: Blood samples (5 mL) for single dose PK were collected on Day 1 of the study according to the following schedule: (predose), 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 26, 48, 60, and 72 hrs. For trough concentrations on Days 10, 15, 16, and 17, blood samples were taken 216, 336, and 360 hrs post-Day 1 dose. For multiple dose PK, blood samples were collected for 72 hrs following the last (14th) QD dose according to the following schedule: 383.75, 384.33, 384.67, 385, 385.5, 386, 387, 388, 389, 390, 393, 396, 400, 408, 420, 432, 444, and 456 hrs post-Day 1 dose. All PK data were collected after 12 hrs of fasting.

Results: The selection of doses 50, 100 and 200 mg that were evaluated in this study was based both pre-clinical pharmacology studies conducted to assess the potency with which avanafil inhibits PDE5 enzyme, and on clinical trial results demonstrating the safety and PK of single doses of avanafil ranging from 12.5 to 800 mg in health male subjects.

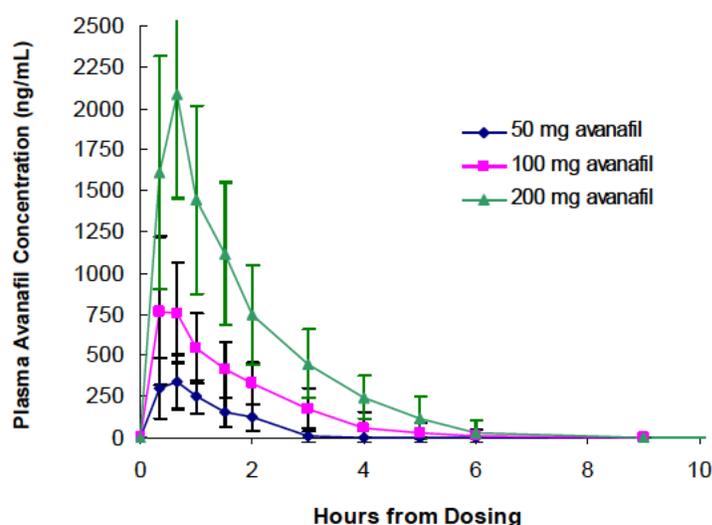
Single Dose PK:

In healthy male subjects given a single dose of avanafil (50, 100 or 200 mg), mean maximum avanafil concentrations (Tmax) were reached between 0.6 and 0.7 hr. Single dose half-life ($t_{1/2}$) ranged from 1.1 to 1.2 hrs. At the proposed dose of 100 mg, AUC_{0-t} and C_{max} is 1.406 $\mu\text{g}\cdot\text{hr}/\text{mL}$ and 0.871 $\mu\text{g}/\text{mL}$, respectively.

The following is the plasma concentration versus time profiles for avanafil (TA-1790) following a single dose (sponsor's figure 14.4.1.1)



The following is the plasma concentration versus time profiles for avanafil (TA-1790) following a single dose (data replotted by this reviewer)



The following table is a summary of mean pharmacokinetic parameters of avanafil in plasma following a single dose of avanafil in healthy male subjects (Day 1) (sponsor's table 11.4.1.2:1).

Pharmacokinetic Parameters	Treatment A		Plasma TA-1790 Treatment B		Treatment C	
	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD
C _{max} (µg/mL)	0.366	0.148	0.871	0.373	2.153	0.607
T _{max} (hr)	0.686	0.290	0.555	0.315	0.593	0.278
AUC(0-t)(µg*hr/mL)	0.4458	0.2408	1.406	0.6684	3.795	1.366
AUC(0-24)(µg*hr/mL)	0.5114	0.2546	1.498	0.6848	3.908	1.423
AUC(0-inf)(µg*hr/mL)	0.8848	0.2112	1.834	0.6674	4.080	1.438
T _{1/2} (hr)	1.07	0.171	1.23	0.436	1.19	0.302
K _{el} (1/hr)	0.661	0.100	0.616	0.170	0.618	0.150
CL/F(L/hr)	58.96	12.55	61.66	22.95	57.74	30.40
V _z /F(L)	89.37	14.66	102.4	33.54	94.30	45.11
C _{max} /Dose(µg/mL/mg)	0.007	0.003	0.009	0.004	0.011	0.003
AUC(0-t)/Dose (µg*hr/mL/mg)	0.00891	0.00481	0.01406	0.00668	0.01897	0.00682
AUC(0-24)/Dose (µg*hr/mL/mg)	0.01023	0.00509	0.01498	0.00684	0.01954	0.00711
AUC(0-inf)/Dose (µg*hr/mL/mg)	0.01770	0.00422	0.01834	0.00667	0.02040	0.00718
ln(C _{max} /Dose)	-5.003	0.4475	-4.842	0.4868	-4.580	0.3541
ln[AUC(0-t)/Dose]	-4.856	0.5533	-4.374	0.4991	-4.043	0.4493
ln[AUC(0-24)/Dose]	-4.697	0.5024	-4.299	0.4671	-4.012	0.4433
ln[AUC(0-inf)/Dose]	-4.056	0.2259	-4.060	0.3715	-3.963	0.4212

Treatment A: avanafil 50 mg QD (1 x 50 mg tablet)
 Treatment B: avanafil 100 mg QD (1x 100 mg tablet)
 Treatment C: avanafil 200 mg QD (2 x 100 mg tablet)

There appears to be dose proportionality: AUC_{0-inf} were 0.8848, 1.834, and 4.080 µg*hr/mL and C_{max} were 0.366, 0.871, and 2.153 µg/mL following a single dose of 50, 100, and 200 mg of avanafil. However, based on the Sponsor's proposed use of the 95% CI including zero for the slopes of ln(C_{max}/Dose) and ln(AUC/Dose), dose proportionality was concluded for AUC_{0-inf} only, not AUC_{0-t}, AUC₀₋₂₄, and C_{max}.

The following table is the dose proportionality assessment for avanafil PK after a single dose (on Day 1) (sponsor's table 14.2.4.1)

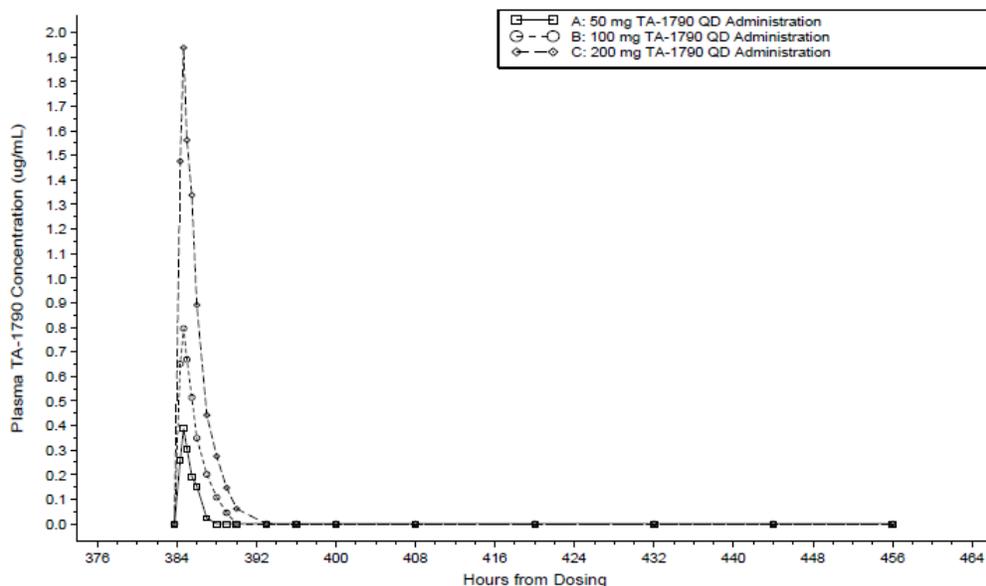
Pharmacokinetic Parameters	Geometric Means			Slope	Confidence Intervals (95% Confidence)	P-Value
	50 mg	100 mg	200 mg			
C _{max} /Dose	0.336	0.394	0.513	0.00279	0.0005 - 0.0051	0.0197
AUC(0-t)/Dose	0.389	0.630	0.877	0.00512	0.0024 - 0.0079	0.0006
AUC(0-inf)/Dose	0.866	0.863	0.950	0.00073	-0.0016 - 0.0030	0.5216

The statistical analyses were performed using the SAS Reg Procedure.
A linear regression model on ln-transformed dose-normalized parameter was used.
If p-value < 0.05, it indicates that the value is significantly different from zero.
Dose proportionality exists if slope is not significantly different from zero.
PK parameters were normalized relative to dose of 50 mg.

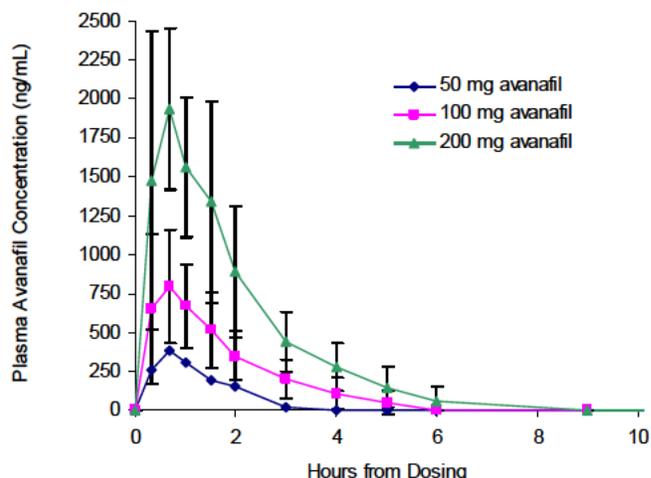
Multiple Dose PK:

In healthy male subjects given 14 daily doses of avanafil (50, 100 or 200 mg) for 14 days, mean maximum avanafil concentrations (T_{max}) were reached between 0.6 and 0.7 hr. Elimination half-life (t_{1/2}) ranged from 1.3 to 1.5 hrs. At the proposed dose of 100 mg, AUC_{0-t} and C_{max} is 1.635 µg*hr/mL and 0.892 µg/mL, respectively. Accumulation (R) was calculated based Day 17 AUC_{0-t}/Day 1 AUC_{0-inf}. R was minimal and ranged from 1.09 to 1.28 for all three doses. A more accurate determination of R would be based on AUC_{0-t} on Days 1 and 17 (Day 17 AUC_{0-t}/Day 1 AUC_{0-t}). This reviewer's calculation of R is 1.29, 1.16, and 1.08 for 50, 100, and 200 mg avanafil; however, concentrations of avanafil were not measurable after 6 hrs, due to the concentrations being less than LOQ.

The following is the plasma concentration versus time profiles for avanafil (TA-1790) following 14 days of daily doses (sponsor's figure 14.4.1.5)



The following is the plasma concentration versus time profiles for avanafil (TA-1790) following 14 days of daily doses (data replotted by this reviewer)



The following table is a summary of mean pharmacokinetic parameters of avanafil in plasma following 14 daily doses of avanafil in healthy male subjects (Day 17) (sponsor's table 11.4.1.2:2).

Pharmacokinetic Parameters	Plasma TA-1790					
	Treatment A		Treatment B		Treatment C	
	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD
C _{max} (ug/mL)	0.401	0.136	0.892	0.419	2.181	0.636
C _{min} (ug/mL)	0.000	0.000	0.000	0.000	0.000	0.000
T _{max} (hr)	0.583	0.208	0.703	0.245	0.723	0.416
AUC(0-tau)(ug*hr/mL)	0.5758	0.1872	1.635	0.7495	4.113	1.504
T _{1/2} (hr)	1.28	0.737	1.46	0.785	1.34	0.363
K _{el} (1/hr)	0.627	0.175	0.615	0.328	0.554	0.154
CL/F(L/hr)	95.86	34.71	72.38	28.30	58.15	33.92
V _z /F(L)	157.8	93.42	147.2	107.1	105.2	44.92
AI	0.743	0.0882	0.961	0.487	1.04	0.321
R	1.28	0.491	1.09	0.608	1.09	0.331
C _{max} /Dose(ug/mL/mg)	0.008	0.003	0.009	0.004	0.011	0.003
AUC(0-tau)/Dose (ug*hr/mL/mg)	0.01152	0.00374	0.01635	0.00749	0.02057	0.00751
ln(C _{max} /Dose)	-4.871	0.3019	-4.843	0.5607	-4.569	0.3535
ln[AUC(0-tau)/Dose]	-4.512	0.3273	-4.202	0.4369	-3.959	0.4372

Treatment A: avanafil 50 mg QD (1 x 50 mg tablet)

Treatment B: avanafil 100 mg QD (1x 100 mg tablet)

Treatment C: avanafil 200 mg QD (2 x 100 mg tablet)

On Day 17, following 14 days of daily dosing of avanafil, dose proportionality was concluded for C_{max} as the 95% CI for the slope of ln(C_{max}/Dose) included zero. Dose proportionality was not concluded for AUC_{0-t} as the 95% CI for the slope of ln(AUC_{0-t}/Dose) did not include zero.

The following table is the dose proportionality assessment for avanafil PK after 14 days of daily dosing (on Day 17) (sponsor's table 14.2.4.2)

Pharmacokinetic Parameters	Geometric Means			Slope	Confidence Intervals (95% Confidence)	P-Value
	50 mg	100 mg	200 mg			
C _{max} /Dose	0.383	0.394	0.519	0.00210	-0.0001 - 0.0043	0.0611
AUC(0-tau)/Dose	0.549	0.748	0.954	0.00352	0.0013 - 0.0057	0.0024

The statistical analyses were performed using the SAS Reg Procedure.
A linear regression model on ln-transformed dose-normalized parameter was used.
If p-value < 0.05, it indicates that the value is significantly different from zero.
Dose proportionality exists if slope is not significantly different from zero.
PK parameters were normalized relative to dose of 50 mg.

Blood samples were taken on Days 10, 17, 18, and 19 during the multiple dose study to assess time to reach steady state. The sponsor were not able to quantify avanafil following 50, 100, and 200 mg avanafil tablets and makes no conclusion about achieving steady state.

Adverse Events

The number of subjects who reported experiencing adverse events was similar among the three groups and placebo. Headache was most frequently reported and was highest in the highest dose group (3 with 50 mg, 3 with 100 mg, 5 with 200 mg, and 3 with placebo).

The following is a summary of adverse event frequency by treatment group – number of subjects reporting the event (% of subjects dosed) (sponsor's table 14.3.1.1)

Adverse Event*	Treatment Group				Total
	50 mg	100 mg	200 mg	Placebo	
Number of Subjects Dosed	12 (100%)	12 (100%)	12 (100%)	12 (100%)	48 (100%)
Number of Subjects With Adverse Events	4 (33%)	5 (42%)	5 (42%)	5 (42%)	19 (40%)
Number of Subjects Without Adverse Events	8 (67%)	7 (58%)	7 (58%)	7 (58%)	29 (60%)
Blood and lymphatic system disorders					
Lymphadenopathy	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Cardiac disorders					
Atrioventricular block first degree	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Eye disorders					
Asthenopia	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (2%)
Gastrointestinal disorders					
Dry mouth	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (2%)
Loose stools	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Nausea	1 (8%)	1 (8%)	0 (0%)	1 (8%)	3 (6%)
Vomiting NOS	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
General disorders and administration site conditions					
Feeling hot	0 (0%)	2 (17%)	2 (17%)	0 (0%)	4 (8%)
Pyrexia	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Musculoskeletal and connective tissue disorders					
Arthralgia	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Back pain	1 (8%)	0 (0%)	1 (8%)	1 (8%)	3 (6%)
Facial pain	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (2%)
Muscle cramp	0 (0%)	1 (8%)	1 (8%)	0 (0%)	2 (4%)
Musculoskeletal stiffness	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Nervous system disorders					
Dizziness	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (2%)
Headache	3 (25%)	3 (25%)	5 (42%)	3 (25%)	14 (29%)

Adverse Event*	Treatment Group				Total
	50 mg	100 mg	200 mg	Placebo	
Renal and urinary disorders					
Dysuria	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Renal pain	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (2%)
Reproductive system and breast disorders					
Spontaneous penile erection	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (2%)
Testicular pain	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (2%)
Respiratory, thoracic and mediastinal disorders					
Pharyngolaryngeal pain	0 (0%)	1 (8%)	0 (0%)	1 (8%)	2 (4%)
Productive cough	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Wheezing	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Skin and subcutaneous tissue disorders					
Sweating increased	0 (0%)	1 (8%)	1 (8%)	0 (0%)	2 (4%)

Study TA-04

Title: A Double-Blind, Randomized, Crossover Evaluation of the Hemodynamic Response to Sublingual Glyceryl Trinitrate in Patients Receiving TA-1790, Sildenafil, and Placebo

Objectives: The objective of this study was to evaluate the hemodynamic response to a sublingual dose of glyceryl trinitrate in subjects receiving oral avanafil, sildenafil, and placebo.

Methods: This was a single center, double blind, randomized, 3-way crossover study in healthy male subjects age 30 to 60 years. Subjects were divided among 5 study groups, with the study groups differing in the time interval between treatment with avanafil, sildenafil, or placebo and glyceryl trinitrate administration. Group 1: 12 hrs; Group 2: 8 hrs; Group 3: 4 hrs; and Group 5: 30 minutes. Of the 106 subjects enrolled, eighty-eight subjects completed the study (Group 1:12; Group 2: 16; Group 3: 26; Group 4: 24; and Group 5: 24). Subjects were assigned to study groups sequentially and hemodynamic results from the previous group were reviewed for serious events before the next group received treatment.

Of the 106 male subjects, 55 were Caucasian, 42 were Hispanic, 8 were Black, and 1 was Asian. The mean age was 43.4 yrs (range 30 to 60 yrs) and the mean weight was 186.7 lbs. Eight subjects were discontinued due to adverse events, 6 subjects were lost to follow-up, 1 subject failed the drug/alcohol screen, 1 subject was unable to return, 1 subject withdrew due to personal reasons, and 1 subject was withdrawn due to a prolonged QTc at baseline.

Each subject was dosed with avanafil, sildenafil, and placebo in random order. Subjects received a single 100 mg (2x50 mg capsules) of sildenafil (Pfizer), a single 200 mg (2x100 mg) of avanafil or placebo (2 capsules). Following the study medication, subjects were challenged with 0.4 mg glyceryl trinitrate (Nitrostat®, Parke-Davis) sublingual tablet. The time intervals between administration of avanafil and glyceryl trinitrate varied from 0.5 to 12 hrs. A waiting period between each treatment period was 2 to 10 days.

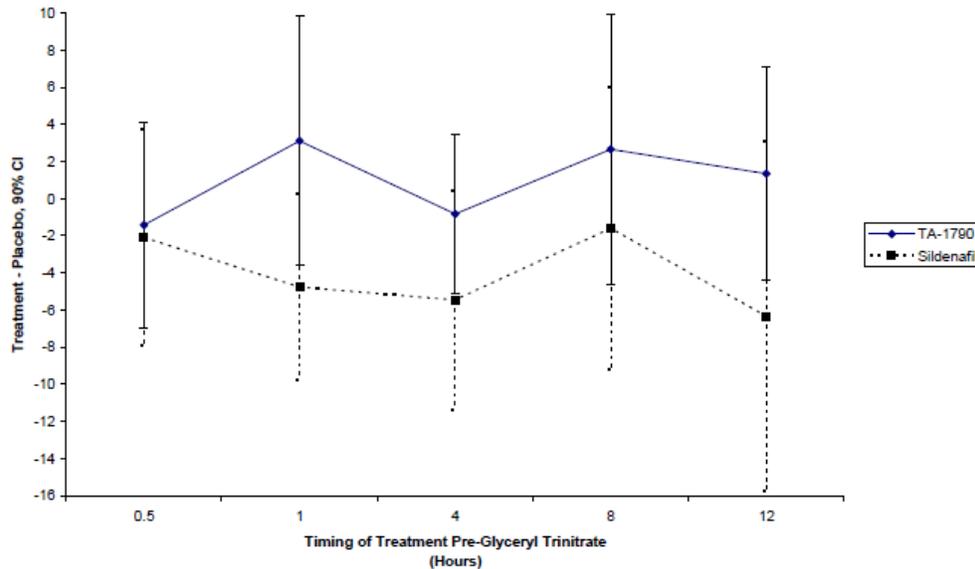
Pharmacokinetic Sampling: No blood samples were taken for PK of avanafil

Hemodynamic Endpoint: The following are hemodynamic endpoints: (1) maximum change (post-dose maximum decrease (blood pressure) or maximum increase (pulse)) from pre-dose hemodynamic values; (2) the mean change in these values from pre-dose across all post-dose time points; and (3) proportion of subjects with clinically significant decreases in blood pressure. Clinically significant decreases in blood pressure was defined by the sponsor as a decrease in systolic blood pressure of >30 mm HG or a decrease in diastolic blood pressure of >20 mm Hg. Symptomatic hypotension were defined as palpitations, tachycardia, visual disturbances, blurry vision, nausea, vomiting, dizziness, syncope, hypotension, and pallor). Baseline vital signs were done at 3 time points (-15, -10, and -5 min) prior to administration of avanafil, sildenafil, or placebo.

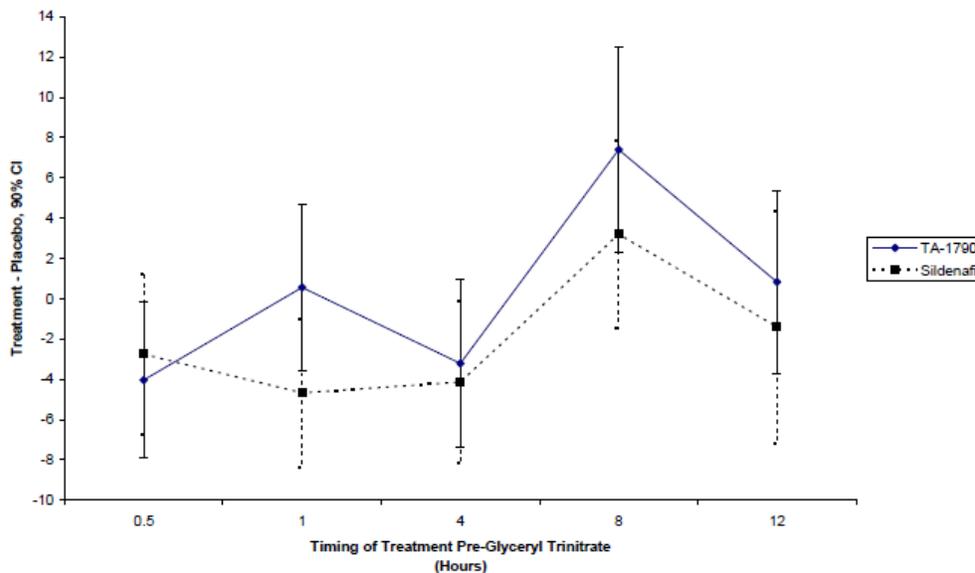
Results: The sponsor states that despite statistically significant differences, there were no clinically significant treatment differences in mean maximum blood pressure or pulse rate changes from baseline for avanafil, compared with placebo, following administration of glyceryl trinitrate. It appears that avanafil has slightly greater effect on standing diastolic blood pressure, compared to placebo. Overall, the effect on blood pressure and pulse rate from avanafil + glyceryl trinitrate or sildenafil + glyceryl trinitrate appears to be slightly greater than placebo + glyceryl trinitrate. The avanafil dose evaluated in this study is a single 200 mg dose, which is higher than the proposed dose of 100 mg. The blood pressure lowering effect can be significant with repeat dosing, which this study was not designed to evaluate.

The standing mean maximum systolic blood pressure decrease appears to be less significant with avanafil, compared with sildenafil, especially after 12 hrs of treatment. However, the degree of variability is high in both groups.

The following figure is the placebo-subtracted point estimates (with 90% CI) of standing mean maximal systolic blood pressure effects of pre-dosing with 200 mg avanafil or 100 mg sildenafil at 0.5, 1, 4, 8, and 12 hrs before 0.4 mg glyceryl trinitrate (sponsor's figure 5)



The following figure is the placebo-subtracted point estimates (with 90% CI) of standing mean maximal diastolic blood pressure effects of pre-dosing with 200 mg avanafil or 100 mg sildenafil at 0.5, 1, 4, 8, and 12 hrs before 0.4 mg glyceryl trinitrate (sponsor's figure 7)



The following table is the mean maximum change from pre-dose to post-dose in systolic and diastolic blood pressure (mm Hg) and pulse (bpm) by study group following glyceryl trinitrate administration (sponsor's table 4)

Group	Sitting			Standing		
	TA-1790	Sildenafil	Placebo	TA-1790	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
<i>Source: Section 14.2, Tables 14.2.1.1 - 14.2.1.8</i> 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 change in systolic and diastolic blood pressure (SBP and DBP) occurred in Group 5 - 30 min between administration of avanafil and glyceryl trinitrate. The mean maximum change from predose to postdose in sitting SBP was -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 change from predose to postdose in standing SBP was -24.1, -24.8, and -22.7 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The difference between treatment groups and placebo are not statistically different.

The mean maximum change from predose to postdose in sitting SDP was -16.7, -17.4, and -14.3 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The mean maximum change from predose to postdose in standing SDP was -21.5, -20.3, and -17.5 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. Only the change in standing DBP with avanafil + glyceryl trinitrate co-administration was statistically different from placebo + glyceryl trinitrate.

The mean maximum change in pulse rate occurred in Group 2 - 8 hrs between administration of avanafil and glyceryl trinitrate. The mean maximum change from predose to postdose in sitting pulse rate was 18.6, 15.7, and 19.1 bpm in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The mean maximum change from predose to postdose in standing pulse rate was 19.8, 24.7, and 16.8 bpm in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. Only the change in standing pulse rate with sildenafil + glyceryl trinitrate co-administration was statistically different from placebo + glyceryl trinitrate.

The following table is the mean change from pre-dose to post-dose in systolic and diastolic blood pressure (mm Hg) and pulse (bpm) by study group following glyceryl trinitrate administration (sponsor's table 4)

Group	Sitting			Standing		
	TA-1790	Sildenafil	Placebo	TA-1790	Sildenafil	Placebo
Systolic Blood Pressure (mmHg)						
1 (12-hour)	-5.35	-8.06	-4.71	-6.31	-8.60	-7.22
2 (8-hour)	-5.94	-8.64	-7.59	-8.72	-10.63	-9.58
3 (4-hour)	-7.59	-8.61	-7.94	-8.84	-11.59	-9.40
4 (1-hour)	-8.90	-10.83	-8.30	-7.40	-13.00	-8.89
5 (0.5-hour)	-8.57	-8.28	-5.72	-9.87	-11.80	-8.36
1-5 combined	-7.52	-8.98	-6.94	-8.34§	-11.40*	-8.73
3-5 combined	-8.35	-9.24	-7.26	-8.72§	-12.13*	-8.86
4-5 combined	-8.73	-9.55	-6.92	-8.66	-12.40*	-8.60
Diastolic Blood Pressure (mmHg)						
1 (12-hour)	-4.36	-4.72	-3.52	-4.50	-5.44	-5.07
2 (8-hour)	-3.18	-5.08	-4.11	-4.17	-5.54	-7.68
3 (4-hour)	-7.10§	-9.31	-8.13	-9.53	-11.15	-9.43
4 (1-hour)	-6.04	-6.91	-6.68	-6.36	-9.87	-7.59
5 (0.5-hour)	-7.76	-9.57*	-6.38	-9.60*	-9.97*	-6.77
1-5 combined	-6.00§	-7.50*	-6.07	-7.23	-8.90	-7.45
3-5 combined	-6.98§	-8.59	-7.05	-8.51	-10.33*	-7.90
4-5 combined	-6.92	-8.24*	-6.52	-8.02	-9.92*	-7.16
Pulse (bpm)						
1 (12-hour)	2.89	1.54	3.20	1.57	5.06	4.34
2 (8-hour)	5.07	3.01	3.60	5.49*	6.42*	3.01
3 (4-hour)	3.78	3.20	5.13	4.94	5.08	5.57
4 (1-hour)	-2.05* §	0.97	1.09	2.09	4.17	4.33
5 (0.5-hour)	2.55	3.63*	0.69	3.58§	8.05*	4.01
1-5 combined	2.21	2.51	2.62	3.51§	5.76*	4.33
3-5 combined	1.44	2.60	2.27	3.53§	5.77	4.62
4-5 combined	0.30§	2.30	0.88	2.85§	6.11*	4.16
<i>Source: Section 14.2, Tables 14.2.2.1 -14.2.2.8</i> 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						

Before administration of glyceryl trinitrate, few subjects exhibited decreases in blood pressure. With the administration of glyceryl trinitrate, the number of subjects with symptomatic hypotension increased in subjects who received avanafil, compared to placebo, and was not different from subjects given sildenafil. There was no difference between treatment groups based on the time of administration of avanafil, sildenafil or placebo and glyceryl trinitrate. Overall, the potentiation of hypotension is a concern in patients requiring sublingual glyceryl trinitrate and taking avanafil.

The following table summarizes the number of subjects with symptomatic hypotension adverse events after administration of glyceryl trinitrate (sponsor's table 10).

Group	TA-1790	Sildenafil	Placebo	Total	P value
1 (12 hour)	2 (13%)	4 (29%)	2 (14%)	5 (31%)	0.0830
2 (8 hour)	2 (13%)	3 (20%)	0 (0%)	4 (25%)	
3 (4 hour)	5 (21%)	7 (32%)	1 (4%)	12 (46%)	
4 (1 hour)	6 (26%)	6 (26%)	3 (14%)	11 (46%)	0.5916
5 (0.5 hour)	9 (38%)	6 (26%)	5 (21%)	15 (63%)	0.2050
1-5 combined	24 (24%)	26 (27%)	11 (11%)	47 (44%)	0.0101
3-5 combined	20 (28%)	19 (28%)	9 (13%)	38 (51%)	0.0137
4-5 combined	15 (32%)	12 (26%)	8 (18%)	26 (54%)	0.1269
<i>Source: Section 14.2, Tables 14.2.3.2</i> 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). * Adverse events that constitute symptomatic hypotension are: palpitations, tachycardia, visual disturbance, blurry vision, nausea, vomiting, dizziness, syncope, hypotension, and pallor.					

Study TA-07

Title: A Study to Assess the Pharmacokinetic Parameters of Avanafil Administered Twice Daily in Healthy Men

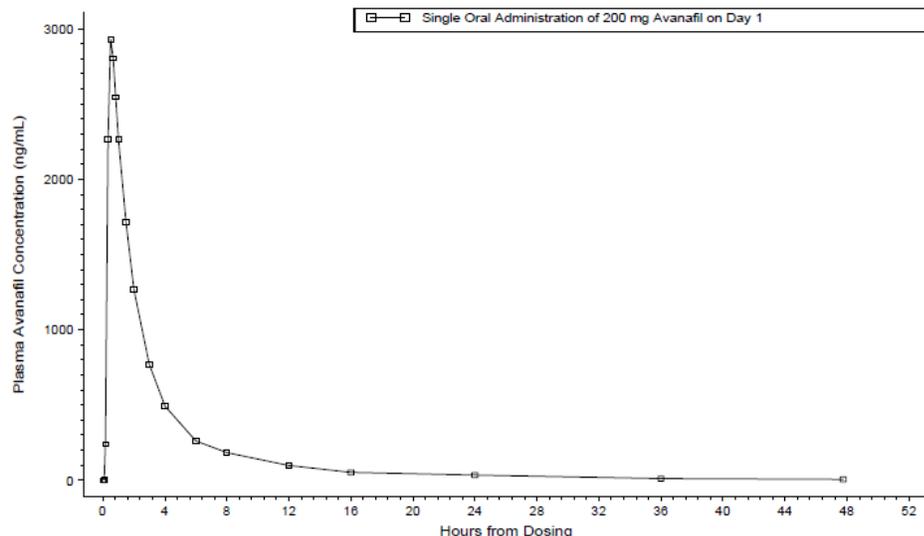
Objectives: The objective of this study was to assess the single dose PK and steady-state PK of avanafil following twice daily (BID) dosing in healthy men.

Methods: This was a single center, non-randomized, non-blinded study to assess and compare the single dose PK and the steady-state PK of 200 mg avanafil taken BID at 12-hr intervals in healthy male subjects. The 200 mg dose was chosen because the sponsor noted that 200 mg was likely the maximum dose. Fifteen subjects healthy male (1 Black, 4 Caucasian, and 10 Hispanic) subjects with a mean age of 40 years (30 and 55 years) were enrolled; 13 completed the study. On Day 1, subjects were given a single 200 mg oral dose of avanafil (2 x 100 mg tablets) followed by a 48-hr washout period. On the morning of Day 3, subjects then received 200 mg avanafil (2 x 100 mg tablets) every 12 hrs (BID) for 7 days (Days 3-9), followed by a single dose on Day 10. Avanafil tablets were administered orally with 240 mL water. Formulation I was evaluated in this study.

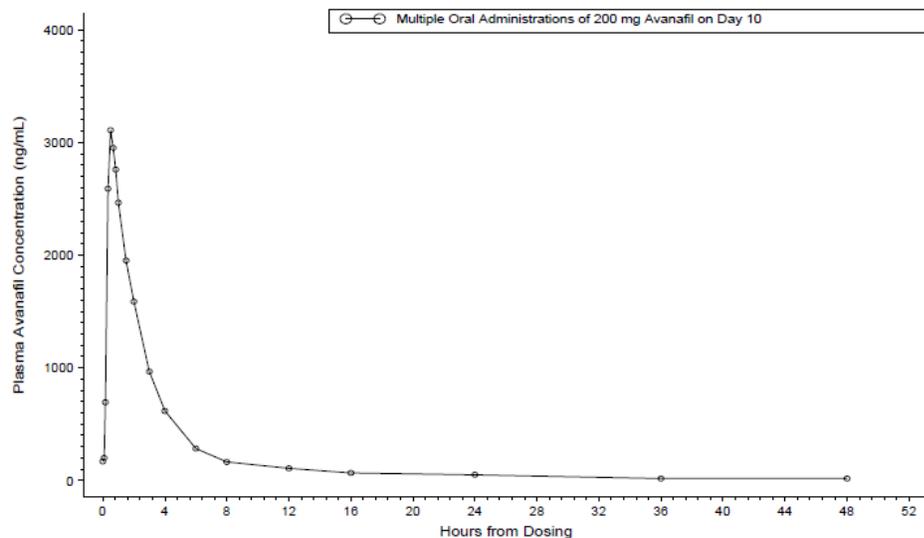
Pharmacokinetic Sampling: Blood samples for single-dose PK were taken at baseline (pre-dose) and at 5, 10, 20, 30, 40, 50, 60, 90, 120, and 180 min and 4, 6, 8, 12, 16, 24, 36, and 48 hrs post-dose on Day 1. Blood sampling was done prior to morning dosing only on Days 3-9. Blood samples for assessment of steady-state PK were drawn at baseline (pre-dose) and at 5, 10, 20, 30, 40, 50, 60, 90, 120, and 180 min and 4, 6, 8, 12, 16, 24, 36, and 48 hrs post-dose on Day 10.

Results: Compared to single-dose PK, steady-state PK parameters of avanafil were slightly higher with a small degree of accumulation. Steady-state was reached by 24 hrs following the initiation of BID dosing.

The following figure is the arithmetic mean (SD) of plasma avanafil versus time on Day 1 (sponsor's figure 14.4.2)



The following figure is the arithmetic mean (SD) of plasma avanafil versus time on Day 10 (sponsor's figure 14.4.5)



Median t_{max} after a single-dose (Day 1) and at steady-state (Day 10) were similar at 0.5 hrs. Mean (SD) $t_{1/2}$ was 8.13 (4.12) and 9.08 (4.09) hrs after a single dose (Day 1) and multiple dosing (Day 10), respectively.

Mean (SD) C_{max} was 3150 (1290) and 3490 (1200) ng/mL after a single dose (Day 1) and after 7 days of BID dosing (Day 10) of avanafil, respectively. The geometric mean ratio for C_{max} is 1.20.

Mean (SD) AUC_{0-t} was 8108 (3136) and 9594 (2658) ng*hr/mL after a single dose (Day 1) and after 7 days of BID dosing (Day 10) of avanafil, respectively. The geometric mean ratio for AUC_{0-t} is 1.26.

Mean (SD) AUC_{0-inf} was 8200 (3084) and 9928 (2709) ng*hr/mL after a single dose (Day 1) and after 7 days of BID dosing (Day 10) of avanafil, respectively. The geometric mean ratio for AUC_{0-inf} is 1.28.

The accumulation ratio (RA_{AUC}), calculated as $AUC_{0-t, Day 10}/AUC_{0-12, Day 1}$ is 1.24. The accumulation index (AI), calculated as $AUC_{0-t, Day 10}/AUC_{0-inf, Day 1}$ is 1.07.

The following table summarizes the single-dose and steady-state mean (\pm SD) PK parameters of avanafil (sponsor's table 11.4.1.2:1)

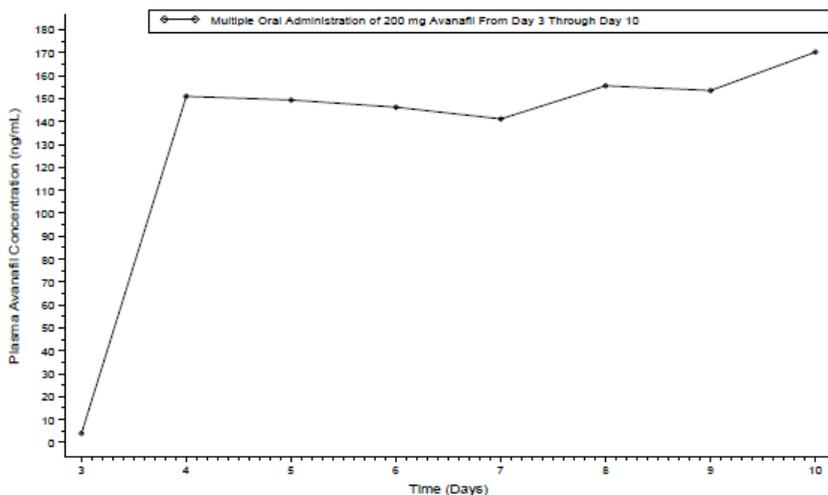
Parameter	Arithmetic Mean \pm SD		% Ratio of Geometric Means ^b	90% CI ^b
	Single Dose PK (N=15)	Steady-State PK (N=13)		
C _{max} (ng/mL)	3150 \pm 1290	3490 \pm 1200	120.06	87.48 – 164.77
T _{max} ^a (hr)	0.501 (0.333, 1.5)	0.505 (0.334, 1.5)		
AUC _(0-t) (ng*hr/mL)	8107.8 \pm 3135.5	9594.3 \pm 2658.4	126.02	102.4 – 155.08
AUC ₍₀₋₂₄₎ (ng*hr/mL)	7791.1 \pm 3080.7	9003.1 \pm 2726.7	122.82	98.34 – 153.38
AUC ₍₀₋₁₂₎ (ng*hr/mL)	7142 \pm 2885.2	8176.3 \pm 2685.9	121.17	95.02 – 154.52
AUC _(0-inf) (ng*hr/mL)	8200.2 \pm 3084.3	9928 \pm 2709.1 [*]	128.18	104.1 – 157.86
K _{el} (1/hr)	0.0997 \pm 0.0338	0.0933 \pm 0.0433 [*]		
T _{1/2} (hr)	8.13 \pm 4.12	9.08 \pm 4.09 [*]		
Cl/F (L/hr)	26.97 \pm 7.85	27.02 \pm 9.118 [*]		
C _{min} (ng/mL)		49.4 \pm 43.2		
C _{avg} (ng/mL)		681 \pm 224		
Degree of Fluctuation (DF)		5.08 \pm 1.33		4.19 – 5.62 [#]
RA _(AUC)		1.24 \pm 0.264		1.07 – 1.35 [#]
Accumulation Index (AI)		1.07 \pm 0.291		0.893 – 1.18 [#]

a = For T_{max}, median (min and max) are presented.
b = Percent geometric mean ratios and 90% CI were obtained from LS means of ln-transformed C_{max}, AUC_(0-t), AUC₍₀₋₁₂₎, AUC₍₀₋₂₄₎, and AUC_(0-inf).
* = The sample size is 12
= CI was constructed around the geometric mean using geometric standard errors.
Single dose PK = 2 x 100 mg avanafil tablets administered once: reference
Steady-state PK = 2 x 100 mg avanafil administered BID for 7 days: test
Source: Tables 14.2.3, 14.2.4, and 14.2.7.

Based on the mean trough (pre-dose) avanafil concentration of approximately 150 ng/mL in the following table and the concentration versus time profile in the following figure, it appears that steady-state is reached on Day 4 (24 hrs after beginning BID dosing). This reviewer concurs that steady-state is reached by 24 hrs after BID dosing.

The following table is the pre-dose plasma avanafil concentrations (ng/mL) following multiple oral administrations of 200 mg avanafil from Day 3-10 (sponsor's table 14.2.6)

The following figure is the mean pre-dose plasma avanafil concentrations versus time following BID dose administrations on Days 3-10 (sponsor's figure 11.4.1.3:1)



The sponsor confirmed that steady-state concentrations were obtained on Day 4 with statistical analysis - regressing pre-dose plasma avanafil concentrations with time. If steady-state is reached, slope of line through the trough points should be zero or near zero (horizontal) and not statistically different from zero. This reviewer concurs that steady-state is reached by 24 hrs after BID dosing on Day 4 and that the statistical analysis demonstrates that there is no difference in the trough concentrations from Day 4 through Day 10.

The following table is the steady-state assessment of plasma avanafil concentrations following BID dose administration (sponsor's table 11.4.1.3:1)

	Mean Slope	N	P-value
Day 3 through Day 10	0.5662	13	<.0001
Day 4 through Day 10	0.0655	13	0.5600

Note: if P-value > 0.05, slope is not statistically different from zero
Source: [Table 14.2.8](#)

Safety:

Two subjects (#9 and #12) withdrew from the study due to adverse events possibly-related to the treatment. Adverse events consisted of bilateral eye redness, blurred vision, bilateral hamstring cramping, low back pain, testicular pain, difficulty sleeping, and acidic stomach.

The most frequent adverse event in the single dose and BID dosing groups was headache. After headache, back pain, muscle pain, and pain in extremity were most prominent in the 200 mg BID group. Compared to one single administration of 200 mg avanafil, it appears as though twice daily administered of 200 mg avanafil resulted in significantly more adverse events such as insomnia, cough, dyspnea, nasal congestion, and rhinorrhea.

Adverse Event	avanafil 200 mg					
	Single Dose		BID		Total	
Number of Subjects Dosed	15	(100%)	15	(100%)	15	(100%)
Number of Subjects With Adverse Events	11	(73%)	14	(93%)	14	(93%)
Number of Subjects Without Adverse Events	4	(27%)	1	(7%)	1	(7%)
Gastrointestinal disorders						
Loose stools	1	(7%)	1	(7%)	2	(13%)
Nausea	1	(7%)	3	(20%)	3	(20%)
General disorders and administration site conditions						
Feeling hot	1	(7%)	2	(13%)	3	(20%)
Investigations						
Gamma-glutamyltransferase increased	0	(0%)	2	(13%)	2	(13%)
Musculoskeletal and connective tissue disorders						
Back pain	0	(0%)	6	(40%)	6	(40%)
Muscle cramp	0	(0%)	2	(13%)	2	(13%)
Pain in extremity	0	(0%)	8	(53%)	8	(53%)
Nervous system disorders						
Dizziness	4	(27%)	1	(7%)	4	(27%)
Headache	9	(60%)	11	(73%)	12	(80%)
Psychiatric disorders						
Insomnia	0	(0%)	3	(20%)	3	(20%)
Respiratory, thoracic and mediastinal disorders						
Cough	0	(0%)	2	(13%)	2	(13%)
Dyspnoea	0	(0%)	2	(13%)	2	(13%)
Nasal congestion	0	(0%)	3	(20%)	3	(20%)
Rhinorrhoea	0	(0%)	2	(13%)	2	(13%)

Study TA-011

Title: A Phase I, Single-Center, Open-Label, Randomized, One-Sequence Crossover, Three Parallel Group Study to Evaluate the Effect of Ketoconazole, Ritonavir and Erythromycin on the Safety and Pharmacokinetics of Avanafil (TA-1790) in Healthy Male Subjects

Objectives: The objectives of this study were to assess the effect of co-administration of ketoconazole, ritonavir or erythromycin on the PK of avanafil and evaluate the safety of avanafil when co-administered with ketoconazole, ritonavir or erythromycin.

Methods: This was an open-label, randomized, one-sequence crossover, three-way parallel study. Forty-four male subjects were enrolled with 41 subjects having completed the study (1 subject from Group 1 failed drug screening and 2 subjects from Group 3 left the study for personal reasons). There were 13-15 subjects per treatment group. All 44 subjects were included in the safety analyses and in the analysis of the PK parameters for avanafil, M4 and M16. Of the forty-four subjects, 36 were Caucasian, 3 were Black, 3 were Hispanic, 1 was American Indian, and 1 Asian. The mean age for all subjects was 27.9 yrs (range 21-43 yrs) and the mean weight was 79.1 kg (range 59.4-98.9 kg).

On Day -1, subjects checked into the study clinic. On Day 1 after an overnight fast of at least eight hrs, subjects were dosed with a single dose (50 mg or 200 mg) of avanafil. On Day 2, subjects were permitted to leave the study site and then return to the site for administration of ketoconazole, erythromycin, or ritonavir (morning and evening, if applicable). When the next avanafil dosing was due on Days 6 or 8, subjects were required to be checked in the night before (Day 5 for Groups 1 & 2 and Day 7 for Group 3). Subjects were randomly assigned to one of three treatment groups:

Group 1: Ketoconazole 400 mg (2 x 200 mg) once daily for 5 days (Days 2-6) and a single 50 mg (1 x 50 mg) dose of avanafil on Days 1 & 6

Group 2: Erythromycin 500 mg (2 x 250 mg) every 12 hrs for 5 days (Days 2-6) and a single 200 mg (2 x 100 mg) dose of avanafil on Days 1 & 6

Group 3: Ritonavir 300 mg (3 x 100 mg) twice daily (BID) for 1 day (Day 2), 400 mg (4 x 100 mg) BID for 1 day (Day 3), 600 mg (6 x 100 mg) BID for 5 days (Days 4-8) and a single 50 mg (1 x 50 mg) dose of avanafil on Days 1 & 8

Pharmacokinetic Sampling: Blood samples were taken 0 (30 min predose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 8, 12, and 24 hrs postdose to determine plasma avanafil concentrations. For Group 1, blood samples to determine plasma ketoconazole concentrations at predose on Days 4 & 5. For Group 2, blood samples to determine plasma erythromycin concentrations at predose on the morning and evening of Day 5. For Group 3, blood samples to determine plasma ritonavir concentrations at predose of Day 7. Steady-state was assessed by the Helmert's contrast method analysis of trough concentrations on Days 4, 5, & 6 for ketoconazole; on Days 5 & 6 for erythromycin; and Days 7 & 8 for ritonavir.

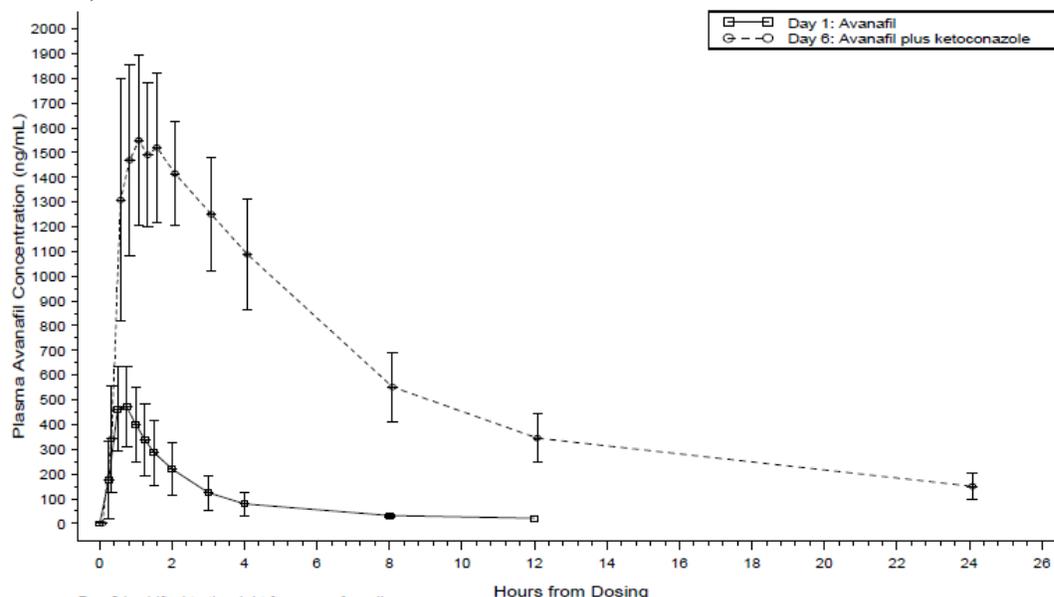
Results: The sponsor concluded from in vitro studies that avanafil is predominately metabolized by CYP3A4 and therefore conducted this clinical study to evaluate the effect of concomitant administration of CYP3A4 inhibitors and avanafil. Group 1 subjects were given ketoconazole, a strong CYP3A4 inhibitor, with the 50 mg avanafil - lowest avanafil dose being sought for approval. Group 3 subjects were given ritonavir, a potent CYP3A4 inhibitor, with the 50 mg avanafil - lowest avanafil dose being sought for approval. Group 2 subjects were given erythromycin, a moderate CYP3A4 inhibitor, with 200 mg avanafil – the highest avanafil dose sought for approval. The sponsor did not evaluate the affect of a mild CYP3A4 inhibitor on avanafil PK.

Strong CYP3A4 inhibitors ketoconazole and ritonavir increased plasma avanafil PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} by approximately 2 to 3-, 12-, and 12-fold, respectively.

Moderate CYP3A4 inhibitor erythromycin increased plasma avanafil exposure AUC_{0-t} and AUC_{0-inf} to a much lower extent, compare to ketoconazole and ritonavir. C_{max}, AUC_{0-t}, and AUC_{0-inf} by approximately 2-, 3.5-, and 3.6-fold, respectively, following avanafil and erythromycin co-administration.

Strong CYP3A4 inhibitor - Ketoconazole & Avanafil (Group 1)

The following figure is the geometric mean (SD) plasma avanafil concentrations vs time profile on Day 1 following 50 mg avanafil and Day 6 following 50 mg avanafil and ketoconazole (sponsor's figure 14.4.1.1)



The following is the arithmetic mean (SD) and geometric mean PK parameters for plasma avanafil 50 mg on Day 1 and Day 6 following avanafil and ketoconazole (sponsor's table 4)

Pharmacokinetic Parameters	Avanafil		Avanafil + Ketoconazole	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	535 ± 164 (15)	506	1660 ± 328 (14)	1630
AUC _{0-t} (ng*hr/mL)	1040 ± 435 (15)	952	13000 ± 2610 (14)	12800
AUC _{0-inf} (ng*hr/mL)	1130 ± 450 (15)	1040	14500 ± 2880 (13)	14300
t _{max} (hr)	0.51 (0.25, 1.5) (15)	.	1.0 (0.50, 2.0) (14)	.
t _{1/2} (hr)	1.8 ± 1.2 (15)	.	8.5 ± 1.3 (13)	.
k _{el} (1/hr)	0.470 ± 0.171 (15)	.	0.0833 ± 0.0132 (13)	.

Group 1: Ketoconazole 400 mg QD for 5 days (Days 2-6) plus a single dose of 50 mg avanafil on Days 1 and 6
t_{max} is presented as Median (Minimum, Maximum)
. = Value missing or not reportable
Source: Tables 14.2.1.3 through 14.2.1.4

The arithmetic mean C_{max} of avanafil increased 3.1-fold from 535 to 1660 ng/mL when avanafil was co-administered with ketoconazole, compared to avanafil alone.

The arithmetic mean AUC_{0-t} of avanafil increased 12.5-fold from 1040 to 13000 ng.hr/mL when avanafil was co-administered with ketoconazole, compared to avanafil alone.

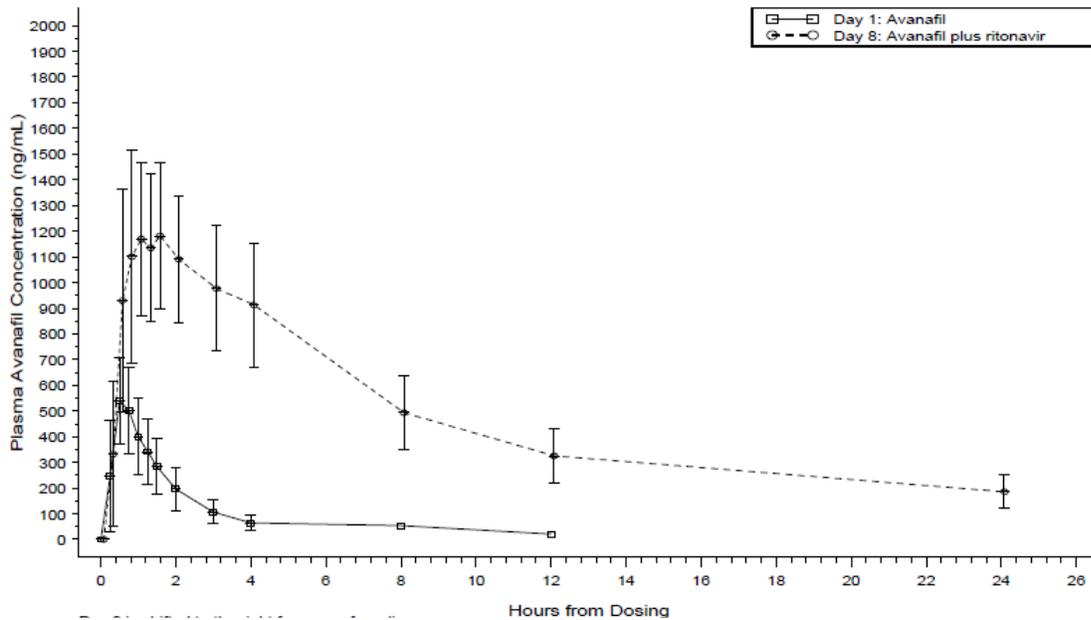
The arithmetic mean AUC_{0-inf} of avanafil increased 12.8-fold from 1130 to 14500 ng.hr/mL when avanafil was co-administered with ketoconazole, compared to avanafil alone.

The median t_{max} increased by 0.5 hr from 0.5 to 1.0 hr when avanafil was co-administered with ketoconazole, compared to avanafil alone.

The arithmetic mean t_{1/2} increased by 6.7 hrs from 1.8 to 8.5 hrs when avanafil was co-administered with ketoconazole, compared to avanafil alone.

Potent CYP3A4 inhibitor - Ritonavir & Avanafil (Group 3)

The following figure is the geometric mean (SD) plasma avanafil concentrations vs time profile on Day 1 following 50 mg avanafil and Day 8 following 50 mg avanafil and ritonavir (sponsor's figure 14.4.3.1)



The following is the arithmetic mean (SD) and geometric mean PK parameters for plasma avanafil 50 mg on Day 1 and Day 6 following avanafil and ritonavir (sponsor's table 24)

Pharmacokinetic Parameters	Avanafil		Avanafil + Ritonavir	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	568 ± 165 (14)	548	1360 ± 253 (13)	1340
AUC _{0-t} (ng*hr/mL)	935 ± 426 (14)	873	11400 ± 2760 (13)	11100
AUC _{0-inf} (ng*hr/mL)	1050 ± 434 (14)	985	13200 ± 2740 (4)	13000
t _{max} (hr)	0.50 (0.25, 0.75) (14)	.	1.5 (0.50, 3.0) (13)	.
t _{1/2} (hr)	1.4 ± 0.53 (14)	.	8.8 ± 1.7 (4)	.
k _e (1/hr)	0.541 ± 0.145 (14)	.	0.0812 ± 0.0170 (4)	.

Group 3: Ritonavir 300 mg BID for 1 day (Day 2), 400 mg BID for 1 day (Day 3), 600 mg BID for 5 days (Days 4-8) plus a single dose of 50 mg avanafil on Days 1 and 8
t_{max} is presented as Median (Minimum, Maximum)
. = Value missing or not reportable
Source: Tables 14.2.3.3 through 14.2.3.4

The arithmetic mean C_{max} of avanafil increased 2.4-fold from 568 to 1360 ng/mL when avanafil was co-administered with ritonavir, compared to avanafil alone.

The arithmetic mean AUC_{0-t} of avanafil increased 12.2-fold from 935 to 11400 ng.hr/mL when avanafil was co-administered with ritonavir, compared to avanafil alone.

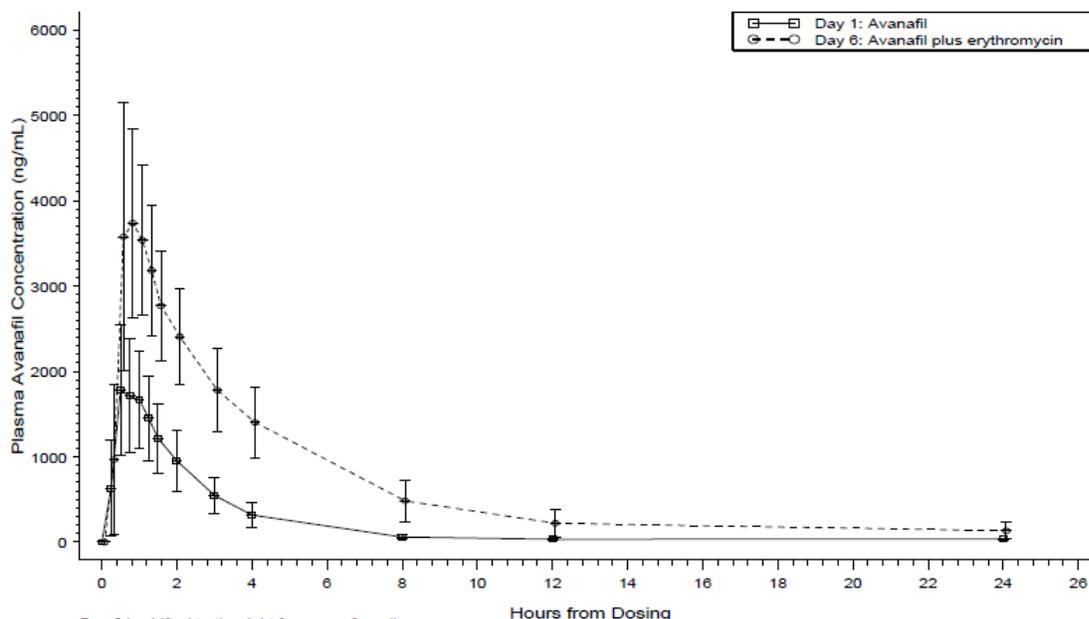
The arithmetic mean AUC_{0-inf} of avanafil increased 12.8-fold from 1050 to 13200 ng.hr/mL when avanafil was co-administered with ritonavir, compared to avanafil alone.

The median t_{max} increased by 1.0 hr from 0.5 to 1.5 hr when avanafil was co-administered with ritonavir, compared to avanafil alone.

The arithmetic mean t_{1/2} increased by 7.4 hrs from 1.4 to 8.8 hrs when avanafil was co-administered with ritonavir, compared to avanafil alone.

Moderate CYP3A4 inhibitor – Erythromycin & Avanafil (Group 2)

The following figure is the geometric mean (SD) plasma avanafil concentrations vs time profile on Day 1 following 200 mg avanafil and Day 6 following 200 mg avanafil and erythromycin (sponsor's figure 14.4.2.1)



The following is the arithmetic mean (SD) and geometric mean PK parameters for plasma avanafil 2000 mg on Day 1 and Day 6 following avanafil and erythromycin (sponsor's table 14)

Pharmacokinetic Parameters	Avanafil		Avanafil + Erythromycin	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C_{max} (ng/mL)	2030 ± 678 (15)	1880	4230 ± 1300 (14)	4020
AUC_{0-t} (ng*hr/mL)	4690 ± 1250 (15)	4510	16400 ± 4740 (14)	15700
AUC_{0-inf} (ng*hr/mL)	5120 ± 1010 (13)	5020	18300 ± 7430 (9)	17000
t_{max} (hr)	0.51 (0.50, 1.5) (15)	.	0.75 (0.50, 1.2) (14)	.
$t_{1/2}$ (hr)	2.4 ± 0.43 (13)	.	8.1 ± 1.6 (9)	.
k_e (1/hr)	0.298 ± 0.0410 (13)	.	0.0888 ± 0.0173 (9)	.

Group 2: Erythromycin 500 mg BID for 5 days (Days 2-6) plus a single dose of 200 mg avanafil on Days 1 and 6
 t_{max} is presented as Median (Minimum, Maximum)
 . = Value missing or not reportable
 Source: Tables 14.2.2.3 through 14.2.2.4

The arithmetic mean C_{max} of avanafil increased 2.0-fold from 2030 to 4230 ng/mL when avanafil was co-administered with erythromycin, compared to avanafil alone.

The arithmetic mean AUC_{0-t} of avanafil increased 3.5-fold from 4690 to 16400 ng.hr/mL when avanafil was co-administered with erythromycin, compared to avanafil alone.

The arithmetic mean AUC_{0-inf} of avanafil increased 3.6-fold from 5120 to 18300 ng.hr/mL when avanafil was co-administered with erythromycin, compared to avanafil alone.

The median t_{max} increased by 0.25 hr from 0.5 to 0.75 hr when avanafil was co-administered with erythromycin, compared to avanafil alone.

The arithmetic mean $t_{1/2}$ increased by 5.7 hrs from 2.4 to 8.1 hrs when avanafil was co-administered with erythromycin, compared to avanafil alone.

Headache was the most frequent adverse event in subjects given avanafil and a strong or moderate CYP3A4 inhibitor and appear to double in frequency compared to avanafil 200 mg alone. The total frequency of headache was 57% in all three treatment groups and was similar among the different groups. The total frequency of headache and dizziness in subjects administered with 200 mg avanafil alone as either 4 x 50 mg, 2 x 200 mg, or 1 x 200 mg (Study TA-022) was 30%.

Treatment-emergent adverse events following avanafil + ketoconazole (Group 1), avanafil + erythromycin (Group 2), and avanafil + ritonavir (Group 3)

Table 14.3.1.1. Adverse Event Frequency by Group - Number of Subjects Reporting the Event

Adverse Event*	Group			Overall
	1	2	3	
Number of Subjects Dosed	15 (100%)	15 (100%)	14 (100%)	44 (100%)
Number of Subjects With Adverse Events	12 (80%)	14 (93%)	13 (93%)	39 (89%)
Number of Subjects Without Adverse Events	3 (20%)	1 (7%)	1 (7%)	5 (11%)
Ear and labyrinth disorders	0 (0%)	1 (7%)	0 (0%)	1 (2%)
Ear pain	0 (0%)	1 (7%)	0 (0%)	1 (2%)
Gastrointestinal disorders	5 (33%)	6 (40%)	13 (93%)	24 (55%)
Abdominal pain upper	1 (7%)	3 (20%)	4 (29%)	8 (18%)
Constipation	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Diarrhoea	0 (0%)	4 (27%)	12 (86%)	16 (36%)
Dyspepsia	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Faeces discoloured	0 (0%)	1 (7%)	0 (0%)	1 (2%)
Hypoaesthesia oral	0 (0%)	0 (0%)	8 (57%)	8 (18%)
Nausea	3 (20%)	1 (7%)	8 (57%)	12 (27%)
Paraesthesia oral	0 (0%)	0 (0%)	3 (21%)	3 (7%)
Stomach discomfort	1 (7%)	1 (7%)	2 (14%)	4 (9%)
Vomiting	0 (0%)	0 (0%)	2 (14%)	2 (5%)
General disorders and administration site conditions	3 (20%)	2 (13%)	10 (71%)	15 (34%)
Asthenia	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Chest discomfort	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Chills	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Fatigue	1 (7%)	2 (13%)	4 (29%)	7 (16%)
Feeling hot	1 (7%)	1 (7%)	4 (29%)	6 (14%)
Feeling of body temperature change	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Hunger	1 (7%)	0 (0%)	0 (0%)	1 (2%)
Pain	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Peripheral coldness	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Sluggishness	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Vessel puncture site pain	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Metabolism and nutrition disorders	0 (0%)	1 (7%)	2 (14%)	3 (7%)
Anorexia	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Increased appetite	0 (0%)	1 (7%)	0 (0%)	1 (2%)
Musculoskeletal and connective tissue disorders	0 (0%)	3 (20%)	1 (7%)	4 (9%)
Arthralgia	0 (0%)	2 (13%)	0 (0%)	2 (5%)
Back pain	0 (0%)	2 (13%)	0 (0%)	2 (5%)
Muscle tightness	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Nervous system disorders	9 (60%)	10 (67%)	11 (79%)	30 (68%)
Ageusia	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Burning sensation	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Dizziness	1 (7%)	1 (7%)	3 (21%)	5 (11%)
Dysgeusia	1 (7%)	0 (0%)	0 (0%)	1 (2%)
Headache	7 (47%)	9 (60%)	9 (64%)	25 (57%)
Hyperaesthesia	0 (0%)	0 (0%)	3 (21%)	3 (7%)
Hypoaesthesia	0 (0%)	0 (0%)	3 (21%)	3 (7%)
Hypoesthesia	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Paraesthesia	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Sinus headache	1 (7%)	1 (7%)	1 (7%)	3 (7%)
Psychiatric disorders	1 (7%)	1 (7%)	1 (7%)	3 (7%)

Anxiety	1 (7%)	0 (0%)	0 (0%)	1 (2%)
Confusional state	0 (0%)	1 (7%)	0 (0%)	1 (2%)
Loss of libido	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Renal and urinary disorders	0 (0%)	1 (7%)	2 (14%)	3 (7%)
Dysuria	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Micturition urgency	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Pollakiuria	0 (0%)	1 (7%)	1 (7%)	2 (5%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	3 (20%)	7 (50%)	10 (23%)
Cough	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Nasal congestion	0 (0%)	1 (7%)	1 (7%)	2 (5%)
Nasal discomfort	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Nasal dryness	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Oropharyngeal pain	0 (0%)	0 (0%)	3 (21%)	3 (7%)
Productive cough	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Rhinorrhoea	0 (0%)	0 (0%)	3 (21%)	3 (7%)
Sinus congestion	0 (0%)	2 (13%)	1 (7%)	3 (7%)
Throat irritation	0 (0%)	0 (0%)	4 (29%)	4 (9%)
Skin and subcutaneous tissue disorders	0 (0%)	1 (7%)	1 (7%)	2 (5%)
Rash papular	0 (0%)	1 (7%)	0 (0%)	1 (2%)
Skin warm	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Vascular disorders	1 (7%)	0 (0%)	2 (14%)	3 (7%)
Flushing	0 (0%)	0 (0%)	2 (14%)	2 (5%)
Pallor	1 (7%)	0 (0%)	0 (0%)	1 (2%)

Ear and labyrinth disorders	0 (0%)	1 (2%)	0 (0%)	1 (0%)
Ear pain	0 (0%)	1 (2%)	0 (0%)	1 (0%)
Gastrointestinal disorders	5 (21%)	12 (24%)	112 (54%)	129 (46%)
Abdominal pain upper	1 (4%)	3 (6%)	6 (3%)	10 (4%)
Constipation	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Diarrhoea	0 (0%)	6 (12%)	53 (26%)	59 (21%)
Dyspepsia	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Faeces discoloured	0 (0%)	1 (2%)	0 (0%)	1 (0%)
Hypoaesthesia oral	0 (0%)	0 (0%)	21 (10%)	21 (7%)
Nausea	3 (13%)	1 (2%)	15 (7%)	19 (7%)
Paraesthesia oral	0 (0%)	0 (0%)	6 (3%)	6 (2%)
Stomach discomfort	1 (4%)	1 (2%)	5 (2%)	7 (2%)
Vomiting	0 (0%)	0 (0%)	3 (1%)	3 (1%)
General disorders and administration site conditions	3 (13%)	5 (10%)	25 (12%)	33 (12%)
Asthenia	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Chest discomfort	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Chills	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Fatigue	1 (4%)	4 (8%)	5 (2%)	10 (4%)
Feeling hot	1 (4%)	1 (2%)	7 (3%)	9 (3%)
Feeling of body temperature change	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Hunger	1 (4%)	0 (0%)	0 (0%)	1 (0%)
Pain	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Peripheral coldness	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Sluggishness	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Vessel puncture site pain	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Metabolism and nutrition disorders	0 (0%)	1 (2%)	2 (1%)	3 (1%)
Anorexia	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Increased appetite	0 (0%)	1 (2%)	0 (0%)	1 (0%)

Musculoskeletal and connective tissue disorders	0 (0%)	5 (10%)	1 (0%)	6 (2%)
Arthralgia	0 (0%)	3 (6%)	0 (0%)	3 (1%)
Back pain	0 (0%)	2 (4%)	0 (0%)	2 (1%)
Muscle tightness	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Nervous system disorders	14 (58%)	18 (35%)	39 (19%)	71 (25%)
Ageusia	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Burning sensation	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Dizziness	1 (4%)	3 (6%)	3 (1%)	7 (2%)
Dysgeusia	1 (4%)	0 (0%)	0 (0%)	1 (0%)
Headache	11 (46%)	14 (27%)	15 (7%)	40 (14%)
Hyperaesthesia	0 (0%)	0 (0%)	4 (2%)	4 (1%)
Hypoaesthesia	0 (0%)	0 (0%)	3 (1%)	3 (1%)
Hypogeusia	0 (0%)	0 (0%)	5 (2%)	5 (2%)
Paraesthesia	0 (0%)	0 (0%)	5 (2%)	5 (2%)
Sinus headache	1 (4%)	1 (2%)	1 (0%)	3 (1%)
Psychiatric disorders	1 (4%)	1 (2%)	1 (0%)	3 (1%)
Anxiety	1 (4%)	0 (0%)	0 (0%)	1 (0%)
Confusional state	0 (0%)	1 (2%)	0 (0%)	1 (0%)
Loss of libido	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Renal and urinary disorders	0 (0%)	1 (2%)	3 (1%)	4 (1%)
Dysuria	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Micturition urgency	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pollakiuria	0 (0%)	1 (2%)	1 (0%)	2 (1%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	4 (8%)	19 (9%)	23 (8%)
Cough	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Nasal congestion	0 (0%)	2 (4%)	2 (1%)	4 (1%)
Nasal discomfort	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Nasal dryness	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Oropharyngeal pain	0 (0%)	0 (0%)	3 (1%)	3 (1%)
Productive cough	0 (0%)	0 (0%)	1 (0%)	1 (0%)

Rhinorrhoea	0 (0%)	0 (0%)	3 (1%)	3 (1%)
Sinus congestion	0 (0%)	2 (4%)	1 (0%)	3 (1%)
Throat irritation	0 (0%)	0 (0%)	5 (2%)	5 (2%)
Skin and subcutaneous tissue disorders	0 (0%)	3 (6%)	1 (0%)	4 (1%)
Rash papular	0 (0%)	3 (6%)	0 (0%)	3 (1%)
Skin warm	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Vascular disorders	1 (4%)	0 (0%)	3 (1%)	4 (1%)
Flushing	0 (0%)	0 (0%)	3 (1%)	3 (1%)
Pallor	1 (4%)	0 (0%)	0 (0%)	1 (0%)

Study TA-012

Title: A Phase I, Open Label, Non-Randomized, Single-Dose, Parallel-Cohort, Matched-Control Study to Evaluate the Pharmacokinetics and Safety of Avanafil (TA-1790) In Subjects With Hepatic Impairment and in Healthy Control Male Subjects

Objectives: The primary objective of this study was to assess a single 200 mg (1 x 200 mg) dose PK of avanafil in subjects with hepatic impairment and in healthy control subjects. The secondary objectives were evaluate the safety and tolerability of avanafil in subjects with hepatic impairment.

Methods: This was an open-label, non-randomized, single-dose, parallel-cohort, matched-control study. Subjects in Cohorts 1 and 2 were matched to the subjects in the moderate hepatic group (Cohort 3) with respect to age and body weight. There were 24 subjects (21 were White/Caucasian and 3 Black/African American). The mean age of all 24 subjects was 58.0, 57.3, and 58.6 yrs (range 45-69 yrs) for Cohorts 1, 2, 3, respectively. The mean weight was 72.1 kg (range 62.0-87.2 kg). Subjects were given a single 200 mg (1 x 200 mg) avanafil, Formulation II (lot # 17TA90090020).

All doses were administered in the morning with 240 mL water following an overnight fast of at least 10 hrs. Subjects reported to the study clinic the evening before treatment on Day 1 and remained at the site until the 24-hr PK sample was taken. Subjects were given a standard meal at approximately 4 and 9 hrs after dosing. Eight subjects were assigned to one of three cohorts based on hepatic function:

Cohort 1: Normal Hepatic Function – Child Pugh Class/Score: not applicable

Cohort 2: Mild Hepatic Impairment – Child Pugh Class A (Score: 5-6)

Cohort 3: Moderate Hepatic Impairment – Child Pugh Class B (Score: 7-9)

Pharmacokinetic Sampling: Blood samples were taken at 0 (predose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 8, 12, 18, and 24 hrs postdose for plasma avanafil, M4, and M16 concentrations. Blood samples were collected predose and at 0.5 hrs postdose for determination of avanafil plasma protein binding.

Results: The sponsor assessed the effect of hepatic impairment on the PK of a single 200 mg dose of avanafil. The sponsor did not evaluate the affect of severe renal impairment or end stage renal disease on PK of avanafil.

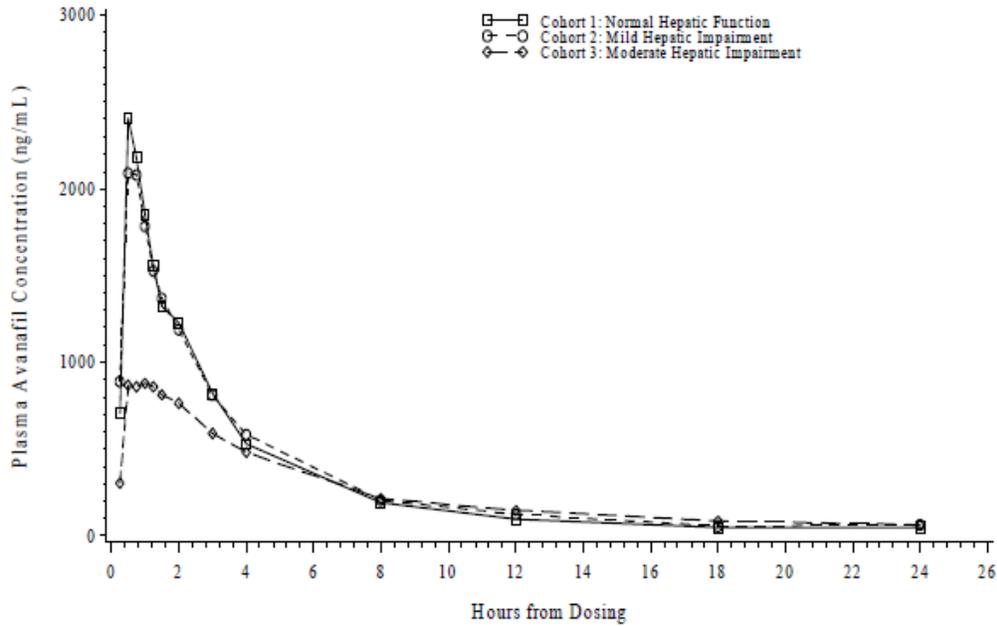
Subjects with normal hepatic function and mild hepatic impairment had similar arithmetic mean (SD) C_{max}, AUC_{0-t}, and AUC_{0-inf} for avanafil. In subjects with mild hepatic impairment, mean (SD) C_{max}, AUC_{0-t}, and AUC_{0-inf} for avanafil decreased by 2.7%, increased by 7.0%, and increased by 3.8%, respectively. Given the degree of inter-subject variability, these changes do not appear to be significant.

In contrast, in subjects with moderate hepatic impairment, the arithmetic mean (SD) C_{max} was reduced by approximately 51% from 2610 (796) to 1270 (739) ng/mL, compared to healthy subjects with normal hepatic function. Arithmetic mean (SD) AUC_{0-t} was reduced by approximately 8.2% from 7960 (2160) to 7310 (4210) ng.hr/mL, whereas arithmetic mean (SD) AUC_{0-inf} increased by approximately 11.2% from 9260 (2210) to 10300 (4490) ng.hr/mL in subjects with moderate hepatic impairment, compared to healthy subjects with normal hepatic function.

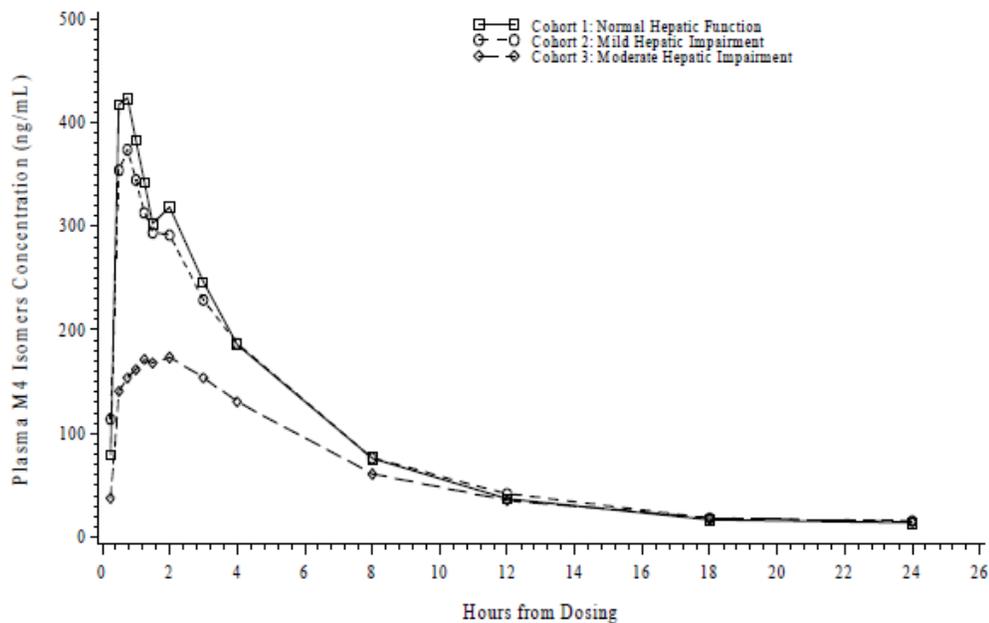
Mild headache was the most common AE. It was reported a total of 12 times by 11 (46%) of all subjects: 5 with normal hepatic function, 3 with mild hepatic impairment, and 3 with moderate hepatic impairment. Despite the reduction of approximately 51% in C_{max} and 11% increase AUC_{0-inf} in subjects with moderate hepatic impairment compared to normal hepatic function, the number and percent of subjects

reporting AEs was similar in all three cohorts. Therefore the small changes in avanafil PK in subjects with mild and moderate hepatic impairment do not appear to contribute to additional adverse events. Because subjects with severe hepatic impairment were not included in this study, avanafil is not recommended for use in that population.

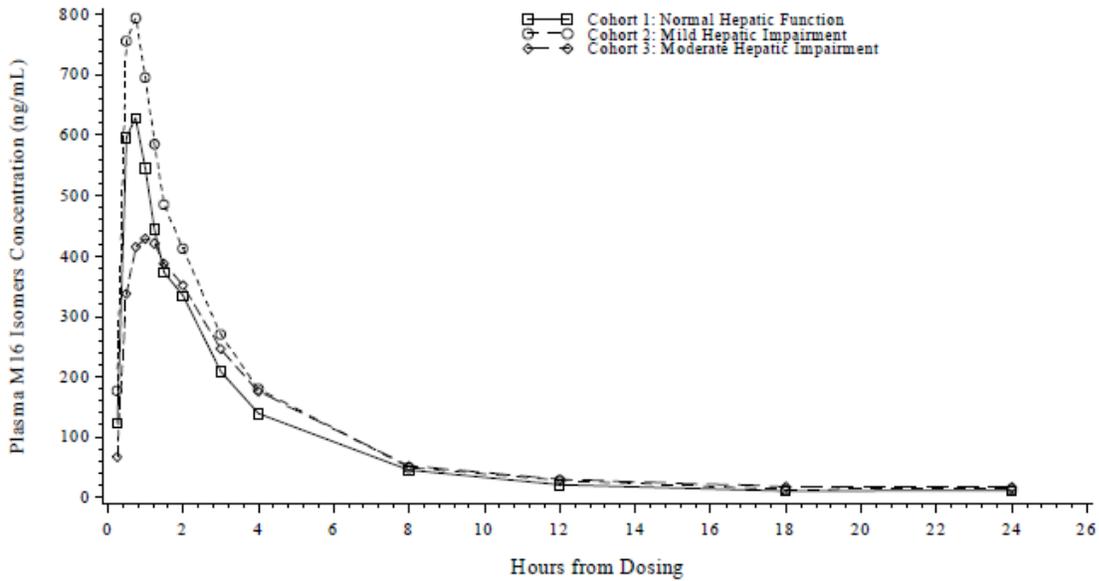
The following is the geometric mean (SD) avanafil concentrations vs time profile in subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (sponsor's figure 2)



The following is the geometric mean (SD) M4 concentrations vs time profile in subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (sponsor's figure 3)



The following is the geometric mean (SD) M16 concentrations vs time profile in subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (sponsor's figure 4)



The following table summarizes the arithmetic mean (SD) and geometric mean PK for avanafil in subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (sponsor's table 3)

Pharmacokinetic Parameters	Normal Hepatic Function Cohort 1		Mild Hepatic Impairment Cohort 2		Moderate Hepatic Impairment Cohort 3	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	2610 ± 796 (8)	2480	2540 ± 886 (8)	2390	1270 ± 739 (8)	1060
AUC _{0-t} (ng*hr/mL)	7960 ± 2160 (8)	7730	8520 ± 2920 (8)	8120	7310 ± 4210 (8)	6250
AUC _{0-inf} (ng*hr/mL)	9260 ± 2210 (6)	9060	9610 ± 3660 (6)	9050	10300 ± 4490 (5)	9290
*t _{max} (hr)	0.50 (0.50, 1.0) (8)	.	0.50 (0.50, 2.1) (8)	.	1.1 (0.50, 3.0) (8)	.
t _{1/2} (hr)	7.5 ± 2.8 (6)	.	6.9 ± 1.8 (6)	.	6.1 ± 1.9 (5)	.
k _{el} (1/hr)	0.103 ± 0.0337 (6)	.	0.108 ± 0.0333 (6)	.	0.124 ± 0.0412 (5)	.
CL/F (L/hr)	22.5 ± 4.84 (6)	.	23.4 ± 8.61 (6)	.	24.5 ± 15.6 (5)	.
V/F (L)	240 ± 93.5 (6)	.	227 ± 94.6 (6)	.	218 ± 173 (5)	.
Cohort 1: Normal hepatic function (reference) Cohort 2: Mild hepatic impairment (test) Cohort 3: Moderate hepatic impairment (test) C _{max} , AUC _{0-t} , AUC _{0-inf} , and k _{el} values are presented with three significant figures. t _{1/2} is presented with two significant figures. *t _{max} is presented as median (minimum, maximum) and is presented with two significant figures. . = Value missing or not reportable. SD = standard deviation Source: Tables 14.2.1.4, 14.2.1.5, and 14.2.1.6						

Subjects with normal hepatic function and mild hepatic impairment had similar arithmetic mean C_{max}, AUC_{0-t}, and AUC_{0-inf} for avanafil. In subjects with mild hepatic impairment, mean C_{max}, AUC_{0-t}, and AUC_{0-inf} for avanafil decreased by 2.7%, increased by 7.0%, and increased by 3.8%, respectively. Given the degree of inter-subject variability, these changes do not appear to be significant.

In contrast, in subjects with moderate hepatic impairment, the arithmetic mean(SD) C_{max} was reduced by approximately 51% from 2610 (796) to 1270 (739) ng/mL, compared to healthy subjects with normal hepatic function. Arithmetic mean (SD) AUC_{0-t} was reduced by approximately 8.2% from 7960 (2160) to 7310 (4210) ng.hr/mL, whereas arithmetic mean (SD) AUC_{0-inf} increased by approximately 11.2% from 9260 (2210) to 10300 (4490) ng.hr/mL in subjects with moderate hepatic impairment, compared to healthy subjects with normal hepatic function.

The following table is a statistical comparison of geometric LS Means PK parameters for avanafil, M4, and M16 from subject with **mild hepatic impairment vs normal hepatic function**

Pharmacokinetic Parameters		Geometric Least-Squares Means ^a		Confidence Intervals		
		Mild Hepatic Impairment	Normal Hepatic Function	90% Confidence	% Mean Ratio ^b	
C _{max} (ng/mL)	Avanafil	2390	2480	(62.61, 147.34)	96.05	
	M4	442	456	(61.92, 151.60)	96.89	
	M16	894	653	(89.65, 209.48)	137.04	
AUC _{0-t} (ng*hr/mL)	Avanafil	8120	7730	(72.96, 151.55)	105.15	
	M4	2140	2150	(72.06, 137.69)	99.61	
	M16	2540	1960	(93.07, 180.54)	129.63	
AUC _{0-inf} (ng*hr/mL) ^b	Avanafil	9050	9060	(67.08, 148.78)	99.90	
	M4	2320	2290	(75.92, 134.41)	101.02	
	M16	3050	2040	(102.74, 218.74)	149.91	
		Treatment Median				
		Mild Hepatic Impairment	Normal Hepatic Function	95% CI	Median Difference ^c	P-value
t _{max} (hr)	Avanafil	0.50	0.50	(0.00, 1.25)	0.000	0.5227
	M4	0.75	0.63	(-0.25, 1.05)	0.000	0.6161
	M16	0.50	0.63	(-0.25, 0.50)	0.000	1.0000
t _{1/2} (hr) ^b	Avanafil	6.9	6.4	(-4.32, 2.50)	0.012	1.0000
	M4	7.5	6.5	(-1.36, 1.45)	0.880	0.3184
	M16	6.2	7.7	(-5.55, 1.53)	-1.402	0.6366

For avanafil, the geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} was 96%, 105%, and 100%, respectively, between subjects with mild hepatic impairment and normal hepatic function.

For M4 (a metabolite of avanafil that accounts for approximately 4% of the pharmacologic activity of avanafil), the geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} was 96.9%, 100%, and 101%, respectively, between subjects with mild hepatic impairment and normal hepatic function.

For M16 (a downstream metabolite of M4 with no pharmacologic activity), the geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} was significantly higher at 137%, 130%, and 150%, respectively, between subjects with mild hepatic impairment and normal hepatic function.

T_{max} was 0.5 hr in both groups. Half-life increased by 0.5 hr from 6.4 to 6.9 hrs in subjects with mild hepatic impairment, compared to subjects with normal hepatic function.

The following table is a statistical comparison of PK parameters for avanafil, M4, and M16 from subject with **moderate hepatic impairment vs normal hepatic function**

Pharmacokinetic Parameters		Geometric Least-Squares Means ^a		Confidence Intervals	% Mean Ratio ^b	
		Moderate Hepatic Impairment	Normal Hepatic Function	90% Confidence		
C _{max} (ng/mL) ^a	Avanafil	1060	2480	(27.82, 65.47)	42.68	
	M4	210	456	(29.42, 72.02)	46.03	
	M16	473	653	(47.40, 110.75)	72.45	
AUC _{0-t} (ng*hr/mL) ^a	Avanafil	6250	7730	(56.14, 116.62)	80.92	
	M4	1480	2150	(49.64, 94.84)	68.61	
	M16	2110	1960	(77.39, 150.13)	107.79	
AUC _{0-inf} (ng*hr/mL) ^b	Avanafil	9290	9060	(67.52, 155.69)	102.53	
	M4	2030	2290	(63.94, 122.62)	88.55	
	M16	2410	2040	(78.16, 179.59)	118.48	
Treatment Median						
		Moderate Hepatic Impairment	Normal Hepatic Function	95% CI	Median Difference ^c	P-value
t _{max} (hr)	Avanafil	1.1	0.50	(0.00, 1.52)	0.500	0.0636
	M4	2.0	0.63	(0.25, 2.50)	1.258	0.0139
	M16	1.1	0.63	(0.00, 0.75)	0.500	0.0174
t _{1/2} (hr) ^b	Avanafil	7.1	6.4	(-5.99, 2.43)	-1.463	0.6481
	M4	8.1	6.5	(-1.39, 3.15)	0.830	0.8262
	M16	5.2	7.7	(-6.87, 2.52)	-1.257	0.3619

For avanafil, the geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} was 43%, 81%, and 103%, respectively, between subjects with moderate hepatic impairment and normal hepatic function.

For M4, the geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} was 46%, 69%, and 89%, respectively, between subjects with moderate hepatic impairment and normal hepatic function.

For M16, the geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} was 73%, 108%, and 119%, respectively, between subjects with moderate hepatic impairment and normal hepatic function.

T_{max} increased by 0.6 hr from 0.5 to 1.1 hrs and t_{1/2} increased 0.7 hr from 6.4 to 7.1 hrs in subjects with moderate hepatic impairment, compared to subjects with normal hepatic function.

The following table summarizes geometric LS mean ratios of PK parameters of M4 and M16 metabolites to avanafil (sponsor's table 21)

Study Cohort	Pharmacokinetic Parameters	Least-Squares Means			% Ratio [®]	
		Avanafil	M4	M16	M4	M16
Cohort 1 (Subjects with Normal Hepatic Function)	C _{max} (ng/mL)	2480	456	653	18.4	26.3
	AUC _{0-t} (ng*hr/mL)	7730	2150	1960	27.8	25.4
	AUC _{0-inf} (ng*hr/mL)	9060	2290	2040	25.3	22.5
Cohort 2 (Subjects with Mild Hepatic Impairment)	C _{max} (ng/mL)	2390	442	894	18.5	37.5
	AUC _{0-t} (ng*hr/mL)	8120	2140	2540	26.4	31.3
	AUC _{0-inf} (ng*hr/mL)	9050	2320	3050	25.6	33.7
Cohort 3 (Subjects with Moderate Hepatic Impairment)	C _{max} (ng/mL)	1060	210	473	19.8	44.6
	AUC _{0-t} (ng*hr/mL)	6250	1480	2110	23.6	33.8
	AUC _{0-inf} (ng*hr/mL)	9290	2030	2410	21.9	26.0

The geometric LS mean ratios of M4/avanafil PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} were similar in subjects in all three cohorts and ranged from 18.4 to 27.8%. However, the geometric LS mean ratios of M16/avanafil PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} appears to be higher in subjects with mild and moderate hepatic impairment ranging from 26.0 to 44.6%, compared to subjects with normal hepatic function with a range of 22.5 to 26.3%.

Mean ± SD Human Plasma Protein Binding of Avanafil, M4 and M16			
Test Compound	Hepatic Function	Protein Binding (%)	Recovery (%)
Avanafil (0.5 hour post-dose)	Normal	99.1 ± 0.07	96.3 ± 4.94
	Mild Impairment	99.0 ± 0.08	96.1 ± 2.51
	Moderate Impairment	98.8 ± 0.44	96.4 ± 2.08
Avanafil (Pre-dose samples fortified with 2000 ng/mL avanafil)	Normal	99.1 ± 0.04	97.3 ± 4.73
	Mild Impairment	99.0 ± 0.12	96.0 ± 1.67
	Moderate Impairment	98.6 ± 0.49	96.2 ± 2.16
M4 (0.5 hour post-dose)	Normal	96.8 ± 0.14	102.2 ± 6.73
	Mild Impairment	96.2 ± 0.46	97.7 ± 2.00
	Moderate Impairment	95.5 ± 1.07	99.4 ± 2.37
M4 (Pre-dose samples fortified with 500 ng/mL M4)	Normal	97.2 ± 0.14	107.1 ± 8.81
	Mild Impairment	96.7 ± 0.39	98.6 ± 2.19
	Moderate Impairment	96.3 ± 0.83	95.9 ± 7.97
M16 (0.5 hour post-dose)	Normal	85.7 ± 1.83	100.2 ± 6.71
	Mild Impairment	82.6 ± 3.70	101.0 ± 3.42
	Moderate Impairment	83.5 ± 1.93	101.9 ± 2.83
M16 (Pre-dose samples fortified with 1000 ng/mL M16)	Normal	84.4 ± 1.72	103.1 ± 5.15
	Mild Impairment	81.2 ± 2.35	98.0 ± 2.31
	Moderate Impairment	81.2 ± 2.22	98.1 ± 6.36
Warfarin	Positive Control	98.9 ± 0.03	91.8 ± 2.52

Plasma protein binding for avanafil, M4, and M16 was generally the same irrespective of hepatic function. For avanafil and M4, protein binding was high and ranged from 95.5 to 99.1% 0.5 hr after avanafil administration. For M16, protein binding was moderate and ranged from 82.6 to 85.7% 0.5 hr after avanafil administration.

The following table presents the incidence of treatment-emergent adverse events (AE) by cohort (sponsor's table 22):

Cohort	Number (%) of Subjects Reporting AEs	Number of AE Episodes Reported
Cohort 1: Normal hepatic function (N = 8)	6 (75%)	9
Cohort 2: Mild hepatic impairment (N = 8)	5 (63%)	5
Cohort 3: Moderate hepatic impairment (N = 8)	6 (75%)	8
Overall (N = 24)	17 (71%)	22
Source: Tables 14.3.1.1 and 14.3.1.2		

Mild headache was the most common AE. It was reported a total of 12 times by 11 (46%) of all subjects: 5 with normal hepatic function, 3 with mild hepatic impairment, and 3 with moderate hepatic impairment.

Despite the reduction of approximately 51% in C_{max} and 11% increase AUC_{0-inf} in subjects with moderate hepatic impairment compared to normal hepatic function, the number and percent of subjects reporting AEs was similar in all three cohorts. Therefore the small changes in avanafil PK in subjects with mild and moderate hepatic impairment do not appear to contribute to additional adverse events. Because subjects with severe hepatic impairment were not included in this study, avanafil is not recommended for use in that population.

Study TA-013

Title: A Phase I, Open-Label, Parallel-Group, Single Dose, Non-Randomized Study to Compare the Pharmacokinetics of Avanafil in Male Subjects with Mild and Moderate Renal Impairment to Subjects with Normal Renal Function

Objectives: The primary objective of this study was to compare the PK of avanafil in subjects with mild and moderate renal impairment to subjects with normal renal function. The secondary objective was to assess the safety and tolerability of avanafil in subjects with mild and moderate renal impairment.

Methods: The sponsor completed this study in February 2010 before FDA issued the new renal impairment guidance in March 2010 with updated classification of chronic kidney disease. At the request of this reviewer and the avanafil Clinical team, the sponsor conducted a post-hoc PK analysis of this study based on reclassification of subjects according to FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010). According to the new guidance, subjects are categorized to various renal function based on the following estimated glomerular filtration rate (eGFR) or estimated creatinine clearance by the Cockcroft-Gault equation (CLcr) (guidance table 1)

Stage	Description ^b	eGFR ^c (mL/min/1.73m ²)	CLcr ^d (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

This was a single-center, open-label, parallel group, non-randomized, single 200 mg (1 x 200 mg) dose PK study in male subjects with varying degrees of renal impairment. Based on post-hoc re-classification of renal function based on CLcr, there were 5 subjects with normal renal function, 9 subjects with mild renal impairment, and 10 subjects with moderate renal impairment.

The mean age was 61.6, 68.9 and 70.4 yrs (range 52-78 yrs) for Cohort 1, 2, and 3, respectively, according to the original classification scheme.

Pharmacokinetic Sampling: Blood samples were taken at 0 (30 min predose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 8, 12, 16, and 24 hrs postdose for determination of avanafil and metabolites M4 and M16 concentrations. Blood samples were collected at 0 and 0.5 hr postdose to assess avanafil plasma protein binding.

Results: The sponsor evaluated the affect of mild and moderate renal impairment on avanafil and metabolites M4 and M16 PK. The sponsor did not evaluate the affect of severe renal impairment or end stage renal disease on PK of avanafil. Overall, there were some small changes in avanafil PK. The most prominent change in avanafil PK was in the total exposure in subjects with moderate renal impairment, compared to normal renal function; however, given the degree of inter-subject variability, these changes do not appear to be significant.

Arithmetic mean (SD) C_{max} was similar in all three groups: 2870 (1060), 2950 (1090), and 2790 (1010) ng/mL in subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Median t_{max} was similar in all three groups: 0.75, 0.5, and 0.75 hr in subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Arithmetic mean (SD) t_{1/2} was similar in subjects with normal renal function and mild renal impairment at 6.4 (4.4) and 6.2 (3.0), respectively. However, mean (SD) t_{1/2} was reduced by 1.5 hrs from 6.4 (4.4) to 4.9 (2.2) in subjects with moderate renal impairment, compared to subjects with normal renal function.

Arithmetic mean (SD) AUC_{0-inf} for avanafil decreased by 3.0% from 8490 (1180) to 8240 (2800) ng*hr/mL and increased by approximately 9.1% from 8490 (1180) to 9260 (2920) ng*hr/mL in subjects with mild renal impairment and moderate renal impairment, respectively, compared to healthy subjects with normal renal function.

Arithmetic mean (SD) and geometric mean PK parameters for avanafil in subjects with normal renal function, and mild and moderate renal impairment based on CL_{cr} (sponsor's table 2, serial 0018)

Pharmacokinetic Parameters	Normal Renal Function (Cohort 1)		Mild Renal Impairment (Cohort 2)		Moderate Renal Impairment (Cohort 3)	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	2870 ± 1060 (5)	2740	2950 ± 1090 (9)	2740	2790 ± 1010 (10)	2600
AUC _{0-t} (ng*hr/mL)	8210 ± 2540 (5)	7880	8060 ± 2460 (9)	7650	9150 ± 3470 (10)	8570
AUC _{0-inf} (ng*hr/mL)	8490 ± 1180 (3)	8430	8240 ± 2800 (7)	7750	9260 ± 2920 (6)	8850
*t _{max} (hr)	0.75 (0.50, 1.0) (5)	.	0.50 (0.50, 0.50) (9)	.	0.75 (0.50, 1.5) (10)	.
t _{1/2} (hr)	6.4 ± 4.4 (3)	.	6.2 ± 3.0 (7)	.	4.9 ± 2.2 (6)	.
k _{el} (1/hr)	0.143 ± 0.079 (3)	.	0.130 ± 0.051 (7)	.	0.184 ± 0.120 (6)	.
CL/F (L/hr)	23.9 ± 3.5 (3)	.	27.8 ± 12.6 (7)	.	23.8 ± 8.6 (6)	.
V/F (L)	216 ± 141 (3)	.	224 ± 80 (7)	.	156 ± 76.8 (6)	.

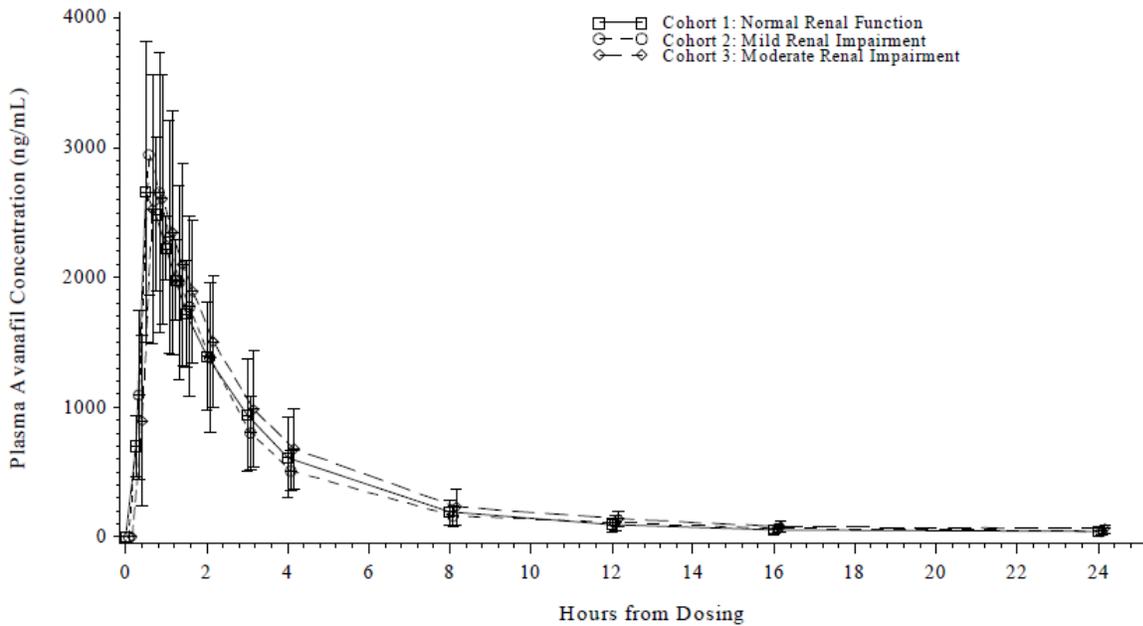
Arithmetic mean (SD) and geometric mean PK parameters for M4 in subjects with normal renal function, and mild and moderate renal impairment based on CLcr (sponsor's table 3, serial 0018)

Pharmacokinetic Parameters	Normal Renal Function (Cohort 1)		Mild Renal Impairment (Cohort 2)		Moderate Renal Impairment (Cohort 3)	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	549 ± 152 (5)	531	558 ± 161 (9)	528	521 ± 161 (10)	495
AUC _{0-t} (ng*hr/mL)	2390 ± 446 (5)	2350	2450 ± 604 (9)	2380	2860 ± 744 (10)	2750
AUC _{0-inf} (ng*hr/mL)	2510 ± 462 (5)	2470	2580 ± 640 (7)	2510	3250 ± 628 (9)	3190
*t _{max} (hr)	0.75 (0.75, 1.5) (5)	.	0.50 (0.50, 2.0) (9)	.	0.75 (0.50, 3.0) (10)	.
t _{1/2} (hr)	7.4 ± 2.4 (5)	.	6.2 ± 1.4 (7)	.	7.1 ± 2.2 (9)	.
k _{el} (1/hr)	0.103 ± 0.036 (5)	.	0.116 ± 0.022 (7)	.	0.106 ± 0.031 (9)	.

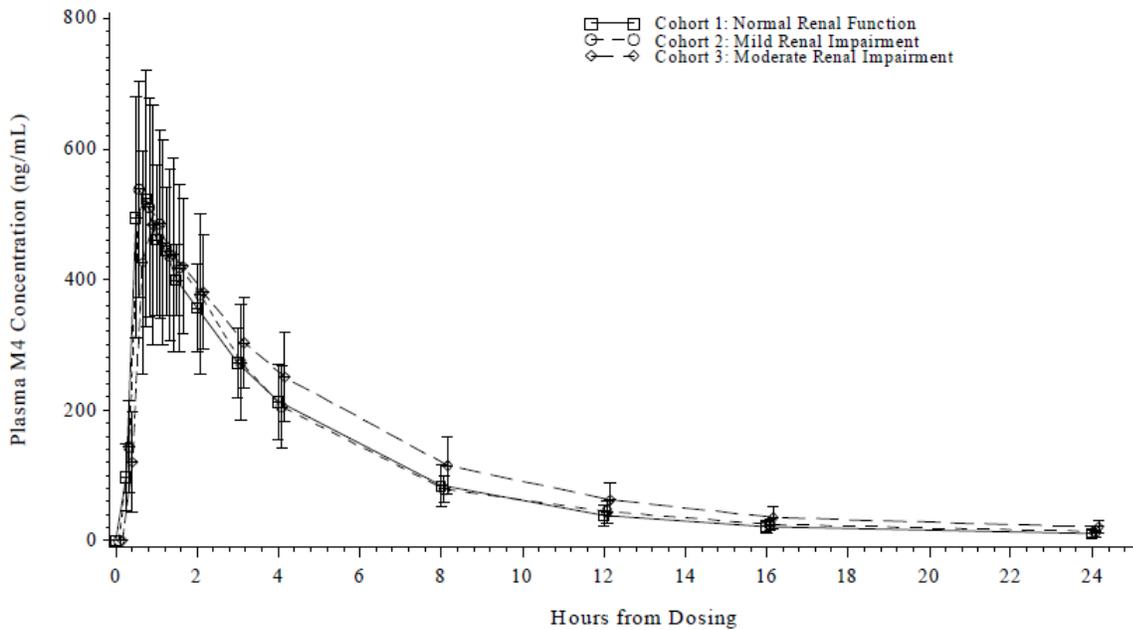
Arithmetic mean (SD) and geometric mean PK parameters for M16 in subjects with normal renal function, and mild and moderate renal impairment based on CLcr (sponsor's table 4, serial 0018)

Pharmacokinetic Parameters	Normal Renal Function (Cohort 1)		Mild Renal Impairment (Cohort 2)		Moderate Renal Impairment (Cohort 3)	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	918 ± 255 (5)	883	1000 ± 361 (9)	926	1220 ± 447 (10)	1130
AUC _{0-t} (ng*hr/mL)	2500 ± 897 (5)	2390	2840 ± 837 (9)	2730	5100 ± 2160 (10)	4710
AUC _{0-inf} (ng*hr/mL)	2580 ± 876 (5)	2480	2970 ± 852 (6)	2880	6100 ± 2280 (8)	5820
*t _{max} (hr)	1.0 (0.75, 1.3) (5)	.	0.50 (0.50, 1.0) (9)	.	1.0 (0.75, 2.0) (10)	.
t _{1/2} (hr)	6.4 ± 3.0 (5)	.	6.2 ± 0.8 (6)	.	6.9 ± 2.2 (8)	.
k _{el} (1/hr)	0.131 ± 0.062 (5)	.	0.114 ± 0.015 (6)	.	0.108 ± 0.030 (8)	.

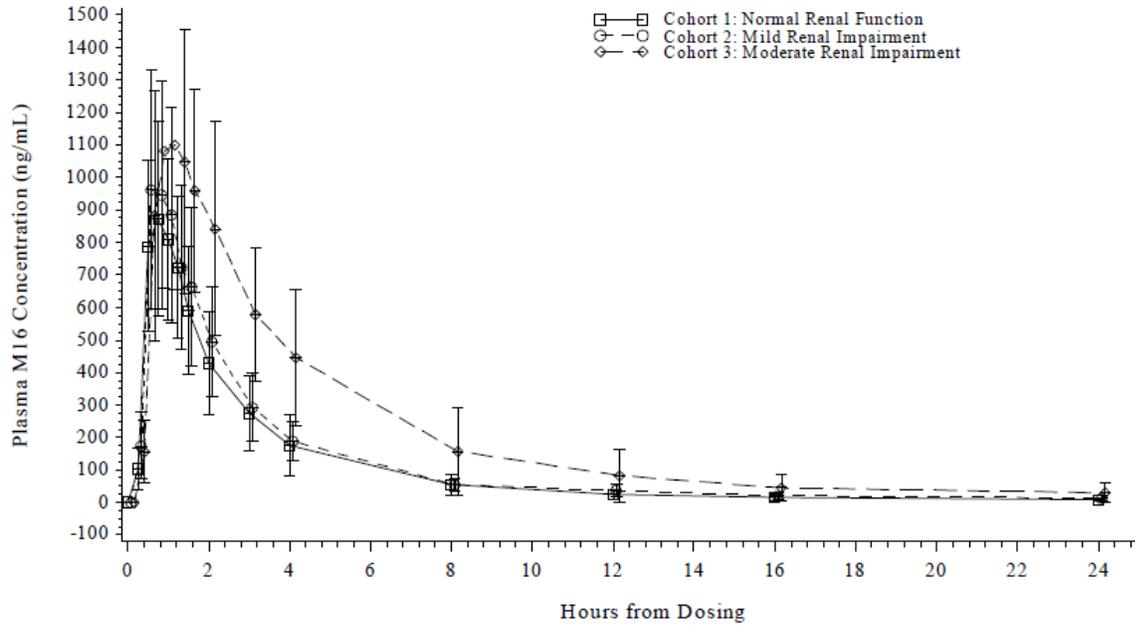
Arithmetic mean (SD) avanafil concentrations vs. time following 200 mg avanafil in subjects with normal renal function, and mild and moderate renal impairment based on CLcr (sponsor's figure 14.4.1.1a)



Arithmetic mean (SD) M4 concentrations vs. time following 200 mg avanafil in subjects with normal renal function, and mild and moderate renal impairment (based on CLcr) (sponsor's figure 14.4.2.1a)



Arithmetic mean (SD) M16 concentrations vs. time following 200 mg avanafil in subjects with normal renal function, and mild and moderate renal impairment (based on CLcr) (sponsor's figure 14.4.3.1a)



Study TA-014

Title: A Phase I, Single-Center, Open-Label, Non-Randomized, Two-Cohort, Pharmacokinetic Study to Assess the Effect of Age on the Pharmacokinetics of Avanafil and to Determine Avanafil Semen Exposure and the Acute Effect of Avanafil on Sperm Function in Healthy Young Male Subjects Following a Single Oral Dose of 200 mg Avanafil

Objectives: The primary objectives of this study were (1) to determine avanafil semen exposure; (2) to determine the acute effect of avanafil on sperm motility, count, density, morphology, vitality, ejaculate volume and viscosity; and (3) to assess the effects of age on the PK of avanafil and its metabolites following a single oral dose of avanafil. The secondary objectives were to evaluate the safety and tolerability of avanafil in healthy young and elderly male subjects.

Methods: This was a single-center, open-label, non-randomized, two-cohort, single 200 mg dose (1 x 200 mg) PK study in healthy young non-vasectomized (Cohort A) and healthy elderly subjects (Cohort B).

There were 32 subjects who were enrolled and completed the study with 18 subjects enrolled in Cohort A (17 Caucasians and 1 Other) and 14 enrolled in Cohort B (14 Caucasians). The mean age was 31.6 yrs (range 19-43 yrs) and 72.6 yrs (range 65-80 yrs) for Cohort A and B, respectively. The mean weight was 73.7 (range 61.7-82.9 kg) and 83.3 (range 69.8-97.1 kg) for Cohort A and B, respectively.

All study drugs were administered in the morning with 240 mL water after an overnight fast for at least 10 hrs. Subjects refrained from food until 4 hrs (± 30 min) after the morning daily dose of avanafil on the PK days (Day 1). Subjects were confined at the clinical site approximately 12-16 hrs prior to avanafil dosing and remained at the site until approximately 24 hrs after the avanafil.

Pharmacokinetic Sampling: Blood samples were taken at 0 (30 min predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 12, 18, and 24 hrs postdose for determination of plasma avanafil, M4, and M16 concentrations. Seminal fluid and plasma were collected from Cohort A. Plasma samples were collected from Cohort B.

Sperm Evaluation: Subjects in Cohort A visited the clinic site on Day -4 for a predose semen sample collection and sperm function test. On Day 1, semen was collected 1 hr postdose for determination of avanafil, metabolites M4 and M16, and sperm function test.

Results: Men treated for ED are generally older; therefore, the sponsor conducted this study to assess whether age affects PK of avanafil. PDE5 inhibitors are known to partition to seminal fluid; therefore, the sponsor conducted this study to assess avanafil localization in semen compared to plasma, the effect of avanafil on sperm motility, count, density, morphology, ejaculate volume and viscosity. This reviewer did not review the sperm morphology and count data.

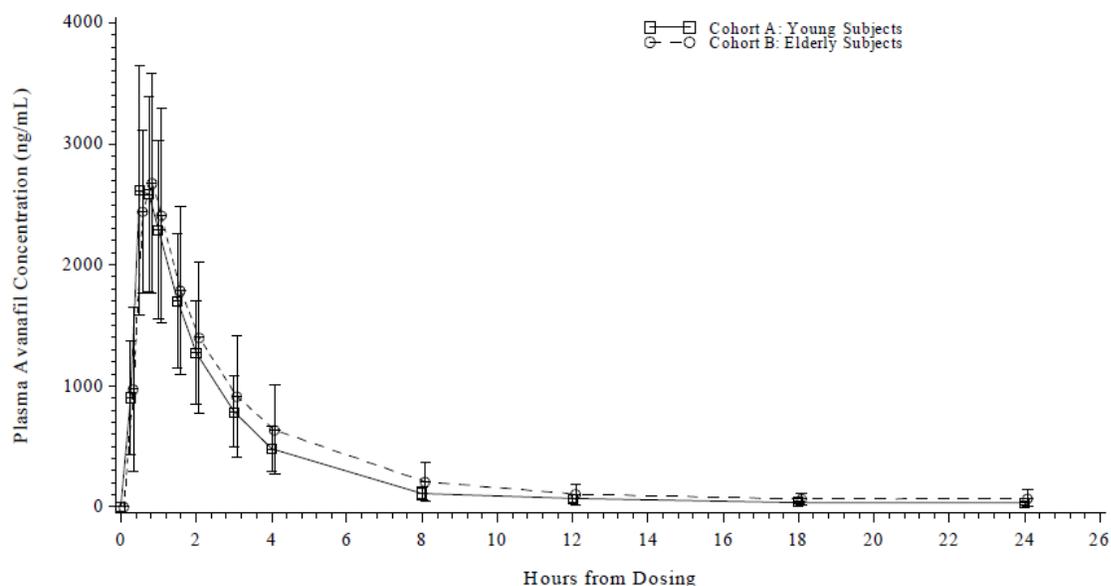
The geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} between elderly and young subjects was 100, 112, and 98%, respectively. The 90% confidence intervals of the mean ratios were outside the 80% to 125% range, but the overall differences observed between the elderly and young subjects are not significantly different given the variability observed between subjects.

Headache was the only adverse event reported by > 10% of the subjects in this study, which was reported by 6 of 32 (19%) subjects (4 young subjects and 2 elderly subjects). Other adverse events due to avanafil include dizziness, fatigue, and myalgia, but were reported less frequently. Overall, there is no difference in the incidence or frequency of adverse events related to avanafil between young and elderly subjects.

The mean semen/plasma concentration ratio of avanafil was 0.07 indicating very low fraction of avanafil in the semen, compared to plasma. The mean semen/plasma concentration ratio of M4 and M16 was 0.83, and 0.74, respectively, indicating that these metabolites are in near equal presence in semen as in plasma. The results from this study has limited applicability to long term sperm outcomes primarily due to a single administration of avanafil and limited sampling (only one at hr postdose).

Pharmacokinetics in Young vs. Elderly

The following figure is the arithmetic mean (SD) plasma **avanafil** concentrations vs time in young and elderly subjects (sponsor's figure 14.4.1.1)



The following table is a summary of arithmetic mean (SD) and geometric mean of **avanafil** PK parameters in young and elderly subjects (sponsor's table 2)

Pharmacokinetic Parameters	Young Subjects Cohort A		Elderly Subjects Cohort B	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C_{max} (ng/mL)	2850 ± 887 (18)	2670	2790 ± 837 (14)	2680
AUC_{0-t} (ng*hr/mL)	7200 ± 2210 (18)	6810	8540 ± 4220 (14)	7650
AUC_{0-inf} (ng*hr/mL)	7970 ± 1960 (15)	7750	8510 ± 4330 (13)	7630
t_{max} (hr)	0.56 (0.25, 1.0) (18)	.	0.75 (0.50, 0.78) (14)	.
$t_{1/2}$ (hr)	6.5 ± 2.9 (15)	.	5.6 ± 3.1 (13)	.
k_{el} (1/hr)	0.144 ± 0.0998 (15)	.	0.169 ± 0.0941 (13)	.

The arithmetic mean (SD) C_{max} for avanafil was similar in young and elderly subjects at 2850 (877) ng/mL and 2790 (837), respectively.

The arithmetic mean AUC_{0-t} for avanafil was 1.19-fold higher in elderly subjects, compared to young subjects. The arithmetic mean AUC_{0-inf} for avanafil was 1.07-fold higher in elderly subjects, compared to young subjects.

Median t_{max} increased by 0.19 hr from 0.56 to 0.75 hr in elderly subjects, compared to young subjects. Mean t_{1/2} decreased by 0.9 hr from 6.5 to 5.6 hrs in elderly subjects, compared to young subjects.

The following table is a statistical comparison of geometric LS means of **avanafil** PK parameters between elderly and young subjects (sponsor's table 4)

Pharmacokinetic Parameters	Elderly Subjects (Cohort B)		Young Subjects (Cohort A)		Cohort B Versus Cohort A	
	Mean	N	Mean	N	90% CI	% Mean Ratio
C _{max} (ng/mL) ^a	2680	14	2670	18	(80.42, 125.29)	100.38
AUC _{0-t} (ng*hr/mL) ^a	7650	14	6810	18	(86.81, 145.53)	112.40
AUC _{0-inf} (ng*hr/mL) ^a	7630	13	7750	15	(77.46, 125.18)	98.47
t _{max} (hr) ^b	0.75 (0.50, 0.78)	14	0.56 (0.25, 1.0)	18	.	.
t _{1/2} (hr) ^c	5.6 ± 3.1	13	6.5 ± 2.9	15	.	.

The geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} between elderly and young subjects was 100, 112, and 98%, respectively. The 90% confidence intervals of the mean ratios were outside the 80% to 125% range, but the overall differences observed between the elderly and young subjects are not significantly different given the variability observed between subjects.

The following table is a summary of arithmetic mean (SD) and geometric mean of **M4** PK parameters in young and elderly subjects (sponsor's table 7)

Pharmacokinetic Parameters	Young Subjects Cohort A		Elderly Subjects Cohort B	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	613 ± 172 (18)	578	585 ± 112 (14)	575
AUC _{0-t} (ng*hr/mL)	2540 ± 645 (18)	2420	2810 ± 682 (14)	2730
AUC _{0-inf} (ng*hr/mL)	2800 ± 468 (16)	2760	2950 ± 763 (13)	2860
t _{max} (hr)	0.76 (0.50, 1.5) (18)	.	0.78 (0.50, 2.0) (14)	.
t _{1/2} (hr)	6.9 ± 1.9 (16)	.	6.9 ± 1.5 (13)	.
k _{e1} (1/hr)	0.108 ± 0.0291 (16)	.	0.105 ± 0.0222 (13)	.

The following table is a summary of arithmetic mean (SD) and geometric mean of **M16** PK parameters in young and elderly subjects (sponsor's table 12)

Pharmacokinetic Parameters	Young Subjects Cohort A		Elderly Subjects Cohort B	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C _{max} (ng/mL)	953 ± 285 (18)	878	1370 ± 383 (14)	1330
AUC _{0-t} (ng*hr/mL)	2290 ± 708 (18)	2150	4040 ± 888 (14)	3950
AUC _{0-inf} (ng*hr/mL)	2560 ± 594 (15)	2500	4300 ± 748 (11)	4240
t _{max} (hr)	0.57 (0.50, 1.0) (18)	.	0.78 (0.55, 1.5) (14)	.
t _{1/2} (hr)	7.9 ± 2.5 (15)	.	7.2 ± 1.5 (11)	.
k _{el} (1/hr)	0.0977 ± 0.0349 (15)	.	0.101 ± 0.0222 (11)	.

Semen Concentration

The sponsor collected seminal fluid to determine avanafil and metabolite concentrations in seminal fluid of young healthy subjects 1 hr administration of 200 mg avanafil. The mean total amount in seminal fluid of avanafil, M4, and M16 was 366, 1030, and 1223 ng, respectively. The mean concentration of avanafil, M4, and M16 in seminal fluid was 151, 443, and 588 ng/mL, respectively. The mean concentration of avanafil, M4, and M16 in plasma was 2290, 531, and 800 ng/mL, respectively. Therefore, the mean semen/plasma concentration ratio of avanafil was 0.07 indicating very low fraction of avanafil in the semen, compared to plasma. The mean semen/plasma concentration ratio of M4 and M16 was 0.83, and 0.74, respectively, indicating that these metabolites are in near equal presence in semen as in plasma.

The results from this study has limited applicability to long term sperm outcomes primarily due to a single administration of avanafil and limited sampling (only one at hr postdose).

Safety

Table 14.3.1.1. Adverse Event Frequency by Cohort - Number of Subjects Reporting the Event

Adverse Event*	Cohort		Overall
	A	B	
Number of Subjects Dosed	18 (100%)	14 (100%)	32 (100%)
Number of Subjects With Adverse Events	7 (39%)	3 (21%)	10 (31%)
Number of Subjects Without Adverse Events	11 (61%)	11 (79%)	22 (69%)
General disorders and administration site conditions	2 (11%)	1 (7%)	3 (9%)
Chills	1 (6%)	0 (0%)	1 (3%)
Fatigue	1 (6%)	0 (0%)	1 (3%)
Feeling hot	1 (6%)	0 (0%)	1 (3%)
Pyrexia	1 (6%)	0 (0%)	1 (3%)
Vessel puncture site haematoma	0 (0%)	1 (7%)	1 (3%)
Musculoskeletal and connective tissue disorders	2 (11%)	0 (0%)	2 (6%)
Myalgia	2 (11%)	0 (0%)	2 (6%)
Nervous system disorders	6 (33%)	3 (21%)	9 (28%)
Dizziness	2 (11%)	1 (7%)	3 (9%)
Headache	4 (22%)	2 (14%)	6 (19%)
Respiratory, thoracic and mediastinal disorders	1 (6%)	0 (0%)	1 (3%)
Cough	1 (6%)	0 (0%)	1 (3%)
Oropharyngeal pain	1 (6%)	0 (0%)	1 (3%)
Skin and subcutaneous tissue disorders	1 (6%)	0 (0%)	1 (3%)
Skin warm	1 (6%)	0 (0%)	1 (3%)

Table 14.3.1.2. Adverse Event Frequency by Cohort - Number of Adverse Events

Adverse Event*	Cohort		Overall
	A	B	
Number of Adverse Events	15 (100%)	4 (100%)	19 (100%)
General disorders and administration site conditions	4 (27%)	1 (25%)	5 (26%)
Chills	1 (7%)	0 (0%)	1 (5%)
Fatigue	1 (7%)	0 (0%)	1 (5%)
Feeling hot	1 (7%)	0 (0%)	1 (5%)
Pyrexia	1 (7%)	0 (0%)	1 (5%)
Vessel puncture site haematoma	0 (0%)	1 (25%)	1 (5%)
Musculoskeletal and connective tissue disorders	2 (13%)	0 (0%)	2 (11%)
Myalgia	2 (13%)	0 (0%)	2 (11%)
Nervous system disorders	6 (40%)	3 (75%)	9 (47%)
Dizziness	2 (13%)	1 (25%)	3 (16%)
Headache	4 (27%)	2 (50%)	6 (32%)
Respiratory, thoracic and mediastinal disorders	2 (13%)	0 (0%)	2 (11%)
Cough	1 (7%)	0 (0%)	1 (5%)
Oropharyngeal pain	1 (7%)	0 (0%)	1 (5%)
Skin and subcutaneous tissue disorders	1 (7%)	0 (0%)	1 (5%)
Skin warm	1 (7%)	0 (0%)	1 (5%)

Table 14.3.1.3.

Adverse Event Frequency by Cohort, Severity, and Relationship to Drug - Number of Subjects Reporting Events

Adverse Event*	Cohort	Number of Subjects with Adverse Events	Severity			Relationship to Drug	
			Mild	Moderate	Severe	Related	Not Related
Chills	A	1	1	0	0	0	1
Cough	A	1	1	0	0	0	1
Dizziness	A	2	2	0	0	1	1
	B	1	1	0	0	1	0
Fatigue	A	1	1	0	0	1	0
Feeling hot	A	1	1	0	0	0	1
Headache	A	4	4	0	0	4	0
	B	2	2	0	0	2	0
Myalgia	A	2	2	0	0	1	1
Oropharyngeal pain	A	1	1	0	0	0	1
Pyrexia	A	1	1	0	0	0	1
Skin warm	A	1	1	0	0	0	1
Vessel puncture site haematoma	B	1	1	0	0	0	1
Cohort A		7	7	0	0	6	1
Cohort B		3	3	0	0	3	0
Overall		10	10	0	0	9	1

There were no severe adverse events reported in this study and the principal investigator did not discontinue any subjects due to an adverse. A total of 19 treatment-emergent adverse events were reported by 10 (31%) subjects dosed – 7 (39%) in young subjects (Cohort A) and 3 (21%) in elderly subjects (Cohort B). The sponsor considered 10 of the treatment-emergent adverse events to be related to avanafil and 9 not related to avanafil. Headache was the only adverse event reported by > 10% of the subjects in this study, which was reported by 6 of 32 (19%) subjects (4 young subjects and 2 elderly subjects). Other adverse events due to avanafil include dizziness, fatigue, and myalgia, but were reported less frequently. Overall, there is no difference in the incidence or frequency of adverse events related to avanafil between young and elderly subjects.

Study TA-015

Title: A Phase 1, Single-Center, Double-Blind, Randomized, Placebo-Controlled, Three-Period, Three-Way Crossover Study of the Hemodynamic Interactions of Avanafil and Alcohol in Healthy Male Subjects.

Objectives: The primary objective of the study was to investigate the pharmacodynamic effects of concomitant administration of avanafil and alcohol on blood pressure and heart rate in healthy male subjects. The secondary objective was to assess the safety and tolerability of co-administration of avanafil and alcohol in healthy male subjects.

Methods: This was a single center, double-blind, randomized, placebo-controlled, three-period, three-way crossover study. There were 15 subjects (14 Hispanic and 1 Caucasian) who were enrolled with 14 completed the study (Subject 7 was discontinued from the study due to elevated blood creatinine phosphokinase level at check-in). The mean age of all 15 subjects was 31.9 yrs (range 22-44 yrs) and mean weight was 72.1 (range 62.0-87.2 kg)

All doses were administered in the morning following an overnight fast of at least 10 hrs. The prepared alcohol or placebo drinks with fruit juice were consumed over a 15-min period. Avanafil or placebo tablets were administered at approximately the same time for each treatment with 50 mL of water after administering the drink. All subjects were confined to the study unit for approximately 13 hrs prior to administration of avanafil and drink and remained confined for approximately 8 hrs following drug administration. Alcohol was Everclear grain alcohol (95% alcohol by volume). Food was restricted until 4 hrs (\pm 30 min) after the morning dose on the Day 1 when pharmacodynamic measurements were taken. Subjects were randomized to one of the following three treatments with a washout period of at least five days between treatments:

Treatment A: a single oral dose of 1 x 200 mg avanafil tablet plus an oral dose of alcohol mixed with fruit juice (0.5 gm of absolute ethanol/kg of body weight)

Treatment B: a single dose of 1 placebo tablet plus an oral dose of alcohol drink mixed with fruit juice (0.5 g of absolute ethanol/kg body weight)

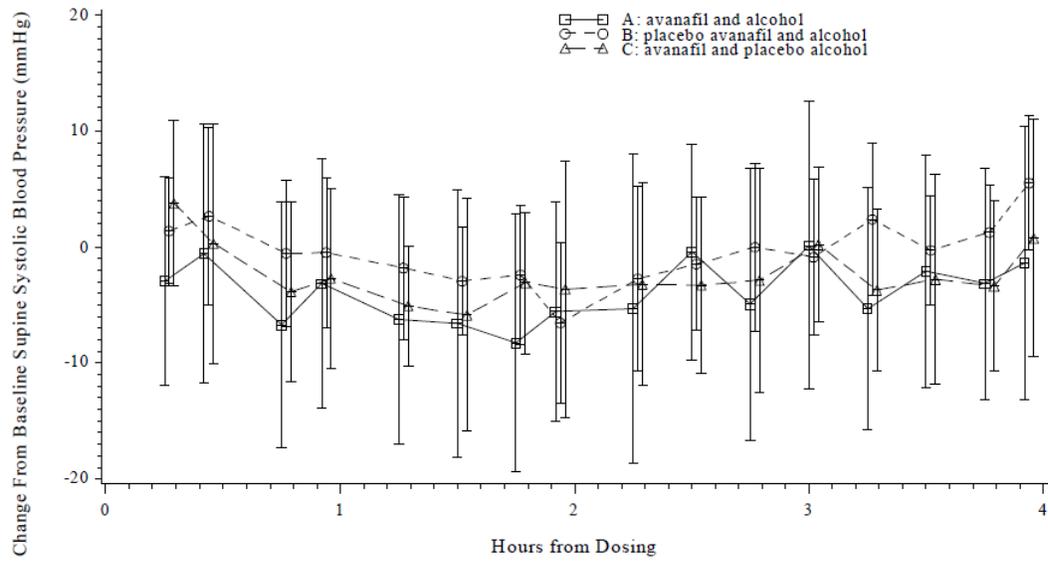
Treatment C: a single oral dose of 1 x 200 mg avanafil tablet plus an oral dose of placebo drink mixed with fruit juice.

Hemodynamic Measurements: Supine blood pressure (BP), including systolic BP (SBP) and diastolic BP (DBP), and pulse rate were recorded every 15 min for 4 hrs postdose with DataScope automatic system. The primary hemodynamic endpoints were AUEC_{0-t} for supine SBP and DBP, and the maximum increase in pulse rate.

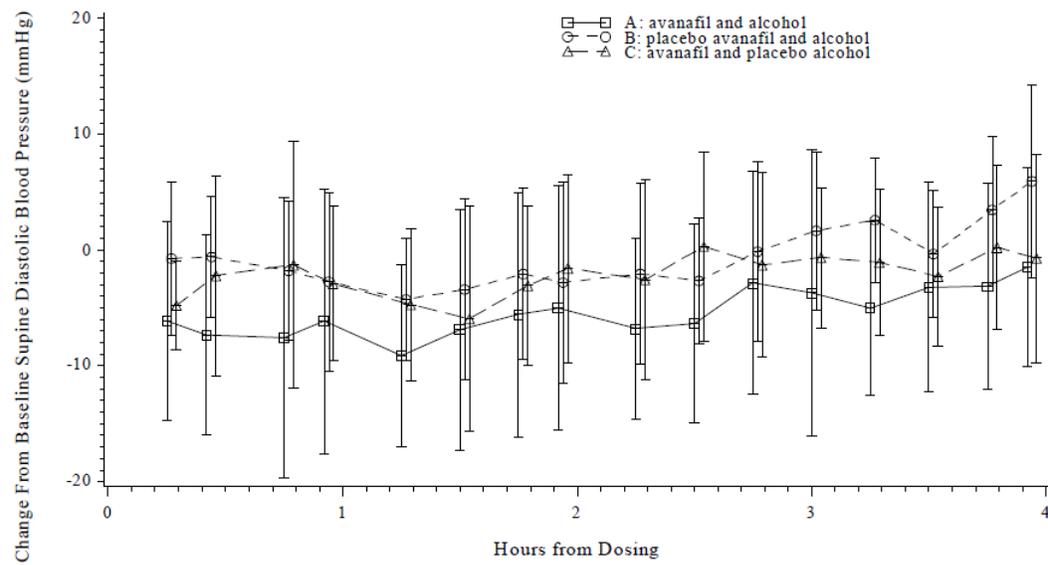
Blood Alcohol Analysis: An alcohol breath test was preformed at screening and at Day -1 of each treatment. After drug administration on Day 1, blood alcohol concentrations were obtained at 0 (30 predose), 0.5, 1, 2, 4, 6, and 8 hrs.

Results: The purpose of this study was to compare avanafil and alcohol (Treatment A) versus placebo and alcohol (Treatment B) and avanafil and placebo alcohol (Treatment C).

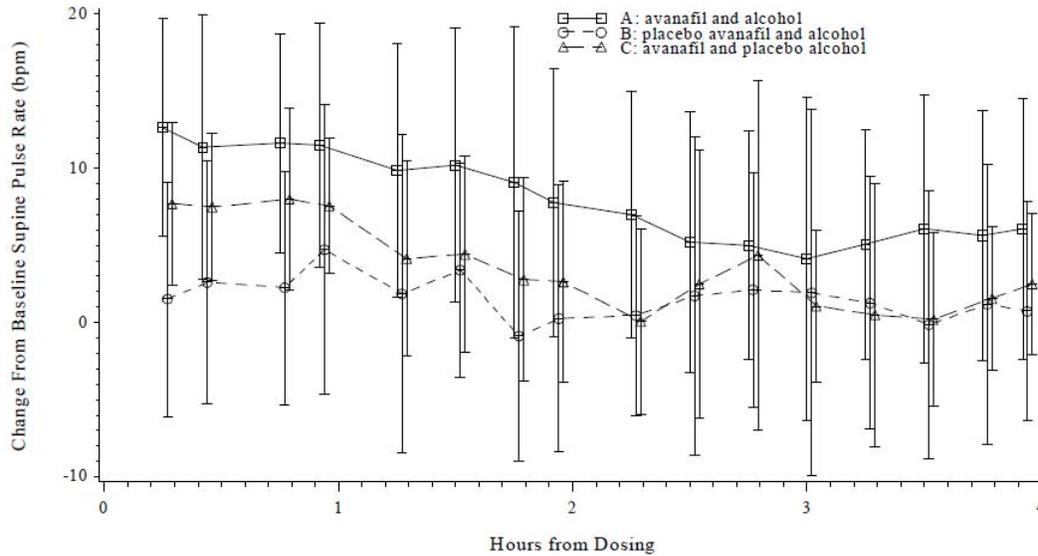
The following figure is the mean (SD) change from baseline for supine SBP vs time (sponsor's figure 14.4.1.2)



The following figure is the mean (SD) change from baseline for supine DBP vs time (sponsor's figure 14.4.1.4)



The following figure is the mean (SD) change from baseline for supine pulse rate vs time (sponsor's figure 14.4.1.6)



The following table is a summary of the mean supine blood pressures, area under the effect vs time curves, and pulse rates by treatment group (sponsor's table 2)

Parameter	Mean ± SD		
	Treatment A (N = 14)	Treatment B (N = 14)	Treatment C (N = 14)
Maximum Decrease Systolic (mmHg)	-14.5 ± 10.78	-10.9 ± 5.70	-11.8 ± 6.58
Systolic AUEC _{0-t} (mmHg*hr)	-15.4 ± 31.93	-2.8 ± 15.17	-10.0 ± 23.42
Maximum Decrease Diastolic (mmHg)	-14.6 ± 7.93	-9.6 ± 6.97	-11.4 ± 5.57
Diastolic AUEC _{0-t} (mmHg*hr)	-21.4 ± 29.88	-3.8 ± 18.63	-8.6 ± 21.53
Maximum Increase Pulse Rate (bpm)	+19.3 ± 9.38	+10.2 ± 10.82	+15.4 ± 7.20
Pulse Rate AUEC _{0-t} (mmHg*hr)	+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

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

Source: [Tables 14.2.1.2.1 through 14.2.1.2.3](#)

The following table is a statistical comparison of the area under the effect vs time curves, and maximum changes in supine blood pressure and pulse rate following administration of avanafil + alcohol (Treatment A) and placebo + alcohol (Treatment B) (sponsor's table 3)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	Confidence Intervals (95%)	P-Value
	Treatment A	Treatment B			
Maximum Decrease, Systolic (mmHg)	-14.46	-10.93	-3.53	-9.68 - 2.63	0.2483
Systolic AUEC _{0-t} (mmHg*hr)	-15.27	-2.79	-12.48	-30.92 - 5.96	0.1752
Maximum Decrease, Diastolic (mmHg)	-14.14	-9.60	-4.54	-8.98 - -0.10	0.0454
Diastolic AUEC _{0-t} (mmHg*hr)	-20.07	-3.75	-16.32	-30.19 - -2.46	0.0230
Maximum Increase, Pulse Rate (bpm)	+19.53	+10.20	+9.33	3.35 - 15.31	0.0037
Pulse Rate AUEC _{0-t} (bpm*hr)	+31.23	+6.16	+25.07	8.58 - 41.56	0.0045
AUEC _{0-t} = Area under effect-time curve from Hour 0 to Hour t 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) Source = Table 14.2.1.3					

When comparing avanafil + alcohol and placebo + alcohol, there was no statistically significant effect (p-value > 0.05) on the maximum mean supine SBP and systolic AUEC_{0-t}. However, despite the lack of statistical difference between the two treatment groups, there was a significant difference in the LS means of SBP of -3.53 mm Hg and systolic AUEC_{0-t} of -12.48 mmHg*hr in subjects given avanafil + alcohol, compared to placebo + alcohol. There were statistically significant changes in the maximum decrease in DBP (p-value 0.0454) and diastolic AUEC_{0-t} (p-value 0.0230) with a mean difference in the LS means of -4.54 mm Hg and -16.32 mmHg*hr, respectively. This trend was also observed with pulse rate - a statistically significant changes in the maximum increase in pulse rate (p-value 0.0454) and pulse rate AUEC_{0-t} (p-value 0.0230) with a mean difference in the LS means of +9.3bpm and +25.07 bpm*hr, respectively. Overall, there was an additive hypotensive effect from avanafil treatment.

The following table is a statistical comparison of the area under the effect vs time curves, and maximum changes in supine blood pressure and pulse rate following administration of avanafil + alcohol (Treatment A) and avanafil + placebo alcohol (Treatment C) (sponsor's table 4)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	Confidence Intervals (95%)	P-Value
	Treatment A	Treatment C			
Maximum Decrease, Systolic (mmHg)	-14.46	-11.58	-2.88	-9.13 - 3.38	0.3520
Systolic AUEC _{0-t} (mmHg*hr)	-15.27	-9.36	-5.91	-24.67 - 12.84	0.5216
Maximum Decrease, Diastolic (mmHg)	-14.14	-11.20	-2.94	-7.44 - 1.56	0.1902
Diastolic AUEC _{0-t} (mmHg*hr)	-20.07	-7.64	-12.43	-26.44 - 1.58	0.0794
Maximum Increase, Pulse Rate (bpm)	+19.53	+15.86	+3.67	-2.38 - 9.72	0.2231
Pulse Rate AUEC _{0-t} (bpm*hr)	+31.23	+14.70	+16.53	-0.20 - 33.25	0.0526
AUEC _{0-t} = Area under effect-time curve from Hour 0 to Hour t 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 Source = Table 14.2.1.4					

When comparing avanafil + alcohol and avanafil + placebo alcohol, there was no statistically significant effect (p-value > 0.05) on the maximum decreases supine SBP/DBP and decreases in systolic and diastolic AUEC_{0-t}. Additionally, there was no statistically significant increase in mean pulse rate and pulse rate AUEC_{0-t}. However, despite the lack of statistical difference between avanafil + alcohol and avanafil + placebo alcohol, there was a significant mean difference in LSM SBP and DBP AUEC_{0-t} of -5.91 and -12.53 mmHg*hr, respectively. Additionally, the mean difference in LSM pulse rate AUEC_{0-t} was +16.53 bpm*hr with avanafil administration with alcohol, compared to avanafil + placebo alcohol. Overall, there was an hypotensive effect from avanafil, irrespective of alcohol co-administration.

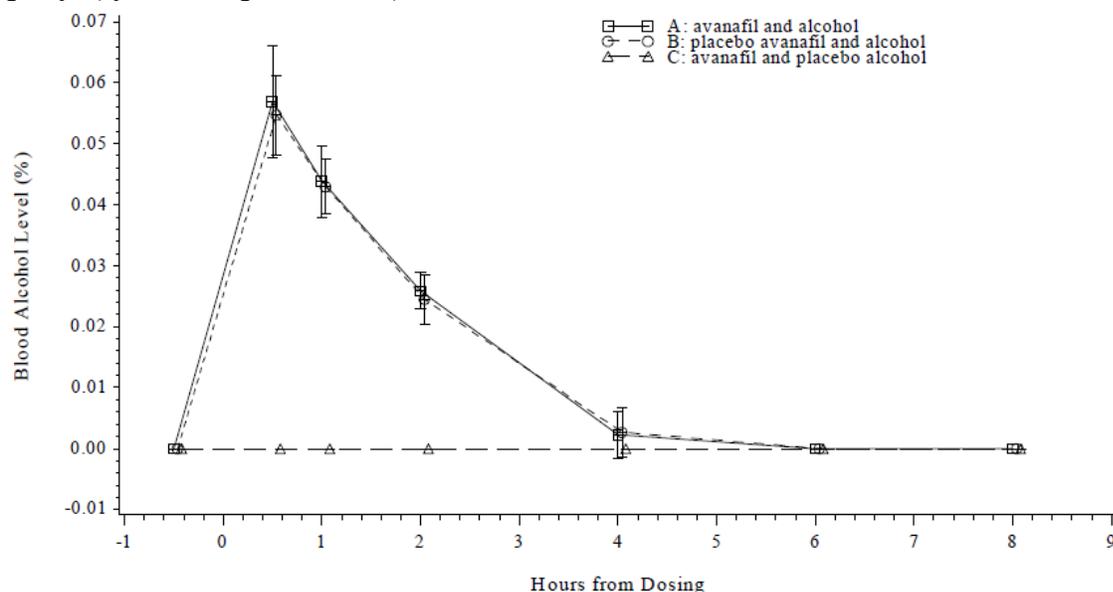
The following table is a statistical comparison of the area under the effect vs time curves, and maximum changes in supine blood pressure and pulse rate following administration of placebo + alcohol (Treatment b) and avanafil + placebo alcohol (Treatment C) (sponsor's table 5)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	Confidence Intervals (95%)	P-Value
	Treatment B	Treatment C			
Maximum Decrease, Systolic (mmHg)	-10.93	-11.58	0.65	-5.50 - 6.80	0.8291
Systolic AUEC _{0-t} (mmHg*hr)	-2.79	-9.36	6.57	-11.87 - 25.01	0.4693
Maximum Decrease, Diastolic (mmHg)	-9.60	-11.20	1.60	-2.84 - 6.04	0.4636
Diastolic AUEC _{0-t} (mmHg*hr)	-3.75	-7.64	3.89	-9.97 - 17.76	0.5679
Maximum Increase, Pulse Rate (bpm)	+10.20	+15.86	-5.66	-11.64 - 0.32	0.0625
Pulse Rate AUEC _{0-t} (bpm*hr)	+6.16	+14.70	-8.54	-25.04 - 7.95	0.2956

AUEC_{0-t} = Area under effect-time curve from Hour 0 to Hour t
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
Source = Table 14.2.1.5

When comparing Treatment Groups B and C, the sponsor essentially compared the blood pressure and pulse rate effect of avanafil against alcohol as measured by hemodynamic changes. Though none of the parameters compared were statistically significant (p-value > 0.05), there were significant decreases in the BP and pulse rate AUEC_{0-t} when avanafil + placebo alcohol was given with placebo alcohol, as compared to placebo + alcohol. The LS mean for systolic and diastolic AUEC_{0-t} was 6.57 and 3.89 mmHg*hr lower, respectively, for avanafil + placebo alcohol compared to placebo + alcohol. Additionally, the LS mean for pulse rate AUEC_{0-t} was 8.54 bpm*hr higher, respectively, for avanafil + placebo alcohol compared to placebo + alcohol.

The following figure is the mean (SD) of blood alcohol concentration vs time profile for all treatment groups (sponsor's figure 14.4.2.1)



There was a rapid increase in maximum alcohol concentration (~0.056%) approximately 30 min after intake with a steady decline to about half the maximum after 2 hrs in Treatment Groups, followed by a return to baseline (0%) by 6 hrs.

Table 14.3.1.1. Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event

Adverse Event*	Treatment			Overall
	A	B	C	
Number of Subjects Dosed	14 (100%)	15 (100%)	14 (100%)	15 (100%)
Number of Subjects With Adverse Events	2 (14%)	1 (7%)	3 (21%)	5 (33%)
Number of Subjects Without Adverse Events	12 (86%)	14 (93%)	11 (79%)	10 (67%)
Eye disorders	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Ocular hyperaemia	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Gastrointestinal disorders	0 (0%)	1 (7%)	1 (7%)	2 (13%)
Nausea	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Vomiting	0 (0%)	1 (7%)	1 (7%)	2 (13%)
General disorders and administration site conditions	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Fatigue	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Investigations	0 (0%)	1 (7%)	0 (0%)	1 (7%)
Blood creatine phosphokinase increased	0 (0%)	1 (7%)	0 (0%)	1 (7%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (7%)	0 (0%)	1 (7%)
Myalgia	0 (0%)	1 (7%)	0 (0%)	1 (7%)
Nervous system disorders	2 (14%)	1 (7%)	2 (14%)	4 (27%)
Headache	2 (14%)	1 (7%)	2 (14%)	4 (27%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	1 (7%)	0 (0%)	1 (7%)
Cough	0 (0%)	1 (7%)	0 (0%)	1 (7%)

Headache occurred with the same frequency (14%) in subjects given avanafil + alcohol and avanafil + placebo drink, and occurred less frequently (7%) in subjects given placebo + alcohol.

Study TA-016

Title: A Phase I, 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 Subjects

Objectives: The primary objective of this study was to evaluate the effect of avanafil on the PK and PD of warfarin in healthy male subjects. PD was measured as prothrombin time (PT) and international normalized ratio (INR). The secondary objectives were to assess the effect of avanafil on the platelet aggregation and to assess the safety and tolerability of co-administration of avanafil and warfarin in healthy male subjects; and effect of avanafil on color discrimination.

Methods: This was a single-center, double-blind, randomized, placebo-controlled, two-way crossover study to assess the interaction of avanafil and warfarin. There were 24 subjects (24 Hispanic) who were enrolled and 23 completed the study (1 subject had elevated creatine kinase). The mean age was 30.5 yrs (range 21-45 yrs) and mean weight was 75.3 (range 60.0-95.3 kg).

Subjects were randomized to receive either 200 mg (1 x 200 mg) avanafil or matching placebo for 9 days. On Day 3 of each period, subjects received a single 25 mg (2 x 10 mg and 1 x 5 mg) oral dose of warfarin Coumadin®). All study drugs were administered with 240 mL of water with at least 21 days for washout between warfarin doses and following an overnight fast of at least 10 hrs. Following warfarin administration, PK and PD sampling were taken for 7 days. Effect of avanafil on color vision impairment was assessed by Farnsworth-Munsell 100-Hue Test at screening, Day -2 (Period 1 only), Day -1, and at approximately 0.667 hrs postdose on Day 1. All subjects were confined to the clinical site beginning on Day -2 for diet equilibration and remained confined for approximately 24 hrs following the last avanafil administration on Day 9.

Pharmacokinetic Sampling: For determination of plasma R- and S-warfarin concentrations, blood samples were taken on Day 3 prior to warfarin administration, and at 0.5, 1, 1.5, 2, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hrs after warfarin administration. For determination of plasma avanafil, M4, and M16 concentrations, blood samples were taken on Day 3 prior to avanafil or placebo administration and at 0.5, 1, and 2 hrs after avanafil or placebo administration.

Pharmacodynamic Measurements: To evaluate PT and INR, blood samples were taken at screening, check-in, on Day 3 prior to warfarin administration, and at 6, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hrs post warfarin administration. To evaluate platelet aggregation, blood samples were taken on Day 3 prior to warfarin administration and at 1, 4, 6, 12, and 24 hrs post warfarin administration. For VKORC1 and CYP2C9 genotyping, a blood sample was taken at check-in at Period 1, but the samples were not analyzed.

Results: The sponsor evaluated the effect of multiple doses of avanafil on the PK and PD of single dose of warfarin in healthy young men. Multiple doses of avanafil had essentially no effect on the PK of a single dose of warfarin; the PK parameters of R-warfarin and S-warfarin were similar in both treatment groups. Multiple doses of avanafil had essentially no effect on the PD of a single dose of warfarin as determined by INR, PT, and platelet aggregation; the % mean ratios were all approximately 100% (range 96% to 110%) between subjects administered with warfarin + avanafil and warfarin+ placebo avanafil.

R-Warfarin PK

Following warfarin + placebo administration, the arithmetic mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of R-warfarin was 1870 (252) ng/mL, 100,000 (18,600) ng*hr/mL, and 120 (19.8) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} was 1.0 (0.5, 4.0) hr and 50 (7.7) hr, respectively

Following warfarin + avanafil administration, the arithmetic mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of R-warfarin was 1840 (283) ng/mL, 101,000 (16,300) ng*hr/mL, and 119 (21.3) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} was 1.5 (0.5, 2.0) hr and 51 (6.8) hr, respectively

S-Warfarin PK

Following warfarin + placebo administration, the arithmetic mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of S-warfarin was 1940 (322) ng/mL, 57,400 (8960) ng*hr/mL, and 208 (35.5) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} was 1.0 (0.5, 2.0) hr and 33 (4.3) hr, respectively

Following warfarin + avanafil administration, the arithmetic mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of S-warfarin was 1840 (312) ng/mL, 58,300 (9850) ng*hr/mL, and 206 (38.8) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} was 1.5 (0.5, 2.0) hr and 34 (4.3) hr, respectively

As expected, elimination rate constant and clearance of R-warfarin was approximately one-half (0.67 and 0.58, respectively) of S-warfarin. Whereas, half-life and exposure of R-warfarin was approximately slightly less than 2-fold higher (1.5 and 1.7 fold, respectively) than S-warfarin.

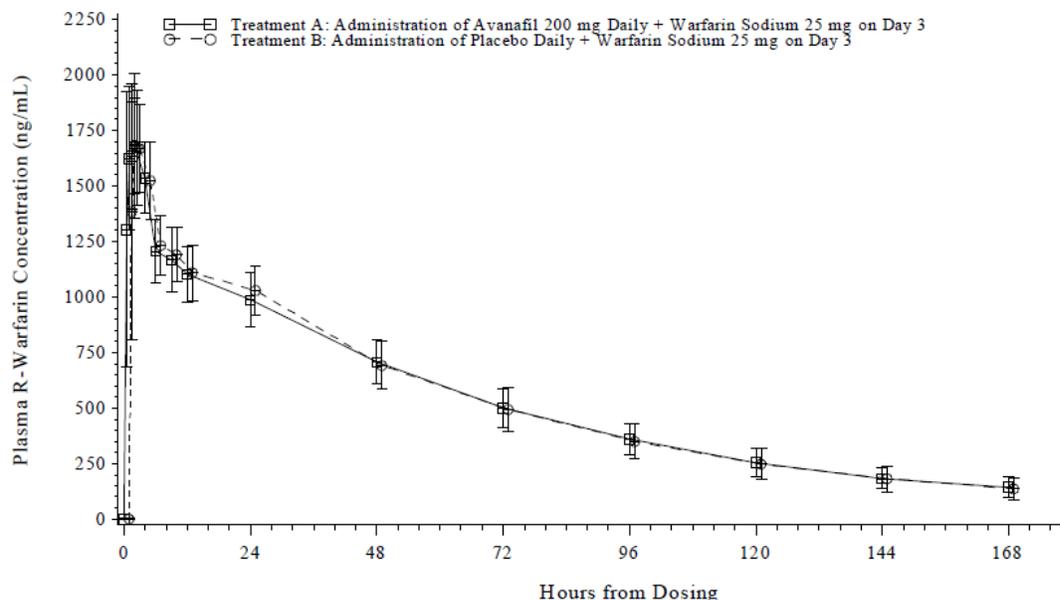
For determination of warfarin PK, the sponsor collected blood samples from 0 to 168 hrs following administration of warfarin. This time frame covered the duration necessary to capture the elimination phase of R- and S-warfarin: 3.4 half-lives of R-warfarin and 4.9 half-lives of S-warfarin.

Warfarin is extensively metabolized by CYP2C9 and to a lesser degree CYP2C19, 2C8, 2C18, 1A2, and 3A4. In vitro, avanafil has been shown to inhibit CYP2C19, 2C8, and 2D6. A clinical study to evaluate the potential inhibitory effect of avanafil on the omeprazole, rosiglitazone, and desipramine was conducted in study TA-018. The results showed avanafil had no effect CYP2C19, 2C8, and 2D6 enzymes. The results of this study with warfarin as the substrate showed that avanafil does not inhibit CYP2C9 in vivo.

Pharmacokinetics Data

Warfarin PK

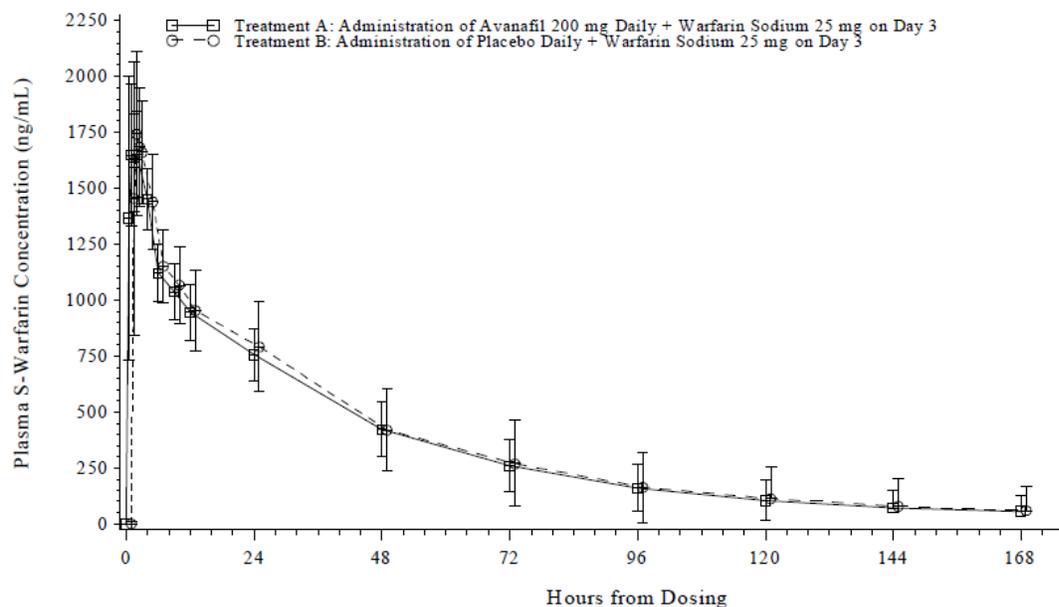
Arithmetic mean (SD) R-warfarin concentration vs. time following administration of warfarin+ avanafil and warfarin + placebo (sponsor's figure 14.4.1.1)



Arithmetic mean (SD) and geometric mean PK parameters for plasma R-warfarin following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 2)

Pharmacokinetic Parameters	Warfarin + Avanafil (Treatment A)		Warfarin + Placebo (Treatment B)	
	Mean \pm SD (N)	Geometric Mean	Mean \pm SD (N)	Geometric Mean
C_{max} (ng/mL)	1840 \pm 283 (23)	1820	1870 \pm 252 (24)	1850
AUC_{0-t} (ng*hr/mL)	89900 \pm 12500 (23)	89000	89800 \pm 13500 (24)	88900
AUC_{0-inf} (ng*hr/mL)	101000 \pm 16300 (23)	99600	100000 \pm 18600 (24)	98700
AUCR	0.895 \pm 0.0322 (23)	.	0.901 \pm 0.0326 (24)	.
* t_{max} (hr)	1.5 (0.50, 2.0) (23)	.	1.0 (0.50, 4.0) (24)	.
$t_{1/2}$ (hr)	51 \pm 6.8 (23)	.	50 \pm 7.7 (24)	.
k_{el} (1/hr)	0.0139 \pm 0.00187 (23)	.	0.0142 \pm 0.00201 (24)	.
CL/F (mL/hr)	119 \pm 21.3 (23)	.	120 \pm 19.8 (24)	.
V_{area}/F (mL)	8570 \pm 941 (23)	.	8470 \pm 859 (24)	.

Arithmetic mean (SD) S-warfarin concentration vs. time following administration of warfarin+ avanafil and warfarin + placebo (sponsor's figure 14.4.2.1)



Arithmetic mean (SD) and geometric mean PK parameters for plasma S-warfarin following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 5)

Pharmacokinetic Parameters	Warfarin + Avanafil (Treatment A)		Warfarin + Placebo (Treatment B)	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C_{max} (ng/mL)	1840 ± 312 (23)	1810	1940 ± 323 (24)	1910
AUC_{0-t} (ng*hr/mL)	59000 ± 16000 (23)	57300	60600 ± 26600 (24)	57600
AUC_{0-inf} (ng*hr/mL)	58300 ± 9850 (22)	57400	57400 ± 8960 (23)	56700
AUCR	0.965 ± 0.0152 (22)	.	0.967 ± 0.0141 (23)	.
* t_{max} (hr)	1.5 (0.50, 2.0) (23)	.	1.0 (0.50, 2.0) (24)	.
$t_{1/2}$ (hr)	34 ± 4.3 (22)	.	33 ± 4.3 (23)	.
k_{el} (1/hr)	0.0209 ± 0.00250 (22)	.	0.0212 ± 0.00277 (23)	.
CL/F (mL/hr)	206 ± 38.8 (22)	.	208 ± 35.5 (23)	.
V_{area}/F (mL)	9860 ± 1110 (22)	.	9820 ± 935 (23)	.

Statistical comparison of plasma R-/S-warfarin PK Parameters following administration of warfarin + avanafil vs. warfarin + placebo

		Geometric LS Means*		Confidence Intervals		
Pharmacokinetic Parameters		Warfarin + Avanafil (Treatment A)	Warfarin + Placebo (Treatment B)	90% Confidence	% Mean Ratio ^b	
R-Warfarin	C _{max} (ng/mL)	1830	1850	(95.63, 102.37)	98.94	
	AUC ₀₋₂₄ (ng*hr/mL)	88900	88900	(97.67, 102.52)	100.07	
	AUC _{0-inf} (ng*hr/mL) ^b	99400	98700	(97.88, 103.68)	100.74	
	CL/F (mL/hr)	117	118	(96.45, 102.17)	99.27	
	V _{dss} /F (mL)	8510	8420	(99.02, 103.14)	101.06	
Treatment Median						
		Warfarin + Avanafil (Treatment A)	Warfarin + Placebo (Treatment B)	95% CI	Median Difference ^c	P-value
R-Warfarin	t _{max} (hr)	1.5	1.0	(-0.27, 0.25)	-0.002	0.3813
		Geometric LS Means*		Confidence Intervals		
Pharmacokinetic Parameters		Warfarin + Avanafil (Treatment A)	Warfarin + Placebo (Treatment B)	90% Confidence	% Mean Ratio ^b	
S-Warfarin	C _{max} (ng/mL)	1830	1910	(91.60, 100.06)	95.74	
	AUC ₀₋₂₄ (ng*hr/mL)	57800	57600	(97.06, 103.70)	100.32	
	AUC _{0-inf} (ng*hr/mL) ^b	57800	56600	(100.19, 104.26)	102.20	
	CL/F (mL/hr)	202	206	(95.92, 99.81)	97.84	
	V _{dss} /F (mL)	9800	9790	(98.11, 102.09)	100.08	
Treatment Median						
		Warfarin + Avanafil (Treatment A)	Warfarin + Placebo (Treatment B)	95% CI	Median Difference ^c	P-value
S-Warfarin	t _{max} (hr)	1.5	1.0	(-0.24, 0.25)	-0.000	0.8715

Pharmacodynamics Data

Prothrombin Time

Table 14.2.6.1. Prothrombin Time (sec) by Nominal Time Following Administration of Avanafil 200 mg Daily + Warfarin Sodium 25 mg on Day 3 (Treatment A)

Subject	Treatment	Study	Check-in	Predose	6	12	24	36	48	72	96	120	144	168
1	EA	2												
2	AB	1												
3	AB	1												
4	EA	2												
5	AB	1												
6	EA	2												
7	EA	2												
8	AB	1												
9	EA	2												
10	AB	1												
11	AB	1												
12	EA	2												
14	AB	1												
15	EA	2												
16	AB	1												
17	AB	1												
18	EA	2												
19	AB	1												
20	EA	2												
21	EA	2												
22	AB	1												
23	AB	1												
24	EA	2												
Mean			10.43	10.67	10.95	12.23	17.94	23.07	22.68	17.45	14.83	12.91	11.75	11.31
SD			0.39453	0.35858	0.37279	0.61897	1.6569	3.3302	5.4590	5.2249	4.7198	4.1072	2.7003	2.1237
CV			3.8	3.4	3.4	5.1	9.2	14.4	24.1	29.9	31.8	31.8	23.0	18.8
SEM			0.082265	0.074768	0.077732	0.12906	0.34549	0.69440	1.1383	1.0895	0.98415	0.85641	0.56305	0.44281
N			23	23	23	23	23	23	23	23	23	23	23	23
Minimum			9.60	9.90	10.0	11.0	15.0	16.8	15.0	12.3	11.0	10.1	10.1	10.1
Maximum			11.1	11.4	11.6	13.3	20.8	29.2	34.1	35.8	34.8	31.1	23.9	20.9
Median			10.40	10.70	10.90	12.20	18.00	22.90	22.10	16.40	14.00	12.00	11.20	10.90

(b) (4)

Table 14.2.6.2. Prothrombin Time (sec) by Nominal Time Following Administration of Placebo Daily + Warfarin Sodium 25 mg on Day 3 (Treatment B)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr)											
			Check-in	Predose	6	12	24	36	48	72	96	120	144	168
1	BA	1	(b) (4)											
2	AB	2												
3	AB	2												
4	BA	1												
5	AB	2												
6	BA	1												
7	BA	1												
8	AB	2												
9	BA	1												
10	AB	2												
11	AB	2												
12	BA	1												
13	B	1												
14	AB	2												
15	BA	1												
16	AB	2												
17	AB	2												
18	BA	1												
19	AB	2												
20	BA	1												
21	BA	1												
22	AB	2												
23	AB	2												
24	BA	1												
Mean			10.45	10.72	11.00	12.28	17.92	22.74	22.97	17.60	14.86	13.01	11.90	11.60
SD			0.359	0.402	0.352	0.630	1.559	3.984	5.564	5.661	5.315	4.635	3.650	3.150
CV			3.431	3.751	3.201	5.134	8.698	17.521	24.220	32.174	35.759	35.617	30.661	27.150
SEM			0.073	0.082	0.072	0.129	0.318	0.813	1.136	1.156	1.085	0.946	0.745	0.643
N			24	24	24	24	24	24	24	24	24	24	24	24
Minimum			9.9	10.0	10.4	11.2	15.2	15.8	13.6	11.7	10.9	10.5	10.0	10.2
Maximum			11.2	11.5	11.5	13.5	21.0	32.1	34.6	40.4	38.7	34.4	28.9	26.3
Median			10.50	10.70	11.05	12.30	17.85	22.40	22.55	16.15	13.75	12.05	11.15	11.05

Treatment Group A received 200 mg avanafil for 9 days and a single 25 mg dose of warfarin on Day 3.

Treatment Group B received avanafil-matched placebo for 9 days and a single 25 mg dose of warfarin on Day 3.

The mean predose PT was 10.7 and 10.7 sec in subjects administered with avanafil + warfarin and placebo + warfarin, respectively. The mean maximum PT was 23.1 and 23.0 in subjects administered with avanafil + warfarin and placebo + warfarin, respectively. PT returned near predose/baseline level by 168 hrs.

Arithmetic mean (SD) prothrombin time change from baseline following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 8)

	Warfarin + Avanafil (Treatment A)	Warfarin + Placebo (Treatment B)
Pharmacodynamic Parameters	Mean ± SD (N)	Mean ± SD (N)
E_{max} (sec)	13.6 ± 4.77 (23)	13.6 ± 5.66 (24)
TE_{max} (hr)	36 (36, 72) (23)	36 (36, 72) (24)
$AUEC_{0-168}$ (sec*hr)	841 ± 526 (23)	849 ± 605 (24)

Statistical comparisons of prothrombin time change from baseline following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 9)

Pharmacodynamic Parameters	Warfarin + Avanafil (Treatment A)	N	Warfarin + Placebo (Treatment B)	N	90% CI	% Mean Ratio
E_{max} (sec) ^a	13.3	23	13.6	24	(90.21, 105.44)	97.83
$AUEC_{0-168}$ (sec*hr) ^a	824	23	849	24	(89.63, 104.31)	96.97

International Normalized Ratio

International normalized ratio change from baseline following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 10)

Table 14.2.8.1. International Normalized Ratio (INR) by Nominal Time Following Administration of Avanafil 200 mg Daily + Warfarin Sodium 25 mg on Day 3 (Treatment A)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr)											
			Check-in	Predose	6	12	24	36	48	72	96	120	144	168
1	EA	2	(b) (4)											
2	AB	1												
3	AB	1												
4	EA	2												
5	AB	1												
6	EA	2												
7	EA	2												
8	AB	1												
9	EA	2												
10	AB	1												
11	AB	1												
12	EA	2												
14	AB	1												
15	EA	2												
16	AB	1												
17	AB	1												
18	EA	2												
19	AB	1												
20	EA	2												
21	EA	2												
22	AB	1												
23	AB	1												
24	EA	2												
Mean														
SD			0.042	0.049	0.051	0.065	0.170	0.349	0.538	0.512	0.468	0.402	0.262	0.206
CV			4.207	4.826	4.874	5.555	9.968	16.068	24.721	30.487	32.919	32.226	23.166	19.023
SEM			0.009	0.010	0.011	0.013	0.036	0.073	0.112	0.107	0.098	0.084	0.055	0.043
N			23	23	23	23	23	23	23	23	23	23	23	23
Minimum			0.9	0.9	1.0	1.1	1.4	1.5	1.4	1.2	1.1	1.0	1.0	1.0
Maximum			1.1	1.1	1.1	1.3	2.0	2.8	3.3	3.5	3.4	3.0	2.3	2.0
Median			1.00	1.00	1.00	1.20	1.70	2.20	2.10	1.60	1.30	1.20	1.10	1.00

Table 14.2.8.2. International Normalized Ratio (INR) by Nominal Time Following Administration of Placebo Daily + Warfarin Sodium 25 mg on Day 3 (Treatment B)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr)											
			Check-in	Predose	6	12	24	36	48	72	96	120	144	168
1	EA	1	(b) (4)											
2	AB	2												
3	AB	2												
4	EA	1												
5	AB	2												
6	EA	1												
7	EA	1												
8	AB	2												
9	EA	1												
10	AB	2												
11	AB	2												
12	EA	1												
13	E	1												
14	AB	2												
15	EA	1												
16	AB	2												
17	AB	2												
18	EA	1												
19	AB	2												
20	EA	1												
21	EA	1												
22	AB	2												
23	AB	2												
24	EA	1												
Mean			1.01	1.03	1.05	1.17	1.73	2.18	2.21	1.69	1.43	1.24	1.15	1.12
SD			0.041	0.044	0.051	0.068	0.152	0.388	0.542	0.547	0.511	0.449	0.354	0.299
CV			4.049	4.315	4.828	5.750	8.775	17.797	24.478	32.327	35.766	36.167	30.657	26.757
SEM			0.008	0.009	0.010	0.014	0.031	0.079	0.111	0.112	0.104	0.092	0.072	0.061
N			24	24	24	24	24	24	24	24	24	24	24	24
Minimum			0.9	1.0	1.0	1.1	1.5	1.5	1.3	1.1	1.0	1.0	1.0	1.0
Maximum			1.1	1.1	1.1	1.3	2.0	3.1	3.3	3.9	3.7	3.3	2.8	2.5
Median			1.00	1.00	1.10	1.20	1.70	2.15	2.15	1.55	1.30	1.15	1.10	1.10

Treatment Group A received 200 mg avanafil for 9 days and a single 25 mg dose of warfarin on Day 3.

Treatment Group B received avanafil-matched placebo for 9 days and a single 25 mg dose of warfarin on Day 3.

The mean predose INR was 1.02 and 1.03 in subjects administered with avanafil + warfarin and placebo + warfarin, respectively. The mean maximum INR was 2.18 and 2.21 in subjects administered with avanafil + warfarin and placebo + warfarin, respectively. INR returned near predose/baseline level by 168 hrs.

	Warfarin + Avanafil (Treatment A)	Warfarin + Placebo (Treatment B)
Pharmacodynamic Parameters	Mean ± SD (N)	Mean ± SD (N)
E _{max}	1.29 ± 0.506 (23)	1.32 ± 0.553 (24)
TE _{max} (hr)	36 (24, 72) (23)	36 (24, 72) (24)
AUEC ₀₋₁₆₈ (INR*hr)	84.0 ± 52.5 (23)	82.9 ± 57.6 (24)

Statistical comparisons of international normalized ratio change from baseline following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 11)

Pharmacodynamic Parameters	Warfarin + Avanafil (Treatment A)	N	Warfarin + Placebo (Treatment B)	N	90% CI	% Mean Ratio
E _{max} ^a	1.26	23	1.32	24	(89.30, 102.34)	95.82
AUEC ₀₋₁₆₈ (INR*hr) ^a	82.1	23	82.9	24	(90.82, 107.33)	99.08

Platelet Aggregation

Table 14.2.10.1. Platelet Aggregation (%) by Nominal Time Following Administration of Avanafil 200 mg Daily + Warfarin Sodium 25 mg on Day 3 (Treatment A)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr)					
			Predose	1	4	6	12	24
1	BA	2	(b) (4)					
2	AB	1						
3	AB	1						
4	BA	2						
5	AB	1						
6	BA	2						
7	BA	2						
8	AB	1						
9	BA	2						
10	AB	1						
11	AB	1						
12	BA	2						
14	AB	1						
15	BA	2						
16	AB	1						
17	AB	1						
18	BA	2						
19	AB	1						
20	BA	2						
21	BA	2						
22	AB	1						
23	AB	1						
24	BA	2						
Mean								68.7
SD			9.42	9.48	9.15	7.93	6.18	10.40
CV			13.71	12.60	12.12	10.52	8.93	14.59
SEM			1.96	1.98	1.91	1.65	1.29	2.17
N			23	23	23	23	23	23
Minimum			49	60	59	59	57	44
Maximum			97	98	96	88	82	95
Median			68.0	73.0	74.0	76.0	69.0	72.0

Treatment Group A received 200 mg avanafil for 9 days and a single 25 mg dose of warfarin on Day 3.

Treatment Group B received avanafil-matched placebo for 9 days and a single 25 mg dose of warfarin on Day 3.

Table 14.2.10.2. Platelet Aggregation (%) by Nominal Time Following Administration of Placebo Daily + Warfarin Sodium 25 mg on Day 3 (Treatment B)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr)					
			Pre-dose	1	4	6	12	24
1	BA	1	(b) (4)					
2	AB	2						
3	AB	2						
4	BA	1						
5	AB	2						
6	BA	1						
7	BA	1						
8	AB	2						
9	BA	1						
10	AB	2						
11	AB	2						
12	BA	1						
13	B	1						
14	AB	2						
15	BA	1						
16	AB	2						
17	AB	2						
18	BA	1						
19	AB	2						
20	BA	1						
21	BA	1						
22	AB	2						
23	AB	2						
24	BA	1						
Mean			68.8	71.9	73.2	76.5	68.5	68.0
SD			11.58	9.05	11.83	7.44	7.48	7.86
CV			16.85	12.58	16.16	9.72	10.92	11.56
SEM			2.36	1.85	2.42	1.52	1.53	1.61
N			24	24	24	24	24	24
Minimum			43	48	45	65	53	53
Maximum			90	88	99	89	84	93
Median			69.0	74.0	74.5	75.5	68.5	67.0

Treatment Group A received 200 mg avanafil for 9 days and a single 25 mg dose of warfarin on Day 3.

Treatment Group B received avanafil-matched placebo for 9 days and a single 25 mg dose of warfarin on Day 3.

The mean pre-dose platelet aggregation was 68.7 and 68.8% in subjects administered with avanafil + warfarin and placebo + warfarin, respectively. The mean maximum platelet aggregation was 75.7 and 76.5% in subjects administered with avanafil + warfarin and placebo + warfarin, respectively. Platelet aggregation returned to pre-dose/baseline level by 24 hrs.

Statistical comparisons of platelet aggregation following administration of warfarin + avanafil vs. warfarin + placebo (sponsor's table 12)

Pharmacokinetic Parameters	Warfarin + Avanafil (Treatment A)	N	Warfarin + Placebo (Treatment B)	N	90% CI	% Mean Ratio
E_{max} (%) ^a	84.1	23	82.2	24	(98.07, 106.42)	102.24
E_{min} (%) ^a	64.0	23	60.7	24	(101.35, 109.68)	105.51

Study TA-017

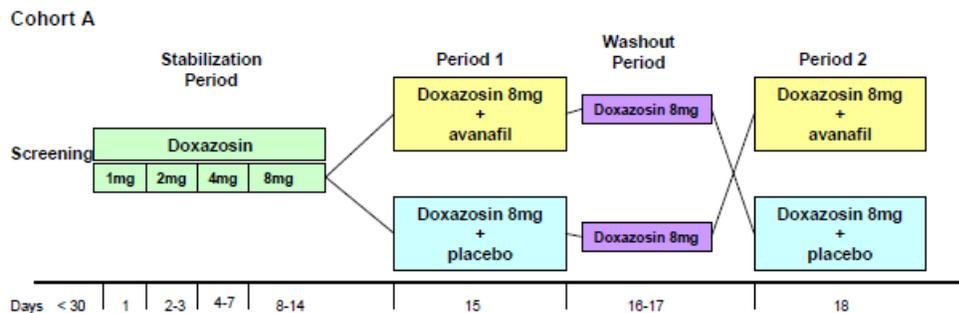
Title: A Phase I, Single-Center, Double-Blind, Randomized, Placebo-Controlled, Two-Cohort, Two-Period Crossover Study of the Hemodynamic Interactions Between Avanafil and Two α -Adrenergic Blockers, Doxazosin and Tamsulosin, in Middle-Aged Healthy Male Subjects

Objectives: The primary objective of the study was to investigate the hemodynamic interactions between avanafil and two α -adrenergic blockers, doxazosin and tamsulosin, in middle-aged healthy male subjects. The secondary objective was to assess the safety and tolerability of co-administration of avanafil and doxazosin or tamsulosin in healthy male subjects.

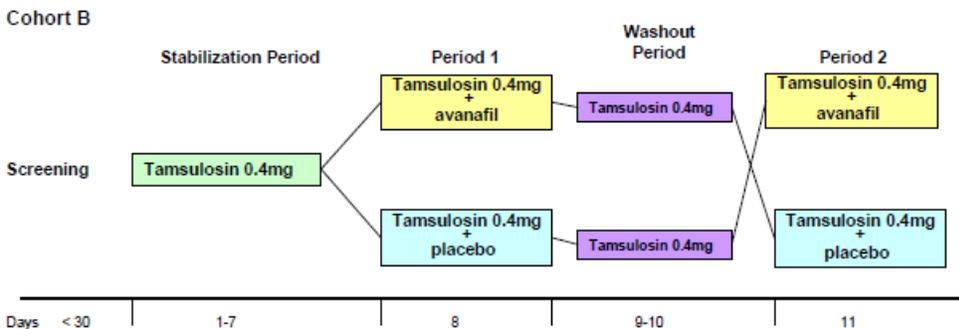
Methods: This study was a single center, randomized, double-blind, placebo-controlled, two-way crossover study in older healthy male subjects. There were 48 subjects (46 Caucasians, 1 Black, and 1 Native Hawaiian/Pacific Islander) who were enrolled and completed the study with 12 subjects randomized to each treatment sequence (2 sequences/cohort). The mean age was 46.5 yrs (range 40-61 yrs) and mean weight was 81.4 (range 58.2-105.6 kg).

All study drugs were administered in the morning with 240 mL water after an overnight fast or at least 10 hrs. Subjects refrained from food until 1.5 hrs (± 30 min) after the morning daily dose of avanafil or placebo each day. On the hemodynamic assessment days after doxazosin or tamsulosin dosing, subjects refrained from food until 4 hrs after the morning dose. Subjects remained at the clinical site throughout the study until approximately 24 hrs after the avanafil or placebo administration on Day 18 (Cohort A) or Day 11 (Cohort B). The two study cohorts were:

Cohort A (doxazosin): subjects received oral doses of doxazosin 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 (1x200mg) avanafil or placebo administered after the doxazosin on Days 15 and 18. (sponsor's figure 1)



Cohort B (tamsulosin): subjects received oral doses of 0.4 mg tamsulosin once daily in the morning for 11 consecutive days (Days 1-11) and a single oral dose of either 200 mg (1x200mg) avanafil or placebo administered 3.3 hrs after tamsulosin on Days 8 and 11. (sponsor's figure 1)



Hemodynamic Measurements: Blood pressure (BP), including systolic BP (SBP) and diastolic BP (DBP), and pulse rate were recorded with DataScope automatic system.

During the alpha blocker only treatment period, sitting BP and pulse rate measurements were taken following the first dose and with each increase in dose. For Cohort A & B: sitting BP and pulse rate were taken pre-dose, 1, 2, 4, and 8 hrs post-dose on Days 1, 2, 4, and 8.

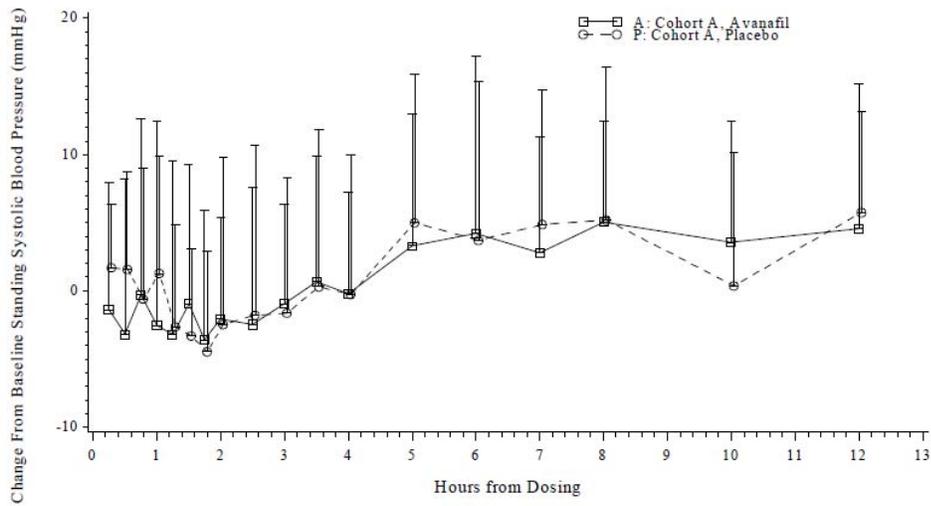
During the alpha blocker + avanafil/placebo treatment days (Cohort A, Days 15 & 18; Cohort B, Days 8 & 11), supine and sitting BP and pulse rate measurements were recorded before avanafil or placebo dosing, then every 15 min for the first 2 hrs, every 30 min for the next 2 hrs, hourly for the next 4 hrs and again at 10, 12, 18, and 24 hrs after avanafil or placebo dosing. The baseline/pre-dose value was the mean of three consecutive measurements 30, 20, and 10 min before dosing. Measurements were taken after subjects had been supine for at least 5 min. Subjects then sat for 1 min, and stood for 2 min, before standing BP and heart rate were measured.

The primary hemodynamic endpoint was the maximum post-baseline decrease in standing SBP (i.e. the most negative change in standing SBP from baseline). The secondary hemodynamic endpoints were the maximum post-baseline decrease in supine SBP, maximum post-baseline decreases in standing and supine DBP, maximum post-baseline compensatory increases in standing and spine pulse rates, and the area under effect-time curve of the supine and standing SBP and DBP and pulse rate from 1 to 12 hrs post dose ($AUEC_{0-12}$)

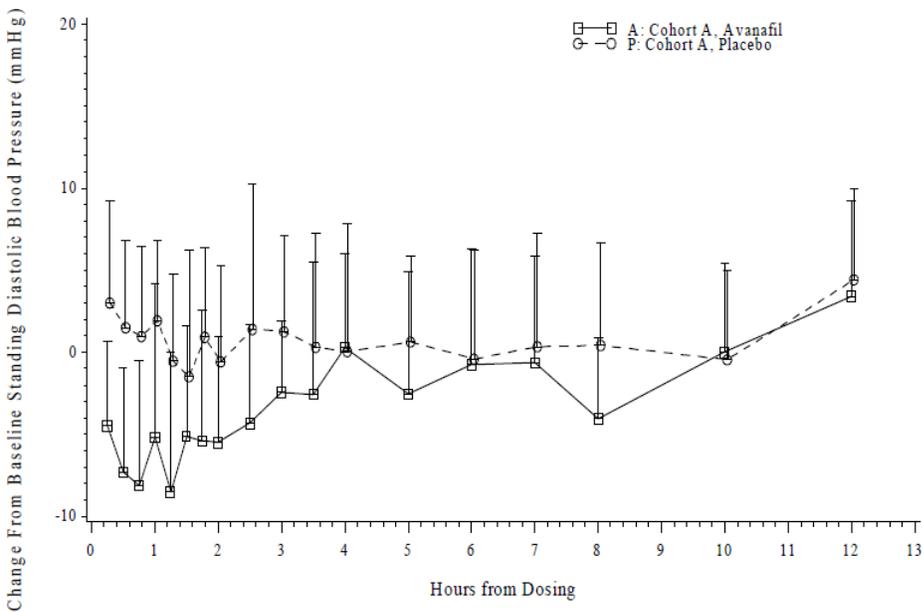
Results: The sponsor states that men with ED have a high incidence of hypertension and benign prostatic hyperplasia (BPH) and are likely to take medications such as alpha blockers that affect blood pressure. This study was conducted to investigate the hemodynamic interactions between avanafil and two alpha blockers, doxazosin or tamsulosin, in healthy male subjects. 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. However, this study was not designed to evaluate the long term effect of co-administration of alpha blockers and avanafil (single dose administered in this study). Additionally, subjects enrolled in this study had a mean age of 46.5 yrs (range 40-61 yrs), which appears to be low and the applicability of these findings may not be relevant to an older population with hypertension and BPH. The effect on blood pressure and heart rate can be more significant with frequent use of alpha blockers and avanafil, and in an older population.

Cohort A: doxazosin + avanafil/placebo

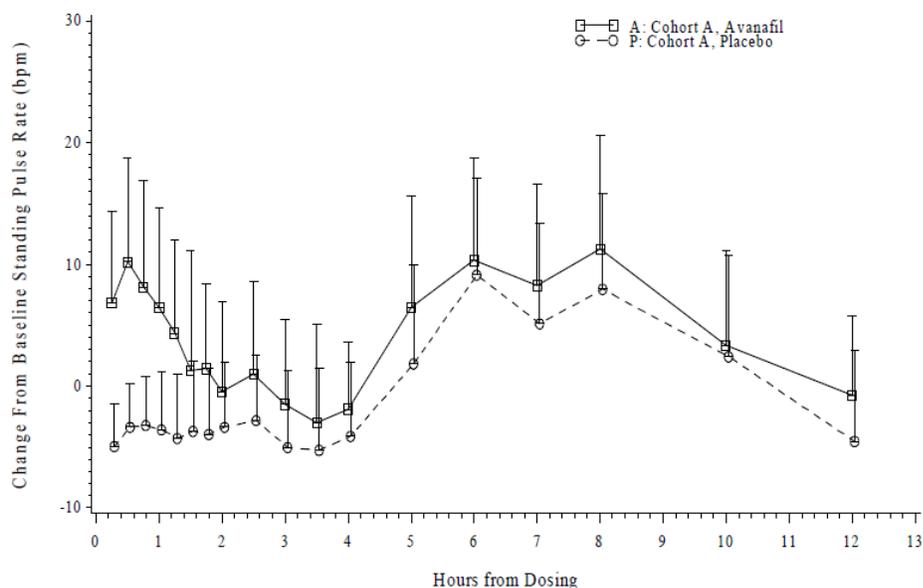
The following figure is the mean (SD) change from baseline for standing SBP vs time following administration of doxazosin with avanafil or placebo (Cohort A) (sponsor's figure 2)



The following figure is the mean (SD) change from baseline for standing DBP vs time following administration of doxazosin with avanafil or placebo (Cohort A) (sponsor's figure 3)



The following figure is the mean (SD) change from baseline for standing pulse rate vs time following administration of doxazosin with avanafil or placebo (Cohort A) (sponsor's figure 4)



The following table is a statistical comparison of the maximum changes in standing blood pressure and pulse rate, and area under the effect vs time curves following administration of doxazosin with avanafil or placebo (Cohort A) (sponsor's table 4)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Doxazosin + Avanafil	Doxazosin + Placebo			
Maximum decrease systolic (mmHg)	-14.46	-11.96	-2.50	-6.53 - +1.53	0.2114
Systolic AUEC ₀₋₁₂ (mmHg*h)	+23.54	+24.12	-0.58	-36.48 - +35.32	0.9737
Maximum decrease diastolic (mmHg)	-14.50	-8.08	-6.42	-9.54 - -3.30	0.0003
Diastolic AUEC ₀₋₁₂ (mmHg*h)	-24.23	+7.94	-32.17	-57.08 - -7.27	0.0137
Maximum increase pulse rate (bpm)	+19.17	+11.96	+7.21	+3.82 - +10.60	0.0002
Pulse rate AUEC ₀₋₁₂ (bpm*h)	+54.70	+10.16	+44.54	+21.32 - +67.76	0.0006

AUEC₀₋₁₂= 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.
Source: [Table 14.2.1.3.1](#)

Statistically significant differences were not observed in the maximum decrease from baseline in the standing SBP (p-value 0.2114) or in the AUEC₀₋₁₂ for standing SBP (p-value 0.9737) between subjects who received avanafil or placebo.

Statistically significant differences were observed in the maximum decrease from baseline in the standing DBP (p-value 0.0003) and in the AUEC₀₋₁₂ for standing DBP (p-value 0.0137) between subjects who received avanafil or placebo. The differences in the least-squares means (LSM) for maximum decrease in standing DBP and AUEC₀₋₁₂ were -6.42 mm Hg and -32.17 mmHg*hr, respectively.

Statistically significant differences were observed in the maximum decrease from baseline in the standing pulse rate (p-value 0.0002) and in the AUEC₀₋₁₂ for standing pulse rate (p-value 0.0006) between subjects who received avanafil or placebo. The differences in the LSM for maximum decrease in standing pulse rate and AUEC₀₋₁₂ were +7.21 bpm and +44.54 bpm*hr, respectively.

The following table is a statistical comparison of the maximum changes in supine blood pressure and area under the effect vs time curves following administration of doxazosin with avanafil or placebo (Cohort A) (sponsor's table 6)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Doxazosin + Avanafil	Doxazosin + Placebo			
Maximum decrease systolic (mmHg)	-13.21	-7.21	-6.00	-9.07 - -2.93	0.0005
Systolic AUEC ₀₋₁₂ (mmHg*h)	+12.26	+45.12	-32.86	-72.15 - +6.43	0.0968
Maximum decrease diastolic (mmHg)	-10.58	-7.00	-3.58	-5.63 - -1.53	0.0015
Diastolic AUEC ₀₋₁₂ (mmHg*h)	-23.90	+7.51	-31.40	-51.22 - -11.59	0.0034
Maximum increase pulse rate (bpm)	+17.12	+13.37	+3.75	-2.92 - +10.42	0.2564
Pulse rate AUEC ₀₋₁₂ (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. Source: Table 14.2.2.3.1					

Statistically significant differences were observed in the maximum decrease from baseline in the supine SBP (p-value 0.0005). The difference in LSM for supine SBP was -6.00 mm Hg. There was no statistically significant difference in the AUEC₀₋₁₂ for supine SBP (p-value 0.0968) between subjects who received avanafil or placebo.

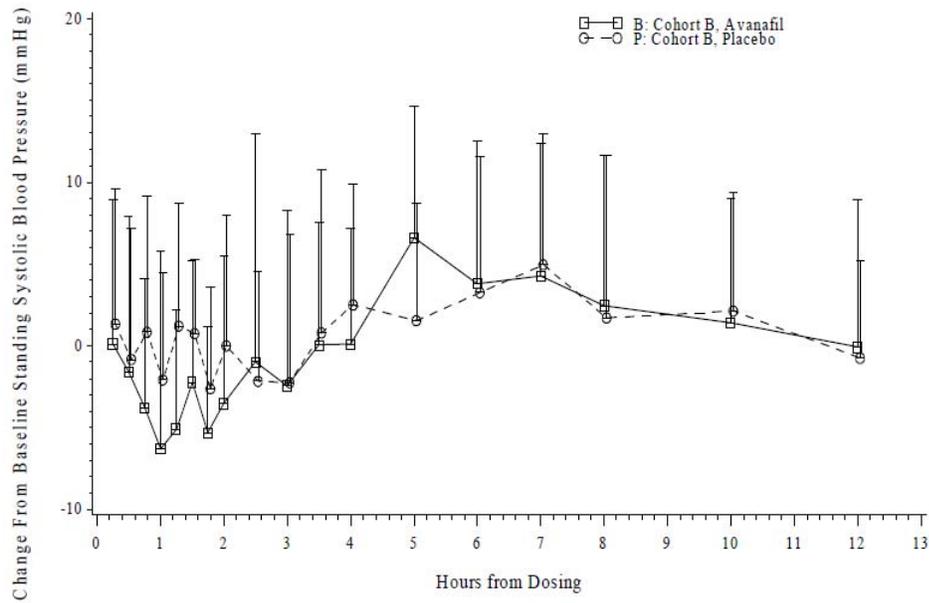
Statistically significant differences were observed in the maximum decrease from baseline in the supine DBP (p-value 0.0015) and in the AUEC₀₋₁₂ for supine DBP (p-value 0.0034) between subjects who received avanafil or placebo. The differences in the LSM for maximum decrease in supine DBP and AUEC₀₋₁₂ were -3.58 mm Hg and -31.40 mmHg*hr, respectively.

Statistically significant differences were not observed in the maximum decrease from baseline in the supine pulse rate (p-value 0.2564) between subjects who received avanafil or placebo. There was a dramatic and statistically significant difference in the AUEC₀₋₁₂ for supine pulse rate (p-value <0.0001) with a difference in LSM for supine pulse rate AUEC₀₋₁₂ of +45.84 bpm.hr.

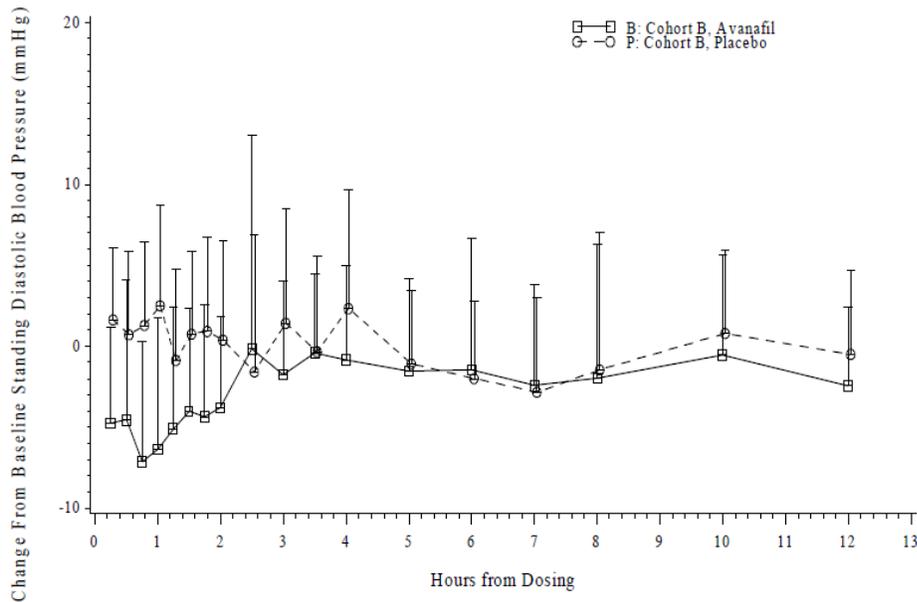
The differences in the LSM for maximum decrease in supine pulse rate and AUEC₀₋₁₂ were +7.21 bpm and +44.54 bpm.hr, respectively.

Cohort B: tamsulosin + avanafil/placebo

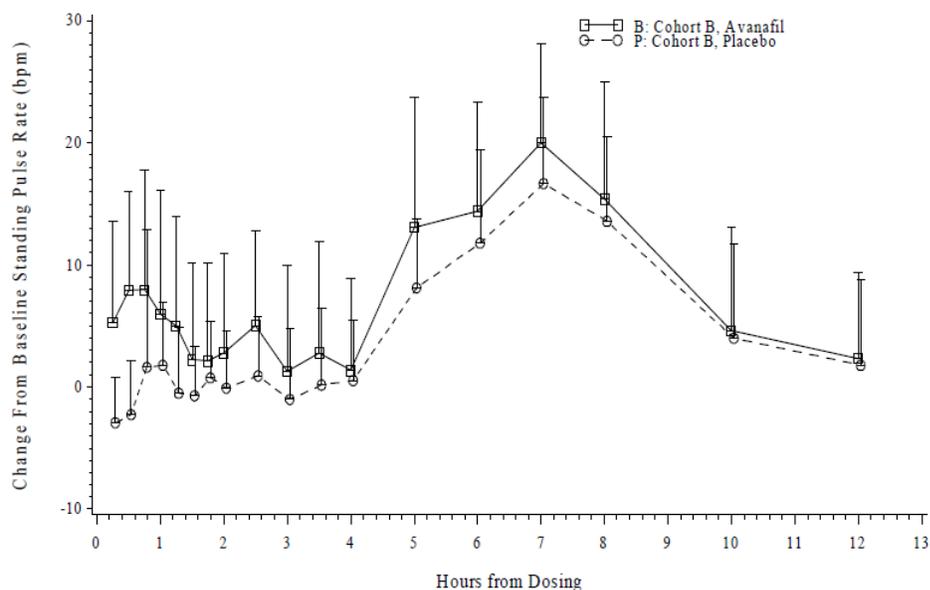
The following figure is the mean (SD) change from baseline for standing SBP vs time following administration of tamsulosin with avanafil or placebo (Cohort B) (sponsor's figure 5)



The following figure is the mean (SD) change from baseline for standing DBP vs time following administration of tamsulosin with avanafil or placebo (Cohort B) (sponsor's figure 6)



The following figure is the mean (SD) change from baseline for standing pulse rate vs time following administration of tamsulosin with avanafil or placebo (Cohort B) (sponsor's figure 7)



The following table is a statistical comparison of the maximum changes in standing blood pressure and pulse rate, and area under the effect vs time curves following administration of tamsulosin with avanafil or placebo (Cohort B) (sponsor's table 9)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Tamsulosin + Avanafil	Tamsulosin + Placebo			
Maximum decrease systolic (mmHg)	-14.50	-10.88	-3.63	-8.14 - +0.89	0.1101
Systolic AUEC ₀₋₁₂ (mmHg*h)	+11.71	+15.41	-3.70	-34.37 - +26.97	0.8047
Maximum decrease diastolic (mmHg)	-13.13	-9.46	-3.67	-7.86 - +0.53	0.0835
Diastolic AUEC ₀₋₁₂ (mmHg*h)	-24.40	-3.69	-20.71	-46.46 - +5.03	0.1094
Maximum increase pulse rate (bpm)	+22.25	+19.79	+2.46	-1.32 - +6.24	0.1913
Pulse rate AUEC ₀₋₁₂ (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.
Source: [Table 14.2.1.3.2](#)

There were no statistically significant differences in the maximum decrease from baseline in standing SBP (p-value 0.1101), standing DBP (p-value 0.0835), the AUEC₀₋₁₂ for standing SBP (p-value 0.8047) or DBP (p-value 0.1094), and the maximum increase from baseline in standing pulse rate (p-value 0.1913) between subjects who received avanafil or placebo. Though not statistically significant, the AUEC₀₋₁₂ mean difference for standing DBP was -20.71 mmHg*hr, which may represent a clinically significant difference.

The only statistically significant difference in the standing hemodynamic measurements was the standing pulse rate (p-value 0.0471). The difference in the LSM for the standing pulse rate was +31.56 bpm.hr.

The following table is a statistical comparison of the maximum changes in supine blood pressure and pulse rate, and area under the effect vs time curves following administration of tamsulosin with avanafil or placebo (Cohort B) (sponsor's table 11)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Tamsulosin + Avanafil	Tamsulosin + Placebo			
Maximum decrease systolic (mmHg)	-11.00	-7.88	-3.13	-6.37 - +0.12	0.0580
Systolic AUEC ₀₋₁₂ (mmHg*h)	+20.86	+28.87	-8.01	-39.41 - +23.40	0.6023
Maximum decrease diastolic (mmHg)	-10.04	-6.71	-3.33	-6.49 - -0.18	0.0392
Diastolic AUEC ₀₋₁₂ (mmHg*h)	-16.52	-1.50	-15.02	-47.21 - +17.18	0.3439
Maximum increase pulse rate (bpm)	+20.75	+16.08	+4.67	+0.37 - +8.96	0.0344
Pulse rate AUEC ₀₋₁₂ (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. Source: Table 14.2.2.3.2					

Statistically significant differences were not observed in the maximum decrease from baseline in the supine SBP (p-value 0.0580), the AUEC₀₋₁₂ for supine SBP (p-value 0.6023), or AUEC₀₋₁₂ for supine DBP (p-value 0.3439) between subjects who received avanafil or placebo.

Statistically significant differences were observed in the maximum decrease from baseline in the supine DBP (p-value 0.0392) between subjects who received avanafil or placebo. The difference in the LSM for maximum decrease in supine DBP was -3.33 mm Hg.

Statistically significant differences were observed in the maximum decrease from baseline in the supine pulse rate (p-value 0.0344) and AUEC₀₋₁₂ for supine pulse rate (p-value 0.0013) with differences in LSM for supine pulse rate and AUEC₀₋₁₂ for supine pulse rate of +4.67 bpm and +40.76 bpm.hr, respectively.

Study TA-018

Title: A Phase I, Single-Center, Open-Label, Crossover Study of the Effect of Avanafil on the Pharmacokinetics of Omeprazole, Desipramine and Rosiglitazone in Healthy Male Subjects

Objectives: The primary objective of this study was to compare the PK of omeprazole, rosiglitazone, and desipramine when administered alone and in combination with a single oral dose of avanafil in healthy male subjects. The secondary objective was to assess the safety of c-administration of avanafil with omeprazole, rosiglitazone, or desipramine in healthy male subjects.

Methods & PK Sampling: This was a single center, open-label, crossover study with three cohorts to evaluate the potential of avanafil to affect the PK of omeprazole (a CYP219 substrate), rosiglitazone (a CYP2C8 substrate), and desipramine (a CYP2D6 substrate). There were a total of 60 subjects enrolled with 57 completed the study (3 subjects were dropped or disenrolled for personal reasons or a failed drug screen; none were related to adverse events). Of the 60 subjects enrolled, 56 were White, 2 were Black or African-American, 1 was American Indian or Alaskan Native, and 1 was Asian. Avanafil dose was given as 1 x 200 mg tablet. Formulation II was used in this study.

Cohort A (omeprazole): This cohort was an open-label, non-randomized, one-sequence crossover study. Twenty healthy male subjects were administered a single oral dose of 40 mg omeprazole delayed-release capsule once daily for 8 days (Days 1 - 8) then a single oral dose of 200 mg avanafil on Day 8. On Days 7 and 8, avanafil and/or omeprazole doses were administered following an overnight fast of at least 10 hrs. All subjects were confined at the clinical site the day prior to the omeprazole administration on Day 7 and remained confined for approximately 13 hrs following the dosing on Day 8. The following are the two treatments in Cohort A:

- Treatment O: once daily 40 mg oral dose of omeprazole for 7 days (Days 1 - 7)
- Treatment O+A: once daily 40 mg oral doses of omeprazole for 8 days plus 200 mg avanafil (Day 8)

Blood samples for determination of plasma omeprazole concentrations were taken from all subjects at 0 (10 min predose), 20 and 40 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hrs postdose on Days 7 and 8. Predose blood samples for determination of omeprazole were also taken in the morning prior to dosing on Days 5 - 6.

Cohort B (rosiglitazone): This cohort was a randomized, open-label, two-period crossover study. Twenty healthy male subjects were administered a single dose of 8 mg rosiglitazone tablet then a single oral dose of 200 mg avanafil in the R+A group. The two treatments in this cohort were separated by a washout period of at least 7 days. All subjects were confined at the clinical site from the morning of Day -1 to the morning of Day 2 in both treatment periods. Subjects were randomized to one of the following treatment groups following an overnight fast of at least 10 hrs:

- Treatment R: a single oral dose of 8 mg rosiglitazone
- Treatment R+A: a single oral dose of 8 mg rosiglitazone plus a single oral dose of 200 mg avanafil

Blood samples for determination of plasma rosiglitazone concentrations were taken from all subjects at 0 (10 min predose) and at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 16, and 24 hrs postdose on Day 2.

Cohort C (desipramine): This cohort was a randomized, open-label, two-period, crossover study. Twenty healthy male subjects, identified as CYP2D6 extensive metabolizers by genotyping, were administered a single oral dose of 50 mg desipramine tablet then a single oral dose of 200 mg avanafil in the D+A group. The two treatments in this cohort were separated by a washout period of at least 10 days. All subjects were

confined at the clinical site from the morning of Day -1 to the morning of Day 2 in both treatment periods. Subjects were randomized to one of the following treatment groups following an overnight fast of at least 10 hrs:

- Treatment D: a single oral dose of 50 mg desipramine
- Treatment D+A: a single oral dose of 50 mg desipramine plus a single oral dose of 200 mg avanafil. The avanafil dose was administered 2 hrs after the desipramine administration

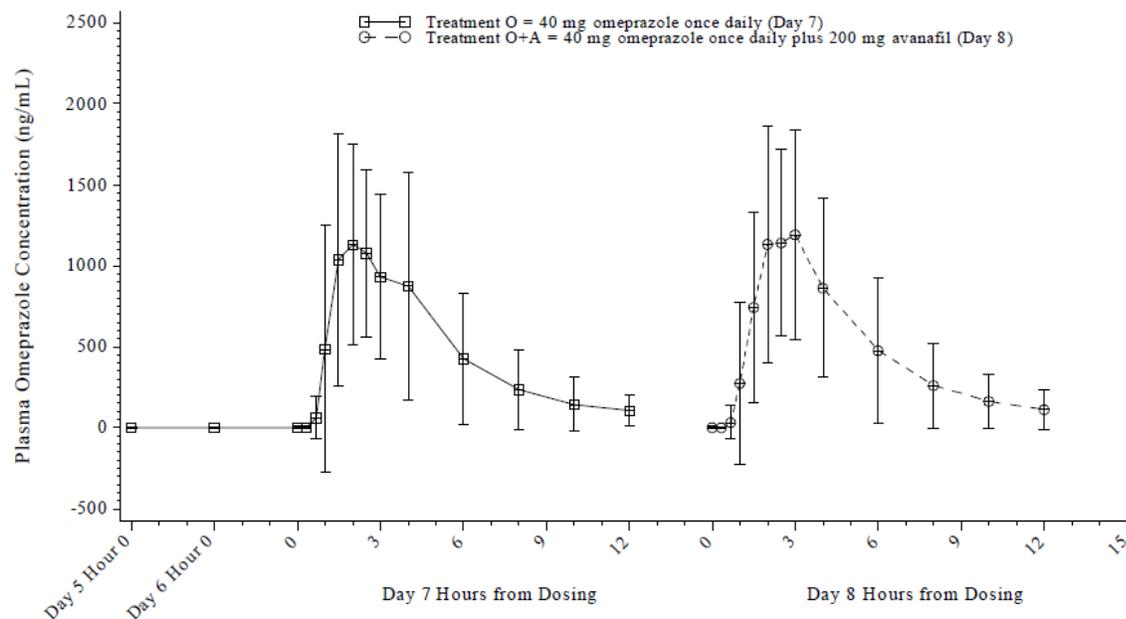
Blood samples for determination of plasma desipramine concentrations were taken from all subjects at 0 (10 min predose) and at 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hrs postdose. Subjects visited the study site as outpatients the morning of Days 3-5 for their remaining PK blood sample collections.

Results: Based on in vitro studies using human hepatocytes, the sponsor found that avanafil inhibited CYP2C19, CYP2C8, and CYP2D6 with a K_i of 2.9, 15.2, and 43.9 μM , respectively. The sponsor indicated that the mean maximum plasma concentration of 200 mg avanafil was about 5.2 μM , thereby resulting in C_{max}/K_i ratios greater than >0.1 . Therefore, the sponsor evaluated the affect of a single 200 mg dose of avanafil on the PK of omeprazole (a CYP2C19 substrate), rosiglitazone (a CYP2C8 substrate), and desipramine (a CYP2D6 substrate) in vivo.

In vivo results from this PK study showed that avanafil is not an inhibitor of CYP2C19, CYP2C8, and CYP2D6 enzymes. The potential of a single dose to affect multiple doses of omeprazole, a single dose rosiglitazone or a single dose of desipramine is unlikely; however, it is unclear what how multiple doses of avanafil can affect multiple doses of rosiglitazone or desipramine. The magnitude of a drug interaction between avanafil and CYP2C19, CYP2C8, and CYP2D6 substrates is unknown in chronic users of avanafil and these CYP substrates.

Cohort A (omeprazole)

The following is the arithmetic mean (SD) plasma omeprazole concentration vs time profile following omeprazole and omeprazole + avanafil administration (sponsor's table 14.4.1.1)



The following table is arithmetic mean (SD) and geometric mean PK parameters for plasma omeprazole (sponsor's table 5)

Pharmacokinetic Parameters	Treatment O		Treatment O+A	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
$C_{max,ss}$ (ng/mL) ^a	1520 ± 773 (19)	1330	1650 ± 572 (19)	1550
AUC_{0-t} (ng*hr/mL) ^a	5380 ± 3290 (19)	4420	5700 ± 2970 (19)	4940
t_{max} (hr) ^b	2.0 (1.0, 4.0) (19)	.	2.0 (1.0, 6.0) (19)	.
$t_{1/2}$ (hr) ^c	1.8 ± 0.66 (18)	.	1.9 ± 0.67 (18)	.
k_{el} (1/hr) ^a	0.437 ± 0.162 (18)	.	0.412 ± 0.124 (18)	.

Cohort A
Treatment O = Once daily 40 mg oral doses of omeprazole for 7 days (Days 1-7)
Treatment O+A = Once daily 40 mg oral doses of omeprazole for 8 Days plus 200 mg avanafil (Day 8)
^a $C_{max,ss}$, AUC_{0-t} , and k_{el} values are presented with three significant figures.
^b t_{max} is presented as median (minimum, maximum) and is presented with two significant figures.
^c $t_{1/2}$ is presented with two significant figures.
. = Value missing or not reportable.
SD = standard deviation
Source: Tables 14.2.1.2 and 14.2.1.3

The arithmetic mean C_{max} of omeprazole increased 1.09 fold (8.6%) from 1520 to 1650 ng/mL following omeprazole and avanafil co-administration, compared to omeprazole alone.

The arithmetic mean AUC_{0-t} of omeprazole increased 1.06 fold from 5380 to 5700 ng.hr/mL following omeprazole and avanafil co-administration, compared to omeprazole alone.

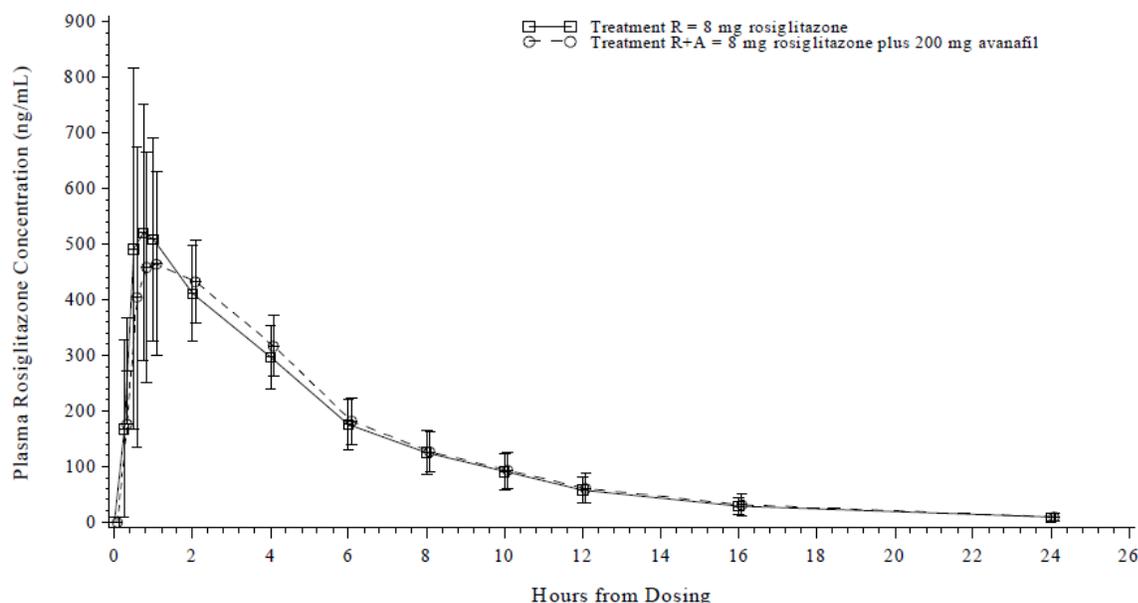
The median t_{max} of omeprazole remained unchanged at 2.0 hrs following omeprazole and avanafil co-administration and omeprazole alone.

The arithmetic mean $t_{1/2}$ of omeprazole increased by 0.1 hr from 1.8 to 1.9 hrs following omeprazole and avanafil co-administration, compared to omeprazole alone.

AUC_{0-inf} was not reported. It appears that blood sampling until 12 hrs was insufficient and may result in a >20% extrapolation to calculate AUC_{0-inf} from AUC_{0-t} .

Cohort B (rosiglitazone)

The following is the arithmetic mean (SD) plasma omeprazole concentration vs time profile following omeprazole and rosiglitazone + avanafil administration (sponsor's table 14.4.2.1)



The following table is arithmetic mean (SD) and geometric mean PK parameters for plasma rosiglitazone (sponsor's table 8)

Pharmacokinetic Parameters	Treatment R		Treatment R+A	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C_{max} (ng/mL) ^a	648 ± 181 (19)	622	560 ± 167 (20)	538
AUC_{0-t} (ng*hr/mL) ^a	2980 ± 620 (19)	2920	3040 ± 647 (20)	2970
AUC_{0-inf} (ng*hr/mL) ^a	3040 ± 647 (19)	2970	3100 ± 691 (20)	3030
t_{max} (hr) ^b	0.75 (0.50, 4.0) (19)	.	1.0 (0.50, 4.0) (20)	.
$t_{1/2}$ (hr) ^c	4.0 ± 0.75 (19)	.	3.9 ± 0.80 (20)	.
k_{el} (1/hr) ^a	0.180 ± 0.0310 (19)	.	0.182 ± 0.0338 (20)	.

Cohort B
 Treatment R = Single oral dose of 8 mg rosiglitazone
 Treatment R+A = Single oral dose of 8 mg rosiglitazone plus a single oral dose of 200 mg avanafil
^a C_{max} , AUC_{0-t} , AUC_{0-inf} , and k_{el} values are presented with three significant figures.
^b t_{max} is presented as median (minimum, maximum) and is presented with two significant figures.
^c $t_{1/2}$ is presented with two significant figures.
 . = Value missing or not reportable.
 SD = standard deviation
 Source: Tables 14.2.2.3 and 14.2.2.4

The arithmetic mean C_{max} of rosiglitazone decreased 14% from 648 to 560 ng/mL following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

The arithmetic mean AUC_{0-t} of rosiglitazone increased 1.02 fold from 2980 to 3040 ng.hr/mL following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

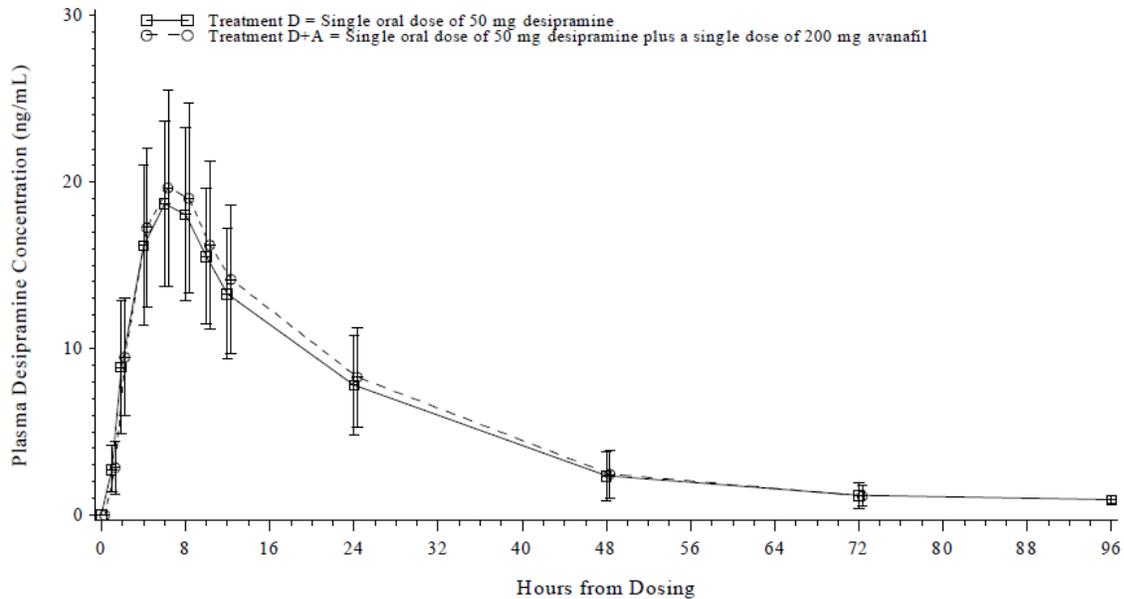
The arithmetic mean AUC_{0-inf} of rosiglitazone increased 1.02 fold from 3040 to 3100 ng.hr/mL following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

The median t_{max} of rosiglitazone increased 0.25 hr from 0.75 to 1.0 hr following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

The arithmetic mean $t_{1/2}$ of rosiglitazone decreased by 0.1 hr from 4.0 to 3.9 hrs following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

Cohort C (desipramine)

The following is the arithmetic mean (SD) plasma desipramine concentration vs time profile following omeprazole and desipramine + avanafil administration (sponsor's table 14.4.3.1)



The following table is arithmetic mean (SD) and geometric mean PK parameters for plasma desipramine (sponsor's table 11)

Pharmacokinetic Parameters	Treatment D		Treatment D+A	
	Mean ± SD (N)	Geometric Mean	Mean ± SD (N)	Geometric Mean
C_{max} (ng/mL) ^a	19.0 ± 5.20 (19)	18.4	20.0 ± 5.95 (20)	19.3
AUC_{0-t} (ng*hr/mL) ^a	452 ± 183 (19)	423	480 ± 186 (20)	448
AUC_{0-inf} (ng*hr/mL) ^a	472 ± 185 (19)	444	499 ± 188 (20)	468
t_{max} (hr) ^b	6.0 (6.0, 8.0) (19)	.	6.0 (6.0, 8.0) (20)	.
$t_{1/2}$ (hr) ^c	14 ± 3.0 (19)	.	14 ± 2.8 (20)	.
k_{el} (1/hr) ^a	0.0509 ± 0.00921 (19)	.	0.0512 ± 0.00932 (20)	.

Cohort C
Treatment D = Single oral dose of 50 mg desipramine
Treatment D+A = Single oral dose of 50 mg desipramine plus a single oral dose of 200 mg avanafil
^a C_{max} , AUC_{0-t} , AUC_{0-inf} , and k_{el} values are presented with three significant figures.
^b t_{max} is presented as median (minimum, maximum) and is presented with two significant figures.
^c $t_{1/2}$ is presented with two significant figures.
. = Value missing or not reportable.
SD = standard deviation
Source: [Tables 14.2.3.3](#) and [14.2.3.4](#)

The arithmetic mean C_{max} of desipramine increased 1.05 fold from 19.0 to 20.0 ng/mL following desipramine and avanafil co-administration, compared to desipramine alone.

The arithmetic mean AUC_{0-t} of desipramine increased 1.06 fold from 452 to 480 ng.hr/mL following desipramine and avanafil co-administration, compared to desipramine alone.

The arithmetic mean AUC_{0-inf} of desipramine increased 1.06 fold from 472 to 499 ng.hr/mL following desipramine and avanafil co-administration, compared to desipramine alone.

The median t_{max} of desipramine was unchanged at 6.0 hrs following desipramine and avanafil co-administration and desipramine alone.

The arithmetic mean $t_{1/2}$ of desipramine was unchanged at 14 hrs following desipramine and avanafil co-administration and desipramine alone.

Study TA-019

Title: A Phase I, Double-Blind, Randomized, Placebo-Controlled, Two-Period, Two-Cohort Crossover Study to Assess the Potential Interaction of Avanafil on the Pharmacokinetic and/or Hemodynamic Effects of Enalapril or Amlodipine in Healthy Subjects

Objectives: The primary objective of this study was to evaluate the hemodynamic interactions between avanafil and two anti-hypertensive drugs (enalapril, an ACE inhibitor, and amlodipine, a calcium channel blocker) in healthy male subjects. The secondary objectives were to assess the PK interaction between amlodipine and avanafil, and to assess the safety and tolerability of co-administration of avanafil and enalapril or amlodipine in healthy male subjects.

Methods: This study was a single center, randomized, double-blind, placebo-controlled, two-way crossover study in older healthy male subjects. There were 48 subjects (43 White, 4 Black or African American, and 1 American Indian or Alaskan Native) who were enrolled and 47 completed the study with 24 subjects randomized to each cohort. The mean age was 48.9 yrs (range 40-63 yrs) and mean weight was 81.4 (range 58.2-105.6 kg).

All study drugs were administered in the morning with 240 mL water after an overnight fast or at least 10 hrs. Sitting and standing blood pressure (BP) and pulse rate were monitored predose and at 4 hrs following the morning and evening doses of enalapril on Day 1 (Cohort A), and predose and at 4 hrs following the amlodipine dose on Day 3 (Cohort B). Sitting and standing BP and pulse rate were monitored daily prior to the morning doses of enalapril and amlodipine except on the days serial hemodynamic measurements were taken. The two study cohorts were:

Cohort A (enalapril): subjects received 10 mg oral doses of enalapril twice daily (every 12 hrs) for 11 days. On Days 8 and 11, subjects also received either 1 x 200 mg avanafil or matching placebo 2 hrs after the morning dose of enalapril. Subjects were confined to the clinical site beginning on Day -1 until Day 12 after completion of all study procedures.

Cohort B (amlodipine): subjects received 1 x 200 mg avanafil on Day 1. On Day 3, subjects received 5 mg oral doses of amlodipine in the morning for 18 days (Days 3-20). On Days 12 & 19, subjects also received either 1 x 200mg oral avanafil or matching placebo 2 hrs after amlodipine. Subjects were confined to the clinical site beginning on Day -1 until Day 21 after completion of all study procedures.

Hemodynamic Measurements: The primary hemodynamic endpoint was the mean difference in maximum post-baseline decrease in standing BP. The secondary hemodynamic endpoints are the mean differences in maximum post-baseline changes in supine BP and maximum post-baseline changes in standing and supine pulse rates and the area under the effect vs time curve of the change from baseline supine and standing SBP and DBP and pulse rate from 0-4 hr (AUEC₀₋₄), 0-10 hrs (AUEC₀₋₁₀), and 0-22 hrs (AUEC₀₋₂₂). Hemodynamic measurements were recorded prior to avanafil/placebo dosing (predose), 0.5, 1, 1.5, 2, 3, 3, 4, 5, 6, 7, 8, 10, and 22 hrs following dosing of avanafil or placebo. Predose baseline BP was calculated as the mean of three consecutive measurements at -30, -20, and -10 min prior to avanafil or placebo dosing.

Pharmacokinetic Sampling: The PK endpoints are the multiple-dose PK parameters for amlodipine and the single-dose PK parameters for avanafil and its metabolites M4 and M16 for Cohort B. The sponsor determined whether steady-state was achieved by evaluating trough concentrations. For trough plasma enalaprilat concentrations, blood samples were taken predose on Day 7 at 0 & 12 hrs, and Day 8 at 0 hr. For trough plasma amlodipine concentrations, blood samples were taken predose on Days 10, 11, and 12 at 0 hr.

Cohort A: Enalapril and enalaprilat concentrations were determined by taking blood samples prior to the morning and evening enalapril dose on Days 7 & 10, prior to the morning dose of enalapril on Days 8 & 11, and at 0.75 hrs following avanafil or placebo dosing on Days 8 & 11. Avanafil, M4, and M16 concentrations were determined by taking blood samples 0.75 hrs following avanafil or placebo dosing on Days 8 & 11.

Cohort B: Amlodipine concentrations were determined by taking blood samples prior to dosing on Days 10, 11, 12, 17, 18, and 19 and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, and 24 hrs after amlodipine dosing on Days 12 & 19. Avanafil, M4, and M16 concentrations were determined by taking blood samples prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 36, and 48 hrs following avanafil or placebo dosing on Days 1, 12 & 19.

Results: A single 200 mg dose of avanafil given to subjects who received 10 mg doses of enalapril twice daily for 11 days had a minor effect on BP and pulse rate. Standing SBP decreased by 0.8 mm Hg, DBP increased by 0.2 mm Hg, 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 -1.75/-3.46 mmHg and increase in pulse rate of 0.96 bpm was observed in subjects co-administered with avanafil and enalapril, compared to placebo and enalapril.

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 and DBP decreased by 1.6 mm Hg and 1.4 mm Hg, 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 change in supine SBP/DBP of -1.18/1.47 mm Hg was observed in subjects co-administered with avanafil and amlodipine, compared to placebo and amlodipine.

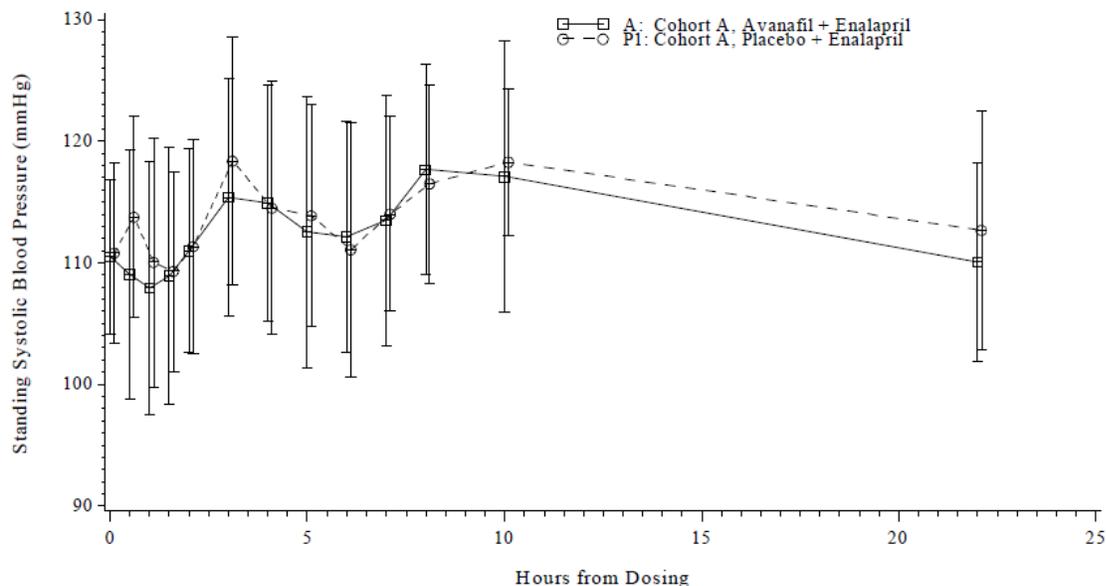
Amlodipine PK: When a single 200 mg dose of avanafil was co-administered with multiple doses of amlodipine, the arithmetic mean C_{max} of amlodipine decreased 8.9% from 12400 to 11300 pg/mL, compared to placebo + amlodipine. Arithmetic mean AUC_{0-t} of amlodipine decreased 3.8% from 234000 to 225000 pg*hr/mL, compared to placebo + amlodipine. Median t_{max} of amlodipine remained unchanged at 8 hrs with a single dose of avanafil + multiple doses of amlodipine and placebo + amlodipine co-administration.

Avanafil PK: When a single 200 mg dose of avanafil was co-administered with multiple doses of amlodipine, the arithmetic mean C_{max} of avanafil increased 22% from 3190 to 3890 ng/mL, compared to avanafil alone. Arithmetic mean AUC_{0-t} of avanafil increased 65% from 9100 to 15000 ng.hr/mL, compared to avanafil alone. Arithmetic mean AUC_{0-inf} of avanafil increased 70% from 9590 to 16300 ng.hr/mL, compared to avanafil alone. Median t_{max} of avanafil increased by 0.12 hr from 0.63 to 0.75 hr with a single dose of avanafil + multiple doses of amlodipine, compared to avanafil alone. Arithmetic mean t_{1/2} of avanafil increased by 2.9 hr from 7.0 to 9.9 hrs with a single dose of avanafil + multiple doses of amlodipine, compared to avanafil alone.

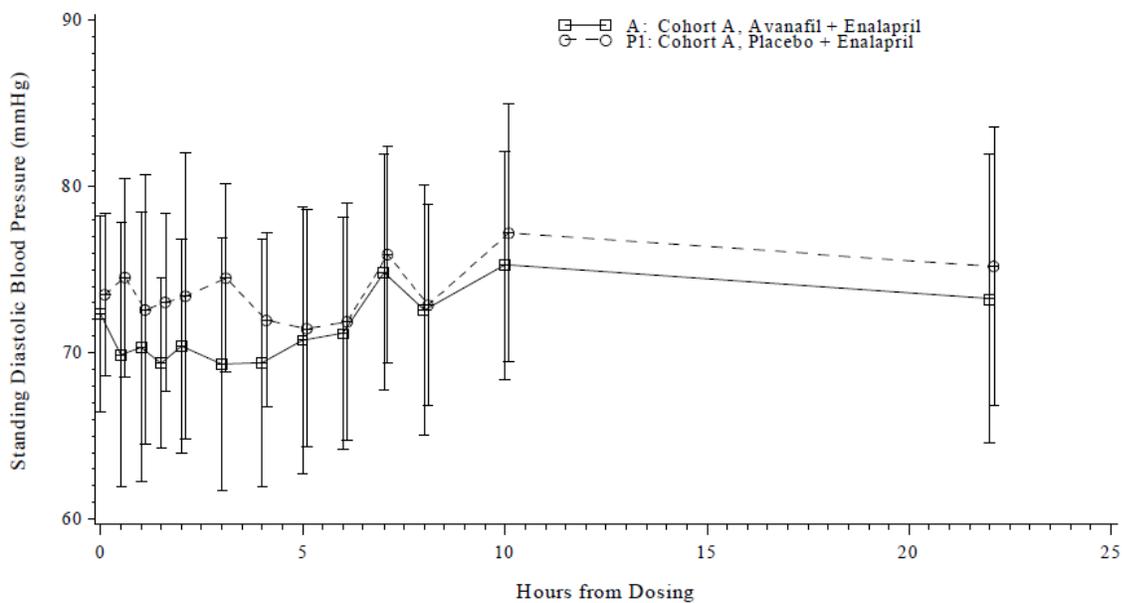
Headache was the most common adverse event in both cohorts and was more prevalent in subjects who received avanafil + amlodipine, and avanafil alone, compared to placebo avanafil + enalapril and placebo avanafil + amlodipine. Number of subjects reporting dizziness was the same in subjects who received 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. It appears that increases in C_{max} and AUC_{0-inf} of avanafil of 22% and 70%, respectively, from co-administration with amlodipine did not result in a corresponding increase in adverse events.

Cohort A: enalapril + avanafil/placebo

The following figure is the arithmetic mean (SD) Standing Systolic Blood Pressure vs. time following avanafil + enalapril and placebo + enalapril (sponsor's figure 14.4.1.1.1)



The following figure is the arithmetic mean (SD) Standing Diastolic Blood Pressure vs. time following avanafil + enalapril and placebo + enalapril (sponsor's figure 14.4.1.3.1)



Statistical comparison of geometric LS means of area under the effect time curve and maximum changes in STANDING blood pressure and pulse rate following avanafil + enalapril and placebo + enalapril (sponsor's table 4)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Avanafil + Enalapril	Placebo + Enalapril			
Maximum decrease systolic (mmHg)	-9.33	-8.50	-0.83	(-3.61, +1.95)	0.5405
Systolic AUEC ₀₋₄ (mmHg*h)	+4.33	+10.04	-5.71	(-14.24, +2.81)	0.1785
Systolic AUEC ₀₋₁₀ (mmHg*h)	+30.40	+34.48	-4.07	(-28.17, +20.02)	0.7292
Systolic AUEC ₀₋₂₂ (mmHg*h)	+66.66	+89.92	-23.26	(-89.44, +42.93)	0.4738
Maximum decrease diastolic (mmHg)	-8.12	-8.33	+0.21	(-1.91, +2.33)	0.8405
Diastolic AUEC ₀₋₄ (mmHg*h)	-9.48	+0.11	-9.59	(-16.30, -2.88)	0.0072
Diastolic AUEC ₀₋₁₀ (mmHg*h)	-7.99	+0.93	-8.92	(-24.12, +6.28)	0.2363
Diastolic AUEC ₀₋₂₂ (mmHg*h)	+14.94	+33.02	-18.07	(-62.73, +26.58)	0.4103
Maximum increase pulse rate (bpm)	+18.17	+17.58	+0.58	(-2.84, +4.00)	0.7269
Pulse rate AUEC ₀₋₄ (bpm*h)	+28.13	+14.66	+13.47	(+2.57, +24.37)	0.0177
Pulse rate AUEC ₀₋₁₀ (bpm*h)	+77.42	+55.32	+22.10	(-5.66, +49.86)	0.1129
Pulse rate AUEC ₀₋₂₂ (bpm*h)	+155.82	+115.50	+40.32	(-20.19, +100.83)	0.1808

AUEC₀₋₄, AUEC₀₋₁₀, AUEC₀₋₂₂= area under effect-time curve from Hour 0 to Hour 4, 10, and 22, respectively; CI= confidence interval
Cohort A: enalapril 10 mg BID on Days 1-11 plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.
Source: Table 14.2.1.3.1

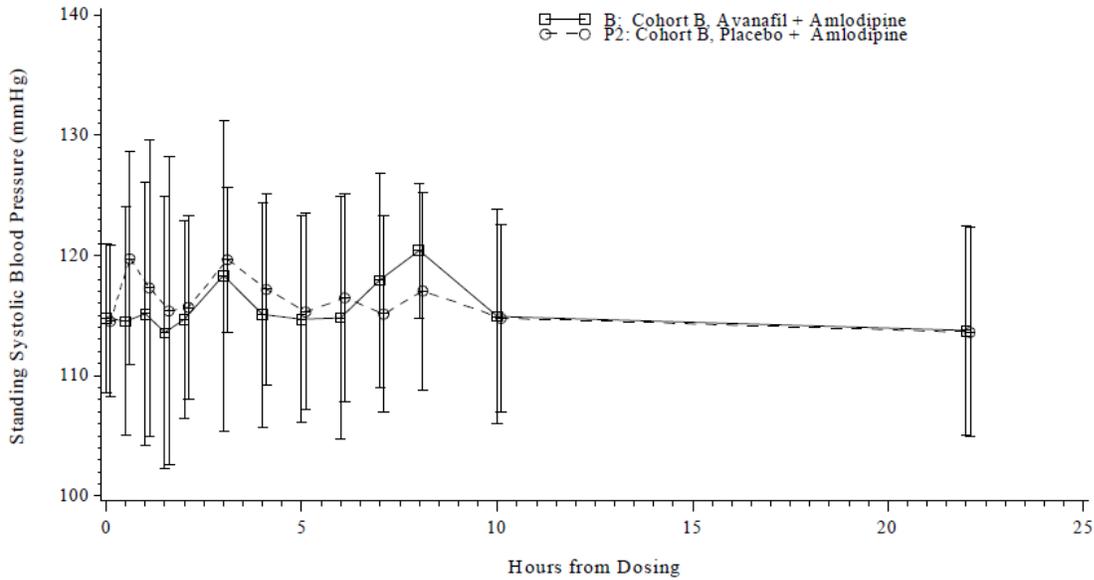
Statistical comparison of geometric LS means of area under the effect time curve and maximum changes in SUPINE blood pressure and pulse rate following avanafil + enalapril and placebo + enalapril (sponsor's table 6)

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Avanafil + Enalapril	Placebo + Enalapril			
Maximum decrease systolic (mmHg)	-9.38	-7.63	-1.75	(-4.91, +1.41)	0.2631
Systolic AUEC ₀₋₄ (mmHg*h)	-2.14	+6.55	-8.68	(-19.37, +2.01)	0.1062
Systolic AUEC ₀₋₁₀ (mmHg*h)	+16.10	+26.10	-10.00	(-36.66, +16.66)	0.4449
Systolic AUEC ₀₋₂₂ (mmHg*h)	+46.31	+83.90	-37.59	(-103.73, +28.55)	0.2511
Maximum decrease diastolic (mmHg)	-9.33	-5.87	-3.46	(-6.29, -0.62)	0.0191
Diastolic AUEC ₀₋₄ (mmHg*h)	-13.22	+0.92	-14.15	(-21.18, -7.11)	0.0004
Diastolic AUEC ₀₋₁₀ (mmHg*h)	-20.59	+2.95	-23.54	(-37.38, -9.70)	0.0019
Diastolic AUEC ₀₋₂₂ (mmHg*h)	-6.89	+30.24	-37.13	(-64.65, -9.61)	0.0105
Maximum increase pulse rate (bpm)	+14.04	+13.08	+0.96	(-1.40, +3.31)	0.4075
Pulse rate AUEC ₀₋₄ (bpm*h)	+19.64	+10.60	+9.04	(+1.34, +16.74)	0.0235
Pulse rate AUEC ₀₋₁₀ (bpm*h)	+59.78	+48.23	+11.55	(-8.90, +32.00)	0.2541
Pulse rate AUEC ₀₋₂₂ (bpm*h)	+126.51	+111.84	+14.67	(-30.53, +59.87)	0.5079

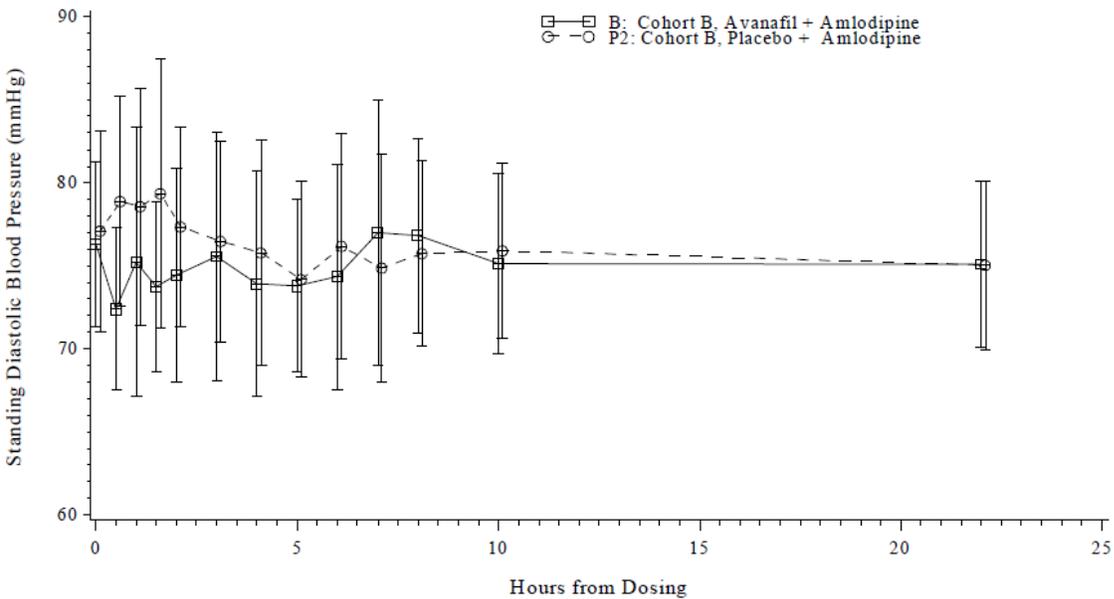
AUEC₀₋₄, AUEC₀₋₁₀, AUEC₀₋₂₂= area under effect-time curve from Hour 0 to Hour 4, 10, and 22, respectively; CI= confidence interval
Cohort A: enalapril 10 mg BID on Days 1-11 plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.
Source: Table 14.2.2.3.1

Cohort B: amlodipine + avanafil/placebo

The following figure is the arithmetic mean (SD) Standing Systolic Blood Pressure vs. time following avanafil + amlodipine and placebo + amlodipine (sponsor's figure 14.4.1.1.2)



The following figure is the arithmetic mean (SD) Standing Diastolic Blood Pressure vs. time following avanafil + amlodipine and placebo + amlodipine (sponsor's figure 14.4.1.3.2)



Statistical comparison of area under the effect vs time curve and maximum changes in STANDING blood pressure and pulse rate

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Avanafil + Amlodipine	Placebo + Amlodipine			
Maximum decrease systolic (mmHg)	-10.44	-8.88	-1.56	(-5.18, +2.06)	0.3796
Systolic AUEC ₀₋₄ (mmHg*h)	+1.62	+11.80	-10.19	(-23.45, +3.08)	0.1249
Systolic AUEC ₀₋₁₀ (mmHg*h)	+14.93	+20.11	-5.18	(-37.61, +27.25)	0.7425
Systolic AUEC ₀₋₂₂ (mmHg*h)	+7.96	+16.69	-8.73	(-69.99, +52.53)	0.7693
Maximum decrease diastolic (mmHg)	-9.39	-7.97	-1.42	(-4.23, +1.38)	0.3023
Diastolic AUEC ₀₋₄ (mmHg*h)	-7.50	+1.25	-8.75	(-16.02, -1.48)	0.0208
Diastolic AUEC ₀₋₁₀ (mmHg*h)	-12.84	-9.03	-3.82	(-23.63, +15.99)	0.6920
Diastolic AUEC ₀₋₂₂ (mmHg*h)	-31.56	-28.67	-2.89	(-51.99, +46.21)	0.9035
Maximum increase pulse rate (bpm)	+17.76	+12.42	+5.34	(+0.37, +10.31)	0.0364
Pulse rate AUEC ₀₋₄ (bpm*h)	+28.94	+10.31	+18.63	(+9.29, +27.97)	0.0005
Pulse rate AUEC ₀₋₁₀ (bpm*h)	+69.80	+37.77	+32.02	(+6.79, +57.26)	0.0155
Pulse rate AUEC ₀₋₂₂ (bpm*h)	+130.86	+86.29	+44.58	(-7.64, +96.79)	0.0901

AUEC₀₋₄, AUEC₀₋₁₀, AUEC₀₋₂₂ = area under effect-time curve from Hour 0 to Hour 4, 10, and 22, respectively; CI= confidence interval
Cohort B: amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil or placebo on Days 12 and 19.
Source: Table 14.2.1.3.2

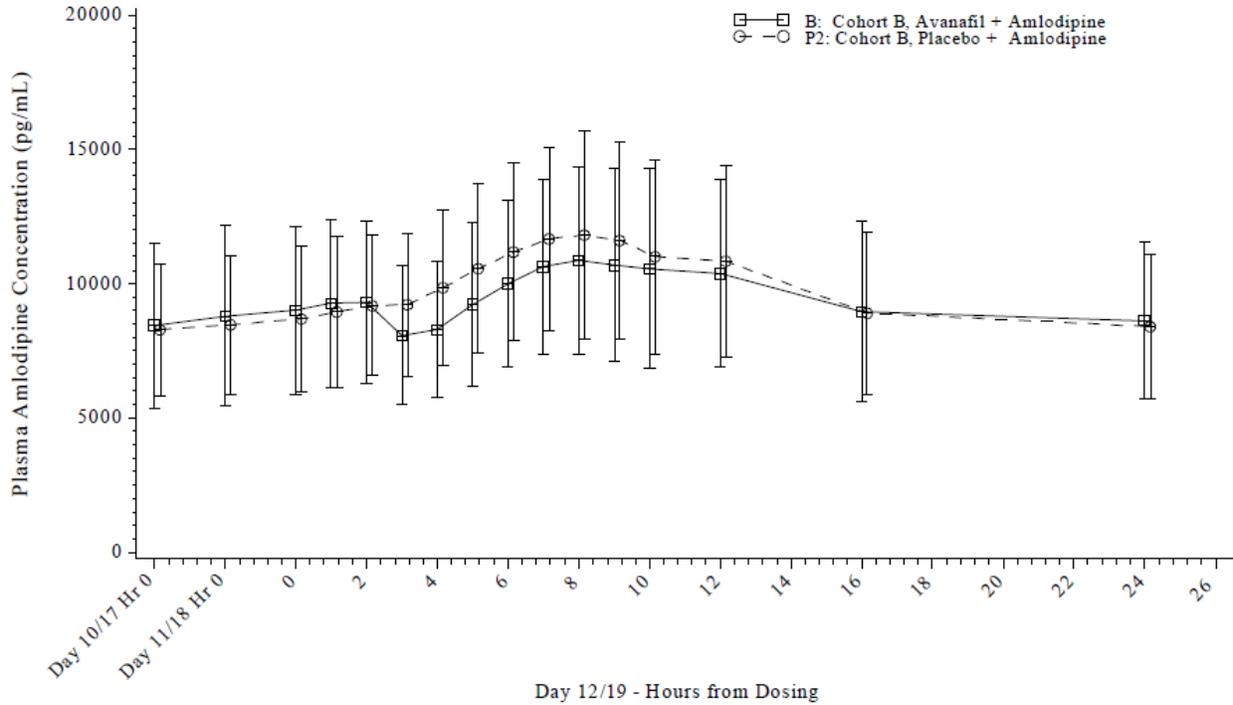
Statistical comparison of area under the effect vs time curve and maximum changes in SUPINE blood pressure and pulse rate

Hemodynamic Parameter	Least-Squares Means		Mean Difference	95% CI	P-Value
	Avanafil + Amlodipine	Placebo + Amlodipine			
Maximum decrease systolic (mmHg)	-10.09	-8.91	-1.18	(-6.44, +4.07)	0.6432
Systolic AUEC ₀₋₄ (mmHg*h)	+1.18	+9.91	-8.73	(-20.14, +2.68)	0.1261
Systolic AUEC ₀₋₁₀ (mmHg*h)	+14.52	+17.88	-3.36	(-33.86, +27.14)	0.8205
Systolic AUEC ₀₋₂₂ (mmHg*h)	+27.83	+24.94	+2.89	(-60.35, +66.13)	0.9250
Maximum decrease diastolic (mmHg)	-8.81	-10.28	+1.47	(-2.35, +5.30)	0.4312
Diastolic AUEC ₀₋₄ (mmHg*h)	-5.47	+3.00	-8.47	(-14.18, -2.76)	0.0057
Diastolic AUEC ₀₋₁₀ (mmHg*h)	-13.73	-9.32	-4.40	(-20.16, +11.36)	0.5666
Diastolic AUEC ₀₋₂₂ (mmHg*h)	-19.70	-30.18	+10.48	(-29.00, +49.96)	0.5859
Maximum increase pulse rate (bpm)	+12.02	+11.02	+1.00	(-1.20, +3.21)	0.3542
Pulse rate AUEC ₀₋₄ (bpm*h)	+19.35	+9.99	+9.35	(+3.40, +15.31)	0.0038
Pulse rate AUEC ₀₋₁₀ (bpm*h)	+57.31	+36.94	+20.36	(+5.30, +35.42)	0.0106
Pulse rate AUEC ₀₋₂₂ (bpm*h)	+110.85	+70.05	+40.80	(+0.83, -80.78)	0.0459

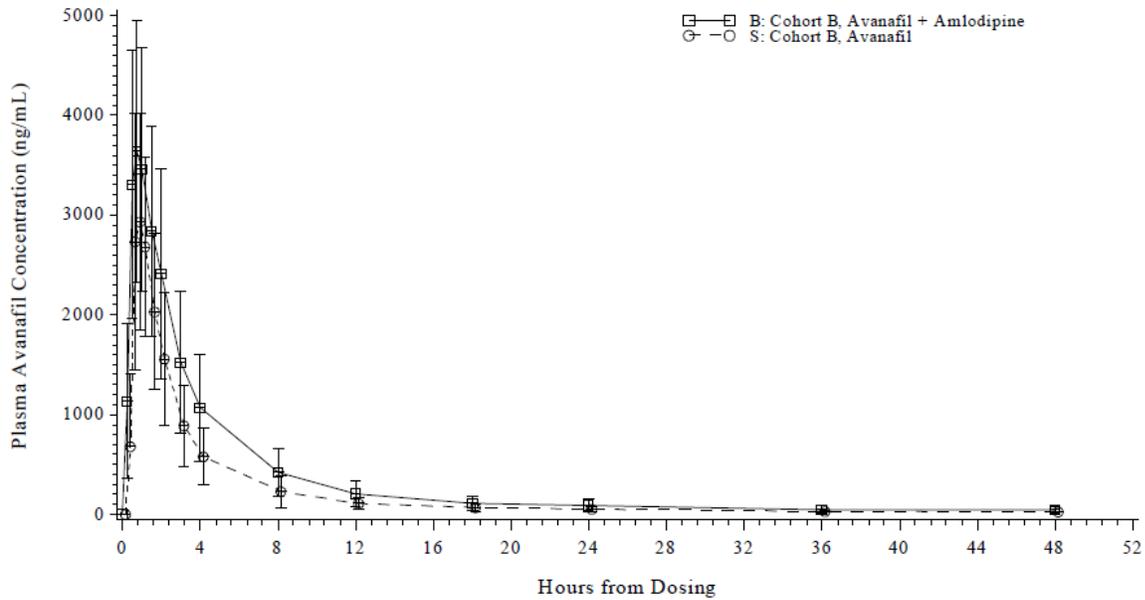
AUEC₀₋₄, AUEC₀₋₁₀, AUEC₀₋₂₂ = area under effect-time curve from Hour 0 to Hour 4, 10, and 22, respectively; CI= confidence interval
Cohort B: amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil or placebo on Days 12 and 19.
Source: Table 14.2.2.3.2

The mean maximum decrease in supine systolic blood pressure was 1.18 mm Hg when a single 200 mg dose of avanafil was co-administered with multiple 5 mg doses of amlodipine (-10.09 mm Hg), compared to placebo and amlodipine (-8.91 mm Hg). The mean maximum decrease in supine diastolic blood pressure was 8.81 mm Hg and 10.28 mm Hg in subjects administered with avanafil + amlodipine and placebo + amlodipine, respectively; therefore, avanafil had no net effect on the supine diastolic blood pressure.

The following figure is the arithmetic mean (SD) amlodipine concentrations vs. time following avanafil + amlodipine and avanafil alone (sponsor's figure 14.4.4.1)



The following figure is the arithmetic mean (SD) avanafil concentrations vs. time following avanafil + amlodipine and avanafil alone (sponsor's figure 14.4.5.1)



The following table is a summary of the arithmetic mean (SD) and geometric mean of amlodipine PK (sponsor's table 15)

PK Parameters	Avanafil + Amlodipine		Placebo + Amlodipine	
	Mean ± SD (N)	Geometric Mean (CV%)	Mean ± SD (N)	Geometric Mean (CV%)
C _{max} (pg/mL)	11300 ± 3730 (22)	10600 (37.8)	12400 ± 3800 (23)	11800 (35.4)
C _{min} (pg/mL)	7910 ± 2560 (22)	7490 (36.2)	8030 ± 2580 (23)	7610 (35.3)
AUC _{0-tau} (pg*hr/mL)	225000 ± 75700 (22)	212000 (37.7)	234000 ± 72500 (23)	222000 (35.3)
t _{max} (hr)	8.0 (7.0, 10) (22)	.	8.0 (5.0, 12) (23)	.

Cohort B: amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil (Treatment B) or placebo (Treatment P2) on Days 12 and 19.
The data for Subject 46 (Treatment B) were excluded from the statistical analysis because the subject vomited after receiving Treatment B on Day 19.
C_{max}, C_{min}, and AUC_{0-tau} are presented with three significant figures.
*t_{max} is presented as median (minimum, maximum) and is presented with two significant figures.
. = Value missing or not reportable.
PK= pharmacokinetic; SD = standard deviation; CV% = geometric CV%
Source: Tables 14.2.4.3 and 14.2.4.4

When a single 200 mg dose of avanafil was co-administered with multiple doses of amlodipine, the arithmetic mean C_{max} of amlodipine decreased 8.9% from 12400 to 11300 pg/mL, compared to placebo + amlodipine.

Arithmetic mean AUC_{0-t} of amlodipine decreased 3.8% from 234000 to 225000 pg*hr/mL, compared to placebo + amlodipine.

Median t_{max} of amlodipine remained unchanged at 8 hrs with a single dose of avanafil + multiple doses of amlodipine and placebo + amlodipine co-administration.

The following table is a summary of statistical comparisons of geometric LS means of amlodipine PK following avanafil + amlodipine vs. placebo + amlodipine

Pharmacokinetic Parameters	Geometric LS Means ^a		Confidence Intervals		
	Avanafil + Amlodipine	Placebo + Amlodipine	90% Confidence		% Mean Ratio ^a
C _{max} (pg/mL) ^b	10500	11800	(86.21, 92.65)		89.37
AUC _{0-tau} (pg*hr/mL) ^b	209000	222000	(91.24, 97.64)		94.39
	Treatment Median ^c		95% CI	Median Difference ^d	P-value
	Avanafil + Amlodipine	Placebo + Amlodipine			
t _{max} (hr) ^b	8.0	8.0	(-0.50, 0.51)	0.0017	0.6260

The following table is a summary of the arithmetic mean (SD) and geometric mean of avanafil PK (sponsor's table 18)

PK Parameters	Avanafil + Amlodipine		Avanafil Alone	
	Mean ± SD (N)	Geometric Mean (CV%)	Mean ± SD (N)	Geometric Mean (CV%)
C _{max} (ng/mL)	3890 ± 1320 (22)	3560 (51.5)	3190 ± 1110 (24)	2980 (43.4)
AUC _{0-t} (ng*hr/mL)	15000 ± 6550 (22)	13700 (48.5)	9100 ± 3510 (24)	8410 (43.8)
AUC _{0-inf} (ng*hr/mL)	16300 ± 6830 (19)	15100 (41.8)	9590 ± 3510 (23)	8920 (42.0)
t _{max} (hr)	0.75 (0.50, 2.0) (22)	.	0.63 (0.50, 2.0) (24)	.
t _{1/2} (hr)	9.9 ± 3.8 (19)	.	7.0 ± 3.4 (23)	.
k _{el} (1/hr)	0.0801 ± 0.0277 (19)	.	0.131 ± 0.0810 (23)	.

Cohort B: a single dose of 200 mg avanafil on Day 1 (Treatment S), amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil (Treatment B) on Day 12 or 19.
The data for Subject 46 (Treatment B) were excluded from the summary statistics because the subject vomited after receiving Treatment B on Day 19.
C_{max}, AUC_{0-t}, AUC_{0-inf} and k_{el} values are presented with three significant figures.
t_{1/2} is presented with two significant figures.
*t_{max} is presented as median (minimum, maximum) and is presented with two significant figures.
. = Value missing or not reportable.
PK= pharmacokinetic; SD = standard deviation; CV% = geometric CV%
Source: Tables 14.2.5.3 and 14.2.5.4

When a single 200 mg dose of avanafil was co-administered with multiple doses of amlodipine, the arithmetic mean C_{max} of avanafil increased 22% from 3190 to 3890 ng/mL, compared to avanafil alone.

Arithmetic mean AUC_{0-t} of avanafil increased 65% from 9100 to 15000 ng.hr/mL, compared to avanafil alone. Arithmetic mean AUC_{0-inf} of avanafil increased 70% from 9590 to 16300 ng.hr/mL, compared to avanafil alone.

Median t_{max} of avanafil increased by 0.12 hr from 0.63 to 0.75 hr with a single dose of avanafil + multiple doses of amlodipine, compared to avanafil alone. Arithmetic mean t_{1/2} of avanafil increased by 2.9 hr from 7.0 to 9.9 hrs with a single dose of avanafil + multiple doses of amlodipine, compared to avanafil alone.

The following table is a summary of statistical comparisons of geometric LS means of avanafil PK following avanafil + amlodipine vs. avanafil alone

Pharmacokinetic Parameters	Geometric LS Means ^a		Confidence Intervals		
	Avanafil + Amlodipine	Avanafil Alone	90% Confidence		% Mean Ratio ^a
C _{max} (ng/mL) ^b	3580	2780	(101.89, 162.02)		128.48
AUC _{0-t} (ng*hr/mL) ^b	13600	8520	(135.25, 188.98)		159.87
AUC _{0-inf} (ng*hr/mL) ^b	15100	9370	(135.08, 191.03)		160.64
	Treatment Median ^c		95% CI	Median Difference ^d	P-value
	Avanafil + Amlodipine	Avanafil Alone			
t _{max} (hr) ^{b1}	0.75	0.63	(0.00, 0.37)	0.12	0.1837
t _{1/2} (hr) ^b	8.2	6.2	(1.6, 4.0)	2.9	0.0008

Safety

Incidence of treatment-emergent adverse events (sponsor's table 24)

Cohort	Treatment*	Number (%) of Subjects Reporting AEs	Number of AE Episodes Reported
A Enalapril (N=24)	Enalapril only	7 (29%)	9
	200 mg avanafil + enalapril	4 (17%)	7
	Placebo + enalapril	0	0
	Overall	11 (46%)	16
B Amlodipine	Single dose 200 mg avanafil (N=24)	2 (8%)	8
	Amlodipine only (N=24)	6 (25%)	27
	200 mg avanafil + amlodipine (N=23)	5 (22%)	12
	Placebo + amlodipine (N=23)	1 (4%)	1
	Overall (N=24)	9 (38%)	48

*Enalapril-only and amlodipine-only rows include AEs that occurred before avanafil or placebo dosing (prior to Day 8 for Cohort A, Day 12 for Cohort B). AEs that occurred after avanafil or placebo dosing were assigned to the most recent treatment received.
Cohort A: enalapril 10 mg BID on Days 1-11 plus a single dose of 200 mg avanafil or placebo on Days 8 and 11.
Cohort B: amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil or placebo on Days 12 and 19.
Source: Tables 14.3.1.1 and 14.3.1.2

Table 14.3.1.1. Treatment-Emergent Adverse Event Frequency by Cohort and Treatment - Number of Subjects Reporting Events

Adverse Event*	Cohort									
	A					B				
	Enalapril Only	Treatment		Overall	Single-Dose Avanafil	Amlodipine Only	Treatment		Overall	
Number of Subjects Dosed	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	24 (100%)	23 (100%)	23 (100%)	24 (100%)	
Number of Subjects With AEs	7 (29%)	4 (17%)	0 (0%)	11 (46%)	2 (8%)	6 (25%)	5 (22%)	1 (4%)	9 (38%)	
Number of Subjects Without AEs	17 (71%)	20 (83%)	24 (100%)	13 (54%)	22 (92%)	18 (75%)	18 (78%)	22 (96%)	15 (63%)	
Cardiac disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Palpitations	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Ear and labyrinth disorders	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Cerumen impaction	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Eye disorders	1 (4%)	1 (4%)	0 (0%)	2 (8%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Dry eye	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Ocular hyperaemia	0 (0%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Photopsia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Gastrointestinal disorders	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	2 (8%)	2 (8%)	0 (0%)	4 (17%)	
Abdominal pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Diarrhoea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Dyspepsia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Eructation	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Nausea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	2 (8%)	
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
General disorders and administration site conditions	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	2 (8%)	
Chest discomfort	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Chills	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Peripheral coldness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Injury, poisoning and procedural complications	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	
Skin laceration	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	
Investigations	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Blood potassium decreased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Musculoskeletal and connective tissue disorders	0 (0%)	1 (4%)	0 (0%)	1 (4%)	1 (4%)	2 (8%)	1 (4%)	0 (0%)	3 (13%)	
Arthralgia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	
Back pain	0 (0%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Groin pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Muscular weakness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Musculoskeletal pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	
Pain in extremity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	
Nervous system disorders	4 (17%)	3 (13%)	0 (0%)	7 (29%)	2 (8%)	4 (17%)	4 (17%)	0 (0%)	6 (25%)	
Dizziness	1 (4%)	1 (4%)	0 (0%)	2 (8%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	2 (8%)	
Dysgeusia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	
Headache	3 (13%)	3 (13%)	0 (0%)	6 (25%)	2 (8%)	2 (8%)	4 (17%)	0 (0%)	5 (21%)	
Paresthesia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Somnolence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Psychiatric disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Anxiety	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Renal and urinary disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Dysuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Reproductive system and breast disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	0 (0%)	2 (8%)	
Erectile dysfunction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	
Testicular pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Respiratory, thoracic and mediastinal disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	2 (8%)	
Dyspnoea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Epistaxis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Skin and subcutaneous tissue disorders	1 (4%)	1 (4%)	0 (0%)	2 (8%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)	2 (8%)	
Erythema	0 (0%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Pruritus	1 (4%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Seborrheic dermatitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Skin warm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)	
Vascular disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	
Flushing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	
Pallor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)	

* Adverse events are classified according to MedDRA Version 11.1.
Enalapril-only or amlodipine-only columns include AEs occurred before avanafil or placebo dosing (prior to Day 8 for Cohort A, Day 12 for Cohort B)
AEs that occurred after avanafil or placebo dosing were assigned to the most recent treatment received.
Cohort A (Enalapril BID): 10 mg (Days 1-11)
Sequence A/P1: a single dose of 200 mg avanafil on Day 8 (Treatment A) followed by placebo avanafil on Day 11 (Treatment P1)
Sequence P1/A: a single dose of placebo avanafil on Day 8 (Treatment P1) followed by 200 mg avanafil on Day 11 (Treatment A)

Cohort B (Amlodipine QD): 5 mg (Days 3-20) with a single dose of 200 mg avanafil on Day 1 (Treatment S)
Sequence B/P2: a single dose of 200 mg avanafil on Day 12 (Treatment B) followed by placebo avanafil on Day 19 (Treatment P2)
Sequence P2/B: a single dose of placebo avanafil on Day 12 (Treatment P2) followed by 200 mg avanafil on Day 19 (Treatment B)

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 avanafil + enalapril and placebo avanafil + 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. It appears that an increase in C_{max} and AUC_{0-inf} of avanafil of 22% and 70%, respectively, from co-administration with amlodipine did not result in a corresponding increase in adverse events.

Study TA-020

Title: A Phase 1, Single-Centre, Open-Label, Randomized, Four-Period Crossover Study to Assess the Effect of Food on the Pharmacokinetics of Avanafil, to Determine the Relative Bioavailability of Two Avanafil Tablet Formulations and to Investigate Dose Proportionality in Healthy Male Subjects

Objectives: The objectives of this study were to assess the effect of food on the PK of avanafil (Formulation II); determine the relative bioavailability of two avanafil tablet formulations (Formulation I vs. Formulation II); and to investigate dose proportionality of Formulation II tablets.

Methods: This was a single-center, open-label, randomized, four-way crossover study. Subjects reported to the study site before each treatment and remained at the study site until the 24-hr PK sample had been drawn. A single oral dose of avanafil tablets was administered with 240 mL water. Subjects fasted at least 10 hrs prior to treatment and at least 4 hrs following dosing in Treatment Groups A, C, and D. Subjects began to eat a standardized high fat (800 to 1000 total calories with 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat) breakfast 30±5 min prior to dosing in Treatment Group B. A washout period of at least 5 days were permitted between treatments.

Twenty-four (22 Caucasian, 1 Black, and 1 American Indian) subjects enrolled; 22 completed the study. The mean age was 30.4 yrs (range 20-39) and mean weight was 71.1 kg (range 53.0-87.1 kg). The sponsor did not include 6, 1, 6, and 2 subjects in Treatment Groups A, B, C, and D, respectively, in the statistical analysis of AUC_{0-inf} due to difficulties in calculating K_{el}. Each subject received the following 4 treatments:

- Treatment A: 2 x 100 mg Formulation II avanafil tablets, fasted
- Treatment B: 2 x 100 mg Formulation II avanafil tablets, fed
- Treatment C: 2 x 100 mg Formulation I avanafil tablets, fasted
- Treatment D: 1 x 50 mg Formulation II avanafil tablets, fasted

Two avanafil immediate-release formulations were developed and used during the clinical development program. Formulation I and Formulation II contained the same excipients (b) (4). The weight ratio was (b) (4) of active:excipients for Formulation I and was available in 12.5, 25, 50, and 100 mg strengths. The weight ratio was approximately (b) (4) of active:excipients for Formulation II and was available in 50, 100, and 200 mg strengths. Formulation I was used in 4 early Phase I and 3 Phase II studies. Formulation II was used 13 Phase I and 3 Phase III studies, and is the to-be-marketed formulation.

Pharmacokinetic Sampling: Blood samples for plasma avanafil and its metabolites (M4 and M16) concentrations were taken at 0 (30 min pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 8, 12, 18 and 24 hrs post-dose for each treatment period.

Composition of Avanafil Tablets Formulation I

Components	Composition (mg / tablet)				% Composition
	12.5 mg	25 mg	50 mg	100 mg	
Avanafil API	12.5	25.0	50.0	100.0	(b) (4)
Mannitol	(b) (4)				(b) (4)
Fumaric acid	(b) (4)				(b) (4)
Hydroxypropylcellulose	(b) (4)				(b) (4)
Low substituted hydroxypropylcellulose	(b) (4)				(b) (4)
(b) (4) calcium carbonate	(b) (4)				(b) (4)
Magnesium stearate	(b) (4)				(b) (4)
Total mass (mg / tablet)	(b) (4)				(b) (4)

Composition of Avanafil Tablets Formulation II

Component	Reference to Quality Standard	Function	50 mg Tablets		100 mg Tablets		200 mg Tablets	
			mg	%	mg	%	mg	%
Avanafil	In-house Standard	Active Ingredient	(b) (4)					
Mannitol	USP	(b) (4)	(b) (4)					
Fumaric Acid	NF	(b) (4)	(b) (4)					
Hydroxypropylcellulose	NF	(b) (4)	(b) (4)					
Low substituted Hydroxypropylcellulose	NF	(b) (4)	(b) (4)					
(b) (4) Calcium Carbonate	USP	(b) (4)	(b) (4)					
Magnesium Stearate	NF	(b) (4)	(b) (4)					
Yellow Ferric Oxide	NF	(b) (4)	(b) (4)					
Total Mass (mg/tablet)	--	(b) (4)	(b) (4)					

Table 3. Summary of Avanafil Formulations Used in Clinical Studies

Study ID	Type of Study	Phase	Avanafil Tablet Strength	Avanafil Doses
Formulation I				
HP-01	PK, food effect, tolerability	1	12.5, 50 , 100 mg	12.5, 25, 50, 100, 200, 400, 600 and 800 mg
TA-02	PK, safety single, multi dose	1	50, 100 mg	50, 100 and 200 mg QD
TA-04	Drug-drug interaction (nitrate)	1	100 mg	200 mg
TA-07	PK, BID dosing	1	100 mg	200 mg BID
TA-01	Visual stimulation	2	50, 100 mg	50, 100 and 200 mg
TA-03	Home administration	2	100 mg	200 mg
TA-05	Safety, efficacy	2	12.5, 50, 100 mg	50, 100, 200 and 300 mg
Formulation II				
TA-011	Drug-drug interaction (ritonavir, erythromycin, ketoconazole)	1	50, 100 mg	50 or 200 mg
TA-012	Drug-disease interaction (hepatic)	1	200 mg	200 mg
TA-013	Drug-disease interaction (renal)	1	200 mg	200 mg
TA-014	Elderly vs. young PK, semen PK	1	200 mg	200 mg
TA-015	Drug-drug interaction (alcohol)	1	200 mg	200 mg
TA-016	Drug-drug interaction (warfarin)	1	200 mg	200 mg
TA-017	Drug-drug interaction (alpha blockers)	1	200 mg	200 mg
TA-018	Drug-drug interaction (omeprazole, desipramine, and rosiglitazone)	1	200 mg	200 mg
TA-019	Drug-drug interaction (enalapril, amlodipine)	1	200 mg	200 mg
TA-020	Food effect, bioequivalence, dose proportionality	1	50, 100 mg (Formulation II) 100 mg (Formulation I)	50 or 200 mg
TA-021	Sperm function	1	200 mg	200 mg
TA-140	TQT	1	100 mg	100 and 800 mg
TA-301	Safety, efficacy in generalized ED	3	50 mg	50, 100, 200 mg
TA-302	Safety, efficacy in diabetics with ED	3	100 mg	100 and 200 mg
TA-314	Long term follow up (rollover from TA-301 and TA-302)	3	50, 100, 200 mg	50, 100 and 200 mg
TA-022	Dose equivalence	1	50, 100, 200 mg	200 mg

TA-022 is a Phase I Study conducted to evaluate the dose equivalence between 4 x 50, 2 x 100, and 1 x 200 mg strengths. The study report was submitted after filing of this NDA.

Results: In this four-way crossover study, the sponsor evaluated the effect of food on Formulation II (to-be-marketed formulation), relative bioavailability of Formulation I vs Formulation II, and dose proportionality of Formulation II. The sponsor selected the 200 mg dose to evaluate food effect and relative bioavailability of two formulations because it was the highest dose planned for the Phase III study and was well tolerated in the Phase I and II studies.

The following figure is the geometric mean plasma avanafil concentration versus time profile following the four different treatment regimens (sponsor's figure 14.4.1.2).

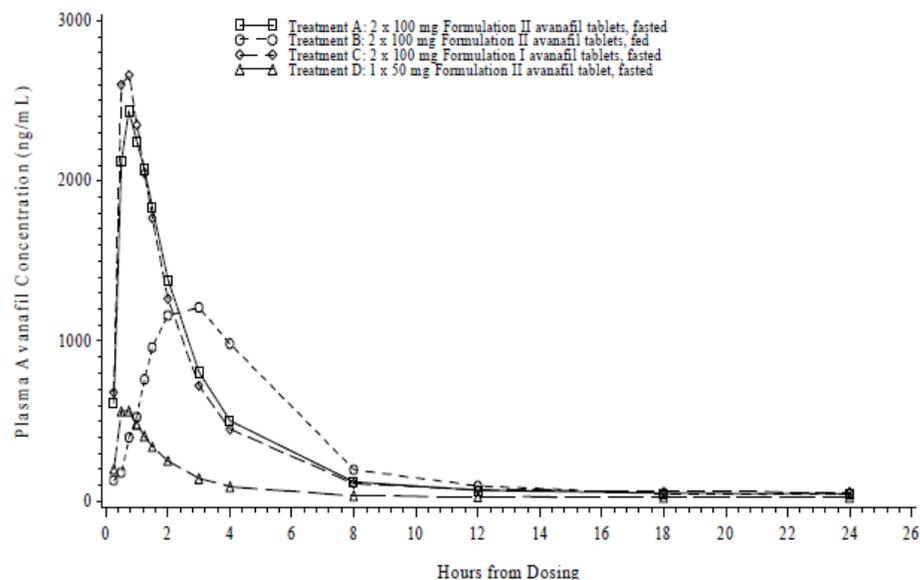
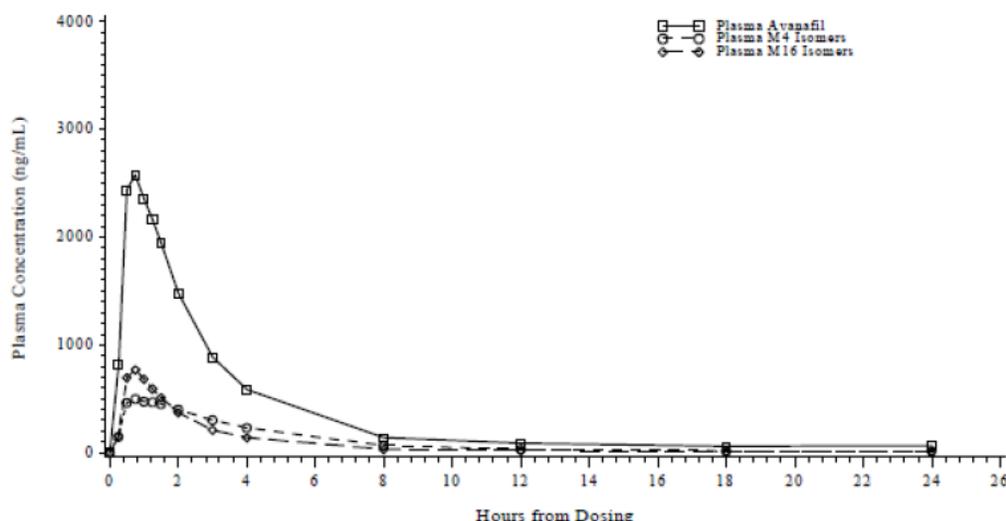


Table of the arithmetic and geometric mean PK parameters of avanafil (sponsor's table 2)

PK Parameters	Treatment A		Treatment B		Treatment C		Treatment D	
	Mean ± SD (N)	Geom. Mean (CV%)	Mean ± SD (N)	Geom. Mean (CV%)	Mean ± SD (N)	Geom. Mean (CV%)	Mean ± SD (N)	Geom. Mean (CV%)
C_{max} (ng/mL) ^a	2920 ± 911 (23)	2780 (34.3)	1760 ± 526 (23)	1690 (32.0)	3080 ± 1040 (23)	2930 (31.3)	672 ± 231 (24)	635 (36.1)
AUC_{0-t} (ng*hr/mL) ^a	8060 ± 2630 (23)	7660 (34.2)	8070 ± 2560 (23)	7690 (32.7)	7790 ± 2370 (23)	7460 (31.1)	1510 ± 636 (24)	1400 (40.2)
AUC_{0-inf} (ng*hr/mL) ^a	8490 ± 3060 (17)	7960 (39.0)	8360 ± 2830 (22)	7920 (34.4)	8140 ± 2820 (17)	7700 (35.5)	1620 ± 681 (22)	1510 (39.1)
%AUC _{extr} (%)	3.28 ± 1.94 (17)	.	3.22 ± 1.95 (22)	.	3.19 ± 2.09 (17)	.	8.18 ± 3.49 (22)	.
t_{max} (hr) ^b	0.75 (0.47, 2.0) (23)	.	2.0 (1.2, 4.0) (23)	.	0.50 (0.50, 1.3) (23)	.	0.50 (0.50, 2.0) (24)	.
$t_{1/2}$ (hr) ^c	5.1 ± 2.9 (17)	.	4.5 ± 1.9 (22)	.	4.7 ± 2.9 (17)	.	2.8 ± 1.7 (22)	.
k_{el} (1/hr)	0.196 ± 0.116 (17)	.	0.185 ± 0.0850 (22)	.	0.212 ± 0.118 (17)	.	0.347 ± 0.192 (22)	.

Treatment A = a single oral dose of two 100 mg avanafil tablets (Formulation II), fasted
 Treatment B = a single oral dose of two 100 mg avanafil tablets (Formulation II), fed
 Treatment C = a single oral dose of two 100 mg avanafil tablets (Formulation I), fasted
 Treatment D = a single oral dose of one 50 mg avanafil tablet (Formulation II), fasted

The following figure is the arithmetic mean plasma avanafil, M4, and M16 concentration vs. time following a single dose of 200 mg avanafil, Formulation II, fasted (sponsor's figure 14.4.4.2)



Effect of Food: To evaluate the effect of food on avanafil PK, subjects were given 200 mg avanafil (2 x 100 mg) under fed (Treatment B) and fasted (Treatment A) conditions. The arithmetic mean (SD) for C_{max} was 1760 (526) and 2920 (911) ng/mL under fed and fasted conditions, respectively. Food reduced the mean C_{max} by approximately 40%. The arithmetic mean (SD) for AUC_{0-t} was 8070 (2560) and 8060 (2630) ng*hr/mL under fed and fasted conditions, respectively. The arithmetic mean (SD) for AUC_{0-inf} was 8360 (2380) and 8490 (3060) ng*hr/mL under fed and fasted conditions, respectively. Food has essentially no effect on the extent of avanafil absorption as both AUC_{0-t} and AUC_{0-inf} remained relatively unchanged.

The following table summarizes the statistical comparison of geometric least squares means of avanafil PK following 2x100 mg tablets Formulation II, fed (Treatment B) versus 2x100 mg tablet Formulation II, fasted (Treatment A) (sponsor's table 3)

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-t} (ng*hr/mL)	7720	23	7660	23	(92.29, 109.95)	100.74
AUC _{0-inf} (ng*hr/mL)	7990	22	8310	17	(88.86, 104.14)	96.20

Relative Bioavailability of Formulations II vs Formulation I: To evaluate the relative bioavailability of Formulation II (the Phase III clinical and to-be-marketed formulation) versus Formulation I (an early development formulation), subjects were given 2 x 100 mg under fasted conditions. The arithmetic mean (SD) for C_{max} was 2920 (911) and 3080 (1040) ng/mL for Formulation II and I, respectively. The arithmetic mean (SD) for AUC_{0-t} was 8060 (2630) and 7790 (2370) ng*hr/mL for Formulation II and I, respectively. The arithmetic mean (SD) for AUC_{0-inf} was 8490 (3060) and 8140 (2820) ng*hr/mL for Formulation II and I, respectively. Based on the above data and statistical comparisons presented in the following table, formulation changes (b) (4)

did not change the rate and extent of avanafil absorption).

The following table summarizes the statistical comparison of geometric least squares means of avanafil PK following 2x100 mg tablets Formulation II, fasted (Treatment A) versus 2x100 mg tablet Formulation I, fasted (sponsor's table 4)

Pharmacokinetic Parameters	Treatment A ^a	N	Treatment C ^a	N	90% CI	% Mean Ratio
C _{max} (ng/mL)	2760	23	2920	23	(81.44, 109.65)	94.50
AUC _{0-t} (ng*hr/mL)	7660	23	7450	23	(94.24, 112.27)	102.86
AUC _{0-inf} (ng*hr/mL)	8310	17	7800	17	(97.78, 116.13)	106.56

Dose Proportionality: To evaluate the dose proportionality of Formulation II avanafil tablets, subjects were given 1 x 50 mg (Treatment D) and 2 x 100 mg (Treatment A) tablets under fasted conditions. The arithmetic mean (SD) for C_{max} was 672 (231) and 2920 (911) ng/mL following administration of 1 x 50 mg and 2 x 100 mg, respectively. The arithmetic mean (SD) for AUC_{0-t} was 1510 (636) and 8060 (2630) ng*hr/mL following administration of 1 x 50 mg and 2 x 100 mg, respectively. The arithmetic mean (SD) for AUC_{0-inf} was 1620 (681) and 8490 (3060) ng*hr/mL following administration of 1 x 50 mg and 2 x 100 mg, respectively. Based on the arithmetic mean values and the mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf}, it appears as though there was a greater increase in the rate and extent of avanafil exposure as the dose increased. It is important to note that only two doses were evaluated in this study and there was significant variability in the data (>30%).

The following table summarizes the statistical comparison of geometric least squares means of dose-normalized avanafil PK following 1 x 50 mg tablets Formulation II, fasted (Treatment D) versus 2 x 100 mg tablets Formulation II, fasted (Treatment A) (sponsor's table 5)

Pharmacokinetic Parameters	Treatment D ^a	N	Treatment A ^a	N	90% CI	% Mean Ratio
C _{max} (ng/mL/200mg)	2540	24	2760	23	(78.26, 107.84)	91.87
AUC _{0-t} (ng*hr/mL/200mg)	5600	24	7620	23	(66.00, 81.92)	73.53
AUC _{0-inf} (ng*hr/mL/200mg)	6080	22	8010	17	(69.58, 82.85)	75.92

Table 14.3.1.1. Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting Events (% of Subjects Dosed)

Adverse Event*	Treatment				Overall
	A	B	C	D	
Number of Subjects Dosed	23 (100%)	23 (100%)	23 (100%)	24 (100%)	24 (100%)
Number of Subjects With Adverse Events	6 (26%)	3 (13%)	8 (35%)	2 (8%)	14 (58%)
Number of Subjects Without Adverse Events	17 (74%)	20 (87%)	15 (65%)	22 (92%)	10 (42%)
Eye disorders					
Ocular hyperaemia	0 (0%)	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Gastrointestinal disorders					
Constipation	0 (0%)	0 (0%)	1 (4%)	0 (0%)	1 (4%)
Nausea	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
General disorders and administration site conditions					
Fatigue	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)
Nervous system disorders					
Dizziness	5 (22%)	3 (13%)	7 (30%)	1 (4%)	11 (46%)
Headache	2 (9%)	1 (4%)	3 (13%)	1 (4%)	4 (17%)
Somnolence	3 (13%)	1 (4%)	5 (22%)	0 (0%)	6 (25%)
Respiratory, thoracic and mediastinal disorders					
Epistaxis	1 (4%)	2 (9%)	0 (0%)	0 (0%)	3 (13%)
Nasal congestion	1 (4%)	0 (0%)	1 (4%)	0 (0%)	2 (8%)

Table 14.3.1.2. Treatment-Emergent Adverse Event Frequency by Treatment - Number of Adverse Events (% of Total Adverse Events)

Adverse Event*	Treatment				Overall
	A	B	C	D	
Number of Adverse Events	8 (100%)	5 (100%)	10 (100%)	2 (100%)	25 (100%)
Eye disorders	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (4%)
Ocular hyperaemia	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (4%)
Gastrointestinal disorders	1 (13%)	0 (0%)	1 (10%)	0 (0%)	2 (8%)
Constipation	0 (0%)	0 (0%)	1 (10%)	0 (0%)	1 (4%)
Nausea	1 (13%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
General disorders and administration site conditions	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (4%)
Fatigue	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (4%)
Nervous system disorders	6 (75%)	4 (80%)	8 (80%)	1 (50%)	19 (76%)
Dizziness	2 (25%)	1 (20%)	3 (30%)	1 (50%)	7 (28%)
Headache	3 (38%)	1 (20%)	5 (50%)	0 (0%)	9 (36%)
Somnolence	1 (13%)	2 (40%)	0 (0%)	0 (0%)	3 (12%)
Respiratory, thoracic and mediastinal disorders	1 (13%)	0 (0%)	1 (10%)	0 (0%)	2 (8%)
Epistaxis	1 (13%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)
Nasal congestion	0 (0%)	0 (0%)	1 (10%)	0 (0%)	1 (4%)

Study TA-022

Title: A Phase 1, Single-Centre, Open-Label, Randomized, Three-Period Crossover Study to Determine the Dose Equivalence of Three Avanafil Tablet Dose Strengths in Healthy Male Subjects.

Objectives: The objective of this study was to assess the dose equivalence of three dose strengths of avanafil tablets (Formulation II) in healthy male subjects.

Methods: This was a Phase I, single-center, open-label, randomized, three-period crossover study in healthy male subjects given the to-be-marketed formulation (Formulation II). Subjects reported to the study site before each treatment and remained at the study site until the 24-hr PK sample had been drawn. A single oral dose of avanafil tablets was administered with 240 mL water. Subjects fasted at least 10 hrs prior to treatment and at least 4 hrs following dosing. A washout period of at least 5 days were permitted between treatments. Standard meals were provided to all subjects at approximately 4 and 9 hrs after dosing, and an evening snack was provided approximately 12-13 hrs after dosing.

Twenty-three (21 White, 1 Black, and 1 American Indian) subjects enrolled; 22 completed the study. The mean age was 32.3 yrs (range 20-45) and mean weight was 78.1 kg (range 50.3-98.4 kg). The sponsor did not include 5, 5, and 4 subjects in Treatment Groups A, B, and C, respectively, in the statistical analysis of AUC_{0-inf} due to difficulties in calculating K_{el}. Each subject received the following 3 treatments:

Treatment A: 4 x 50 mg avanafil tablets

Treatment B: 2 x 100 mg avanafil tablets

Treatment C: 1 x 200 mg avanafil tablets

Pharmacokinetic Sampling: Blood samples for plasma avanafil concentrations were taken at 0 (30 min pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hrs post-dose for each treatment period.

Results: In this study, the sponsor evaluated the dose proportionality of 4 x 50 mg, 2 x 100 mg, and 1 x 200 mg avanafil tablets.

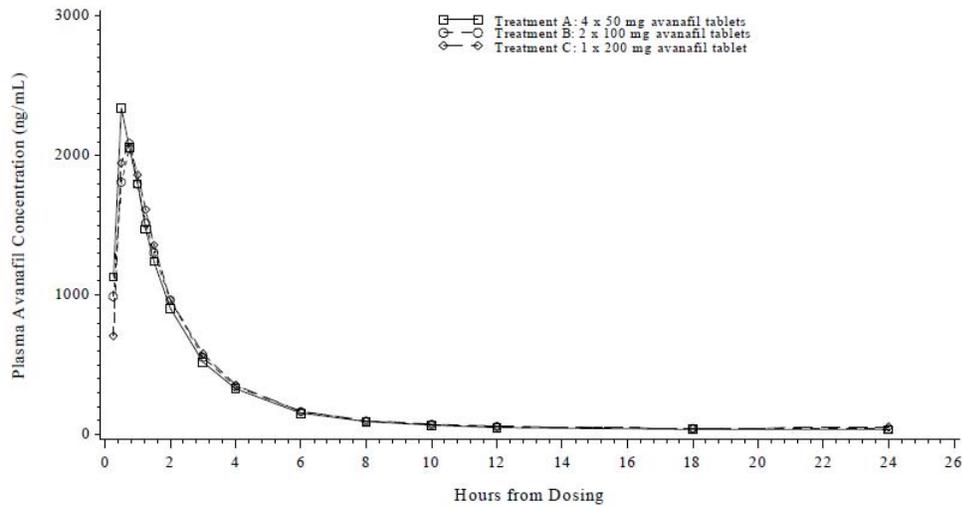
The arithmetic mean \pm SD for C_{max} in subjects given a total dose of 200 mg avanafil as either 4x50 mg (Treatment A), 2x100 mg (Treatment B) and 1x200 mg (Treatment C) was similar at 2660 ± 1150 , 2520 ± 971 , and 2620 ± 1150 ng/mL, respectively.

The arithmetic mean \pm SD for AUC_{0-t} in subjects given a total dose of 200 mg avanafil as either 4x50 mg (Treatment A), 2x100 mg (Treatment B) and 1x200 mg (Treatment C) was similar at 6000 ± 2750 , 6340 ± 3430 , and 6240 ± 2800 ng*hr/mL, respectively.

The arithmetic mean \pm SD for AUC_{0-inf} in subjects given a total dose of 200 mg avanafil as either 4x50 mg (Treatment A), 2x100 mg (Treatment B) and 1x200 mg (Treatment C) was similar at 6510 ± 3360 , 6990 ± 4020 , and 7000 ± 3050 ng*hr/mL, respectively.

Based on statistical comparisons of the geometric mean for C_{max}, AUC_{0-t}, and AUC_{0-inf}, the sponsor demonstrated dose proportionality between 50 mg, 100 mg, and 200 mg with Formulation II (to-be-marketed formulation).

The following figure is the geometric mean plasma avanafil concentration versus time profile (sponsor's figure 2).



The following table summarizes the mean (SD) PK parameters of avanafil after administration of 200 mg avanafil given as 4x100 mg (Treatment A), 2x100 mg (Treatment B), and 1x200 mg tablets (Treatment C) (sponsor's table 2)

PK Parameters	Treatment A		Treatment B		Treatment C	
	Mean ± SD (N)	Geom. Mean (Geom. CV%) (N)	Mean ± SD (N)	Geom. Mean (Geom. CV%) (N)	Mean ± SD (N)	Geom. Mean (Geom. CV%) (N)
C_{max} (ng/mL) ^a	2660 ± 1150 (22)	2420 (48.8) (22)	2520 ± 971 (23)	2300 (50.1) (23)	2620 ± 1150 (22)	2320 (61.8) (22)
AUC_{0-t} (ng*hr/mL) ^a	6000 ± 2750 (22)	5500 (45.2) (22)	6340 ± 3430 (23)	5670 (50.3) (23)	6240 ± 2800 (22)	5700 (46.7) (22)
AUC_{0-inf} (ng*hr/mL) ^a	6510 ± 3360 (17)	5850 (51.1) (17)	6990 ± 4020 (18)	6160 (54.9) (18)	7000 ± 3050 (18)	6450 (43.6) (18)
t_{max} (hr) ^b	0.50 (0.33, 0.76) (22)	.	0.51 (0.50, 1.5) (23)	.	0.75 (0.25, 2.0) (22)	.
$t_{1/2}$ (hr) ^c	6.4 ± 3.2 (17)	.	6.0 ± 2.9 (18)	.	5.0 ± 2.6 (18)	.
k_{el} (1/hr) ^a	0.158 ± 0.118 (17)	.	0.155 ± 0.103 (18)	.	0.180 ± 0.101 (18)	.

Treatment A = 4 x 50 mg avanafil tablets
 Treatment B = 2 x 100 mg avanafil tablets
 Treatment C = 1 x 200 mg avanafil tablet

^a C_{max} , AUC_{0-t} , AUC_{0-inf} , and k_{el} values are presented with 3 significant figures.
^b t_{max} is presented as median (minimum, maximum) and is presented with 2 significant figures.
^c $t_{1/2}$ is presented with 2 significant figures.
 . = Value not calculated.
 Geom. Mean = geometric mean; Geom. CV% = geometric CV%; PK= pharmacokinetic; SD = standard deviation
 Source: Tables 14.2.4 through 14.2.6

Statistical comparison of C_{max} , AUC_{0-t} , and AUC_{0-inf} showed that the rate and extent of exposure of avanafil were equivalent following a total dose of 200 mg given as either one 200 mg or four 50 mg tablets. The 90% CIs of the LSM ratios fell within 80% to 125% and the point estimate is nearly 100%; thereby demonstrating dose proportionality between 50 and 200 mg.

The following table is a statistical comparison of plasma avanafil PK parameters following Treatment C (1x200 mg) versus Treatment A (4x50 mg) (sponsor's table 3)

Pharmacokinetic Parameters	Geometric LS Mean Treatment C	N	Geometric LS Mean Treatment A	N	90% CI	% Mean Ratio
C _{max} (ng/mL) ^a	2380	22	2410	22	(83.60, 116.67)	98.76
AUC _{0-t} (ng*hr/mL) ^a	5720	22	5560	22	(93.31, 113.79)	103.04
AUC _{0-inf} (ng*hr/mL) ^a	6460	18	6350	17	(93.57, 110.71)	101.78

Statistical comparison of C_{max}, AUC_{0-t}, and AUC_{0-inf} showed that the rate and extent of exposure of avanafil were equivalent following a total dose of 200 mg given as either one 200 mg or two 100 mg tablets. The 90% CIs of the LSM ratios fell within 80% to 125% and the point estimate is nearly 100%; thereby demonstrating dose proportionality between 100 and 200 mg.

The following table is a statistical comparison of plasma avanafil PK parameters following Treatment C (1x200 mg) versus Treatment B (2x100 mg) (sponsor's table 4)

Pharmacokinetic Parameters	Geometric LS Mean Treatment C	N	Geometric LS Mean Treatment B	N	90% CI	% Mean Ratio
C _{max} (ng/mL) ^a	2380	22	2330	23	(86.66, 120.27)	102.09
AUC _{0-t} (ng*hr/mL) ^a	5720	22	5720	23	(90.76, 110.29)	100.05
AUC _{0-inf} (ng*hr/mL) ^a	6460	18	6200	18	(96.09, 113.03)	104.21

Safety

There were no SAEs reported in this study, and the PI did not discontinue any subjects due to an AE. A total of 32 TEAEs were reported by 12 (52%) subjects following avanafil, with 5 (23%) subjects following Treatment A, 6 (26%) subjects following Treatment B, and 7 (30%) subjects following Treatment C. Of the 32 TEAEs, all were mild in severity with the exception of 1 moderate headache episode. The PI considered 28 TEAEs to be related to the study drug and 4 not related. Table 6 presents the incidence of TEAEs.

Table 6 Incidence of Treatment-Emergent Adverse Events

Treatment Group	Number of Subjects Reporting AEs (%)	Number of AE Episodes Reported
A 4 x 50 mg avanafil tablets	5 (23%)	8
B 2 x 100 mg avanafil tablets	6 (26%)	12
C 1 x 200 mg avanafil tablet	7 (30%)	12

Source: Tables 14.3.1.1 and 14.3.1.2

Table 14.3.1.1 Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting Events

Adverse Event*	Treatment			Total
	A	B	C	
Number of Subjects Dosed	22 (100%)	23 (100%)	23 (100%)	23 (100%)
Number of Subjects With Adverse Events	5 (23%)	6 (26%)	7 (30%)	12 (52%)
Number of Subjects Without Adverse Events	17 (77%)	17 (74%)	16 (70%)	11 (48%)
Eye disorders	0 (0%)	1 (4%)	0 (0%)	1 (4%)
Vision blurred	0 (0%)	1 (4%)	0 (0%)	1 (4%)
Gastrointestinal disorders	1 (5%)	2 (9%)	2 (9%)	5 (22%)
Dry mouth	0 (0%)	1 (4%)	0 (0%)	1 (4%)
Hypoaesthesia oral	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Nausea	1 (5%)	1 (4%)	0 (0%)	2 (9%)
Vomiting	0 (0%)	0 (0%)	1 (4%)	1 (4%)
General disorders and administration site conditions	1 (5%)	2 (9%)	0 (0%)	2 (9%)
Feeling hot	1 (5%)	2 (9%)	0 (0%)	2 (9%)
Musculoskeletal and connective tissue disorders	0 (0%)	2 (9%)	0 (0%)	2 (9%)
Neck pain	0 (0%)	1 (4%)	0 (0%)	1 (4%)
Pain in extremity	0 (0%)	1 (4%)	0 (0%)	1 (4%)
Nervous system disorders	4 (18%)	3 (13%)	6 (26%)	10 (43%)
Dizziness	1 (5%)	1 (4%)	2 (9%)	4 (17%)
Headache	4 (18%)	1 (4%)	5 (22%)	7 (30%)
Sinus headache	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Somnolence	0 (0%)	1 (4%)	1 (4%)	2 (9%)
Psychiatric disorders	1 (5%)	0 (0%)	0 (0%)	1 (4%)
Disturbance in sexual arousal	1 (5%)	0 (0%)	0 (0%)	1 (4%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Nasal congestion	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Vascular disorders	0 (0%)	2 (9%)	0 (0%)	2 (9%)
Flushing	0 (0%)	2 (9%)	0 (0%)	2 (9%)

Table 14.3.1.2 Treatment-Emergent Adverse Event Frequency by Treatment - Number of Adverse Events

Adverse Event*	Treatment			Total
	A	B	C	
Number of Adverse Events	8 (100%)	12 (100%)	12 (100%)	32 (100%)
Eye disorders	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Vision blurred	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Gastrointestinal disorders	1 (13%)	2 (17%)	2 (17%)	5 (16%)
Dry mouth	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Hypoaesthesia oral	0 (0%)	0 (0%)	1 (8%)	1 (3%)
Nausea	1 (13%)	1 (8%)	0 (0%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	1 (8%)	1 (3%)
General disorders and administration site conditions	1 (13%)	2 (17%)	0 (0%)	3 (9%)
Feeling hot	1 (13%)	2 (17%)	0 (0%)	3 (9%)
Musculoskeletal and connective tissue disorders	0 (0%)	2 (17%)	0 (0%)	2 (6%)
Neck pain	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Pain in extremity	0 (0%)	1 (8%)	0 (0%)	1 (3%)
Nervous system disorders	5 (63%)	3 (25%)	9 (75%)	17 (53%)
Dizziness	1 (13%)	1 (8%)	2 (17%)	4 (13%)
Headache	4 (50%)	1 (8%)	5 (42%)	10 (31%)
Sinus headache	0 (0%)	0 (0%)	1 (8%)	1 (3%)
Somnolence	0 (0%)	1 (8%)	1 (8%)	2 (6%)
Psychiatric disorders	1 (13%)	0 (0%)	0 (0%)	1 (3%)
Disturbance in sexual arousal	1 (13%)	0 (0%)	0 (0%)	1 (3%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	0 (0%)	1 (8%)	1 (3%)
Nasal congestion	0 (0%)	0 (0%)	1 (8%)	1 (3%)
Vascular disorders	0 (0%)	2 (17%)	0 (0%)	2 (6%)
Flushing	0 (0%)	2 (17%)	0 (0%)	2 (6%)

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/s/

LAI M LEE
03/09/2012

HYUNJIN KIM
03/09/2012

EDWARD D BASHAW
03/09/2012

As noted in the QBR portion of this NDA review, the calculation of half-life was affected by the sampling program used by the sponsor. In study TA-02 the terminal half-life was reported by the sponsor as ~1.2hr, while in study TA-07 the terminal half-life was ~8.4hrs. Avanafil undergoes a biphasic elimination, and thus the calculation of elimination half-life can be affected by sub-optimal sampling schemes. In the QBR portion of this review the Review Team has discussed this issue in more detail and has determined that the "hybrid" elimination rate is ~5hrs and represents a melding of the amount and relative contributions toward AUC of the resulting elimination rates. I concur with this approach and acknowledge that the data presented in these study reports reflects the Sponsors calculation of half-life and not the FDA's. The reader is referred to the QBR portion of the review for more details on this issue.

REVIEW OF CLINICAL PHARMACOLOGY

NDA 202276 sdn1-13; sdn16	Submission Date(s)	6/29/11; 8/10/11; 9/15/11; 9/21/11; 9/28/11; 9/30/11; 10/5/11; 10/20/11; 10/27/11; 11/3/11; 12/21/11
Brand Name	Pending review	
Generic Name	Avanafil	
Reviewer	LaiMing Lee, Ph.D.	
Acting Team Leader	Hyunjin Kim, Pharm.D., M.S.	
OCP Division	Division of Clinical Pharmacology 3	
OND Division	Division of Reproductive and Urologic Products (DRUP)	
Sponsor	Vivus, Inc.	
Relevant IND	051235	
Submission Type; Code	Original; 1S	
Formulation; Strengths; Regimen	Immediate Release Oral tablet; 50 mg, 100 mg, 200 mg; 100 mg approximately 30 min before sexual activity on an as needed basis, no more than once a day	
Proposed Indication	Treatment of erectile dysfunction	

A Required OCP Inter-Division Level briefing was held on March 8, 2012 and was attended by Shiew-Mei Huang, Edward D. Bashaw, Hyunjin Kim, Myong-Jin Kim, Audrey Gassman, Mark Hirsch, Mehul Mehta, David Lee, Chongwoo Yu, JiHong Shon, Li Li, Satjit Brar, Sayed Al Habet, Arun Agrawal, Xinning Yang, Michiyo Yamazaki, Dongyang Liu, Li Li (contractor), Christian Grimstein, and LaiMing Lee.

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1 Executive Summary

Vivus, Inc. is seeking approval of avanafil (also referred to as TA-1790) for the treatment of erectile dysfunction (ED). Avanafil is a phosphodiesterase 5 (PDE5) inhibitor, which increases penile blood flow and erection in response to sexual stimulation.

Avanafil is a solid, oval, pale yellow immediate-release (IR) oral tablet and is intended to be used on an as needed basis. The proposed dosing regimen is one 100 mg tablet 30 minutes prior to initiation of sexual activity and no more than once daily. The dose may

be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability. The Sponsor is seeking approval for 50 mg, 100 mg, and 200 mg tablets. To support approval of this NDA, the sponsor conducted 18 Phase I, 3 Phase II, and 2 Phase III clinical studies.

The distinctive difference between avanafil and the other PDE5 inhibitors is when the drug can be taken prior to the sexual activity. Cialis® (tadalafil), Levitra® (vardenafil), Staxyn® (vardenafil) and Viagra® (sildenafil) are currently approved PDE5 inhibitors under NDA 021368 (November 21, 2003), NDA 021400 (August 19, 2003), NDA 200179 (June 17, 2010) and NDA 020895 (March 27, 1998), respectively. The dosing instruction for Viagra and Levitra/Staxyn specifies that the drug should be taken approximately 60 min (1 hr) before sexual activity. For Cialis, the dosing instruction indicates that the drug be taken as needed prior to sexual activity; no time interval between dose administration and the time of sexual activity is specified.

1.1 Recommendations

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

1.2 Post-Marketing Commitment/Post-Marketing Requirement

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

During the clinical development program, there were two avanafil immediate-release formulations used – Formulation I and Formulation II (b) (4)

(b) (4)
Formulation I tablets were (b) (4)
available in 12.5, 25, 50, and 100 mg strengths. Formulation II tablets are oval, light-yellow coated tablet and are available in 50, 100, and 200 mg strengths, (b) (4)

Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and is the proposed to-be-marketed formulation. However, the Phase 3 studies were conducted using multiple units of 50 or 100 mg tablets. The three proposed dosage strengths of Formulation II are produced (b) (4).

Single dose pharmacokinetic (PK) for Formulation I was characterized in healthy male subjects. AUC_{0-inf} ranged from 381 to 24457 ng*hr/mL after a single dose of 12.5 to 800 mg and is dose proportional from 12.5 to 600 ng*hr/mL. C_{max} ranged from 166 to 7249 µg/mL after a single dose of 12.5 to 800 mg and is dose proportional from 12.5 to 600 mg. The median T_{max} ranged from 0.63 to 1.25 hr.

Multiple dose PK for Formulation I was evaluated in healthy male subjects with 50 mg, 100 mg, and 200 mg doses. In healthy male subjects given 14 daily doses of avanafil (50, 100 or 200 mg) for 14 days, mean maximum avanafil concentrations (t_{max}) were reached

between 0.6 and 0.7 hr. At the proposed dose of 100 mg, AUC_{0-t} and C_{max} is 1.6 µg*hr/mL and 0.9 µg/mL, respectively. Accumulation (R) is 1.3, 1.2, and 1.1 for 50, 100, and 200 mg avanafil, respectively.

Avanafil showed biphasic elimination. The sponsor reports a half-life of approximately 1.2-1.5 hrs following single and multiple doses of avanafil in Study TA-02. This half-life was based mainly on the first elimination phase as the second phase was not well characterized. On the other hand, the sponsor reports a half-life of approximately 5 hrs (range 4.5 to 6.4 hrs) following a single 50 to 200 mg avanafil in the majority of other clinical pharmacology studies. This half-life was mostly based on second elimination phase. Therefore, the terminal elimination half-life is approximately 5 hrs.

Avanafil was approximately 99% bound to albumin, 43% to γ-globulin, and 66% to α₁-acid glycoprotein.

C_{max} was reached 0.5 to 0.75 hrs in healthy young men given a single 200 mg dose of avanafil, Formulation II.

The following table is a summary of the PK parameters for avanafil following a single dose 200 mg avanafil, Formulation II, fasted in healthy young male subjects (data from Study TA-022).

PK parameter*	Avanafil 200 mg (N=22)
AUC _{0-inf} (ng*hr/mL)	7000 (3050)
AUC _{0-t} (ng*hr/mL)	6240 (2800)
C _{max} (ng/mL)	2620 (61.8)
t _{max} (hr) [†]	0.75 (0.25, 2.0)
t _{1/2} (hr)	5.0 (2.6)
K _{el} (1/hr)	0.18 (0.10)

*arithmetic mean (SD)

[†]t_{max}: median and range

Dose-Response Relationship

Efficacy Endpoints

The three co-primary efficacy endpoints for the two 12-week pivotal Phase III studies are (1) change from baseline in the percentage of sexual attempts resulting in successful intercourse [Sexual Encounter Profile question 3 (SEP3)]; (2) change from baseline in the percentage of sexual attempts resulting in successful vaginal penetration (SEP2); and (3) change from baseline in the International Index of Erectile Function (IIEF) erectile function domain score.

Efficacy

In study TA-301, treatment with avanafil at 50 mg, 100 mg, and 200 mg doses leads to statistically significant improvements in SEP3, SEP2, and IIEF erection function domain score compared to placebo. As the dose increased 2-fold from 50 to 100 mg, SEP3, SEP2, and IIEF domain score increased approximately 2-fold. SEP3 was higher by 13.8%, 29.3% and 30.2% following 50 mg, 100 mg and 200 mg avanafil, respectively, compared to placebo. SEP2 was higher by 11.1%, 20.1% and 22.7% following 50 mg,

100 mg and 200 mg avanafil, respectively, compared to placebo. The change from baseline in the IIEF erectile function domain score was 2.6, 5.5 and 6.7 following 50 mg, 100 mg and 200 mg avanafil, respectively, compared to placebo.

In study TA-302, treatment with avanafil at 100 and 200 mg doses leads to statistically significant improvements in SEP3, SEP2, and IIEF erection function domain score, compared to placebo. SEP3 was higher by 15.6% and 16.4% following 100 mg and 200 mg avanafil, respectively, compared to placebo. SEP2 was higher 9.0% and 11.7% following 100 mg and 200 mg avanafil, respectively, compared to placebo. The change from baseline in the IIEF erectile function domain score was 2.9 and 4.1 following 100 mg and 200 mg avanafil, respectively, compared to placebo.

Safety

The most frequently reported drug-related treatment-emergent adverse events (TEAEs) by treatment are as follows:

Placebo: hot flush (0.6%), feeling hot (0.6%), nasal congestion (0.6%), and postnasal drip (0.6%)

Avanafil 50 mg: headache (3.8%), flushing (3.8%), and back pain (1.3%)

Avanafil 100 mg: headache (6.2%), flushing (6.2%), and nasal congestion (2.5%)

Avanafil 200 mg: headache (7.4%), flushing (3.7%), and nasal congestion (1.9%)

Similar to the efficacy outcome, of the three doses evaluated in the Phase III study TA-301, the highest frequency of adverse events occurred at the two highest doses (100 and 200 mg), compared to placebo. It is difficult to distinguish if a difference in frequency of adverse events exists between 100 and 200 mg dose.

Intrinsic and Extrinsic Factors

The sponsor conducted studies to evaluate intrinsic and extrinsic factors that may affect the PK of avanafil. Factors that may affect the PK of avanafil were evaluated in the following studies: renal impairment, hepatic impairment, age effect, food effect, drug interaction with ketoconazole (a strong CYP3A4 inhibitor), drug interaction with ritonavir (a strong CYP3A4 inhibitor), and drug interaction with erythromycin (a moderate CYP3A4 inhibitor).

The sponsor conducted studies to evaluate the effect of avanafil on the PK and/or pharmacodynamic (PD) of other drugs. Clinical studies were conducted to evaluate the PD effects of avanafil and glyceryl trinitrate, avanafil and alcohol, avanafil and alpha-blockers (doxazosin and tamsulosin), and avanafil and antihypertensives (enalapril and amlodipine), and avanafil and warfarin. Clinical studies were conducted to evaluate the effect of avanafil on the PK of omeprazole (a CYP2C19 substrate), rosiglitazone (a CYP2C8 substrate), and desipramine (a CYP2D6 substrate).

Renal impairment on avanafil PK

Mild and moderate renal impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. AUC_{0-inf} decreased by 3.0% and increased by 9.1% in subjects with mild and moderate renal impairment, respectively. C_{max} increased by 2.8% and decreased by 2.8% in subjects with mild and moderate renal impairment, respectively. In the context of inter-subject variability of approximately 30%, the changes in C_{max} and AUC_{0-inf} of approximately 3-9% are not significant. The sponsor did not evaluate the effect of severe and end stage renal impairment on avanafil PK. No dose adjustment in patients with mild and moderate renal impairment is recommended.

Hepatic impairment on avanafil PK

Mild and moderate hepatic impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. AUC_{0-inf} increased by 3.8% and 11.2% in subjects with mild and moderate hepatic impairment, respectively. C_{max} decreased by 2.7% and 51% in subjects with mild and moderate hepatic impairment, respectively. In the context of inter-subject variability of approximately 30%, the change in AUC_{0-inf} of 3.8% and C_{max} of 2.7% in subjects with mild hepatic impairment is not significant. Maximum concentration was significantly reduced in subjects with moderate hepatic impairment. On the other hand, systemic exposure in subjects with moderate impairment increased by 11.2%; therefore, moderate hepatic impairment does not significantly impact the total exposure of avanafil. Clearance increased slightly – 4.0% and 9.0% in subjects with mild and moderate hepatic impairment, compared with subjects with normal hepatic function. The sponsor did not evaluate the effect of severe hepatic impairment on avanafil PK. No dose adjustment in patients with mild and moderate hepatic impairment is recommended.

QT Prolongation

The suprathreshold dose (800 mg) produced avanafil C_{max} values 6.8-fold higher than the mean C_{max} for the starting therapeutic dose (100 mg). The LS mean of $\Delta\Delta\text{QTcF}$ was 9.4 ms and the 90% confidence interval (CI) for $\Delta\Delta\text{QTcF}$ was 7.2 – 11.6 ms with 800 mg avanafil dose. The upper bound of the 90% CI for $\Delta\Delta\text{QTcF}$ exceeded 10 ms (11.6 ms) at one time point for the suprathreshold dose and therefore failed to exclude a 10 ms increase in QT, the regulatory threshold for regulatory concern.

Interaction with strong CYP3A4 inhibitors such as ketoconazole and ritonavir increased C_{max} by 3.1- and 2.4-fold, respectively, while AUC_{0-inf} increased by approximately 13-fold. Renal and hepatic impairment did not significantly increase avanafil concentrations. The therapeutic dose of avanafil or the proposed adjusted avanafil dose co-administered with a strong CYP3A4 inhibitor is not expected to prolong the QT interval greater than 10 ms.

Effect of strong CYP3A4 inhibitors, ketoconazole and ritonavir, on avanafil PK

Ketoconazole 400 mg inhibited avanafil 50 mg metabolism leading to an approximate 13-fold increase in avanafil mean AUC_{0-inf}. C_{max} increased 3.1-fold. T_{max} increased slightly from 0.5 to 1.0 hr.

Ritonavir 300-600 mg inhibited avanafil 50 mg metabolism leading to an approximate 13-fold increase in avanafil mean AUC_{0-inf}. C_{max} increased 2.4-fold. T_{max} increased slightly from 0.5 to 1.5 hrs.

The sponsor reports an increase in avanafil half-life from 1.8 to 8.5 and from 1.4 to 8.8 hrs following administration of ketoconazole and ritonavir, respectively. This increase in half-life is reported by the sponsor due to a low estimation of half-life for avanafil alone. The estimation of half-life was based on the first elimination phase and, in the study with CYP3A4 inhibitors, was likely due to a deficiency in time points between 12 and 24 hrs. With the exception of the CYP3A4 inhibition study TA-011 and SD/MD PK study TA-02, all other clinical pharmacology studies report an elimination half-life of approximately 5 hrs (range 4.5 to 6.4 hrs) following a single 50 to 200 mg avanafil. Therefore, half-life of avanafil is estimated to increase approximately by 3-4 hrs with administration of a strong CYP3A4 inhibitor.

The incidence of headache, postural hypotension, nausea, and fatigue increased significantly in the subjects given a single dose of 400 mg, 600 mg, and 800 mg as shown

in a single dose PK study in healthy male subjects (HP-01). This dose-adverse events relationship was also noted in the pivotal Phase II study (TA-05) in which the incidence of flushing, nausea, and back pain increased 1 to 2-fold as the dose was increased from 200 mg to 300 mg. (b) (4)

Concomitant administration of avanafil and a strong CYP3A4 inhibitor increased avanafil exposure by approximately 13-fold. With linear PK, a 50 mg avanafil dose would be equivalent to approximately 650 mg when given with a strong CYP3A4 inhibitor. The maximum dose evaluated in Phase III studies is 200 mg; it is also the highest recommended dose. Therefore, an adjustment in avanafil dose is needed for patients taking a strong CYP3A4 inhibitor. The dose should be reduced to address the 13-fold increase in AUC. Increasing the dosing interval from 24 to 48 hrs can address the increase in half-life and ensure that 4-5 half-lives have elapsed between doses. Assuming the highest approvable dose will be 200 mg, a dose of approximately 15 mg would account for the 13-fold increase in exposure. Considering the inter-subject variability of approximately 30%, non-life threatening adverse event profile, as needed dosing regimen, and manufacturing of another dose strength, an avanafil dose of “no more than 25 mg once every 48 hrs as needed” is recommended for patients taking avanafil with a strong CYP3A4 inhibitor, although it would achieve approximately 63% higher exposure compared to the exposure from 200 mg avanafil alone.

Effect of moderate CYP3A4 inhibitor, erythromycin, on avanafil PK

Erythromycin 500 mg inhibited avanafil 200 mg metabolism leading to a 3.6-fold increase in avanafil mean AUC_{0-inf}. C_{max} increased 2.0-fold. T_{max} increased slightly from 0.5 to 0.75 hrs.

The sponsor reports an increase in avanafil half-life from 2.4 to 8.1 hrs following administration of erythromycin. This increase in half-life is reported by the sponsor due to a low estimation of half-life for avanafil alone. The estimation of half-life was based on the first elimination phase and, in the study with CYP3A4 inhibitors, was likely due to a deficiency in time points between 12 and 24 hrs. With the exception of the CYP3A4 inhibition study TA-011 and SD/MD PK study TA-02, all other clinical pharmacology studies report an elimination half-life of approximately 5 hrs (range 4.5 to 6.4 hrs) following a single 50 to 200 mg avanafil. Therefore, half-life of avanafil is estimated to increase by approximately 3 hrs with administration of a moderate CYP3A4 inhibitor.

Patients who take a moderate CYP3A4 inhibitor and avanafil are susceptible to higher systemic concentrations of avanafil. In the scenario evaluated, the 200 mg dose would be equivalent to approximately 720 mg. Assuming the highest approvable dose will be 200 mg, a reduced avanafil dose of approximately 56 mg would account for a 3.6-fold increase in exposure in the presence of a moderate CYP3A4 inhibitor. An avanafil dose of “no more than 50 mg once every 24 hrs as needed” is recommended for patients taking avanafil with a moderate CYP3A4 inhibitor.

The sponsor did not evaluate the effect of weak CYP3A4 inhibitors on avanafil PK.

Effect of food on avanafil PK

Compared to the fasted condition, the exposure (AUC_{0-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%). Based on these small changes, no dose adjustment or special dosing instructions in the presence of food is necessary. Additionally, the Phase III study was conducted with no restrictions on food intake.

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-inf} 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 significantly different given the variability observed between subjects.

Effect of avanafil and glyceryl trinitrate on blood pressure and pulse rate

Avanafil and glyceryl trinitrate decreased sitting and standing systolic and diastolic blood pressure to a greater degree than glyceryl trinitrate and placebo avanafil. The mean maximum decrease in standing systolic blood pressure/diastolic blood pressure (SBP/DBP) was 24/22 mmHg. Overall, avanafil lowered blood pressure and increased pulse rate. The blood pressure lowering effect can be significant with repeat dosing, which this study was not designed to evaluate. 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.

Effect of avanafil and alcohol on blood pressure and pulse rate

When comparing avanafil + alcohol and placebo + alcohol, there was no statistically significant effect on the maximum mean supine SBP and systolic area under the effect curve (AUEC_{0-t}). However, despite the lack of statistical difference between the two treatment groups, there was a decrease in the SBP of 3.5 mmHg and systolic AUEC_{0-t} of 12.5 mmHg*hr in subjects given avanafil + alcohol, compared to placebo + alcohol. There were statistically significant changes in the maximum decrease of 4.5 mmHg in DBP and 16.3 mmHg*hr in diastolic AUEC_{0-t}. This trend was also observed with pulse rate - a statistically significant changes in the maximum increase in pulse rate of 9.3 beats per minute (bpm) and pulse rate AUEC_{0-t} of 25.1 bpm*hr. Overall, there was an additive hypotensive effect from avanafil treatment with a decrease SBP/DBP of 3.5/4.5 mmHg.

Effect of avanafil and alpha-blockers (doxazosin and tamsulosin) on blood pressure and pulse rate

Blood pressure decreased and pulse rate increased with the administration of avanafil after subjects were given doxazosin or tamsulosin for 18 days prior to avanafil dosing. The mean maximum supine SBP/DBP decrease was 6.0/3.6 mmHg. The mean maximum increase in pulse rate was 7.2 bpm. The clinical effect appeared to have diminished after several hours with blood pressure and pulse rate returning to baseline.

Effect of avanafil and antihypertensives (enalapril and amlodipine) on blood pressure and pulse rate

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.

Standing SBP/DBP decreased by 1.6/1.4 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 1.2 mmHg and increase in DBP of 1.5 mmHg was observed in subjects co-administered with avanafil and amlodipine, compared to placebo and amlodipine.

Effect of avanafil and warfarin PK/PD

Avanafil had no effect on the PK of a single 25 mg dose of warfarin; the PK parameters of R-warfarin and S-warfarin were similar in both treatment groups. Multiple doses of avanafil had essentially no effect on the PD of a single dose of warfarin as determined by international normalized ratio (INR), prothrombin time (PT), and platelet aggregation; the % mean ratios (subjects administered with warfarin + avanafil/ subjects administered with warfarin+ placebo) of INR, PT, and platelet aggregation were all approximately 100% (range 96% to 110%)

Effect of avanafil on omeprazole, a CYP2C19 substrate, PK

Avanafil given to subjects who received omeprazole delayed-release capsules had a 1.1-fold increase in AUC_{0-t}, compared to omeprazole alone. C_{max} of omeprazole increased 1.1-fold, compared to omeprazole alone. The median t_{max} of omeprazole remained unchanged at 2.0 hrs and the arithmetic mean t_{1/2} of omeprazole increased by 0.1 hr from 1.8 to 1.9 hrs following omeprazole and avanafil co-administration, compared to omeprazole alone.

Effect of avanafil on rosiglitazone, a CYP2C8 substrate, PK

Avanafil given to subjects who received rosiglitazone had a 1.0-fold increase in AUC_{0-inf}, compared to rosiglitazone alone. C_{max} of rosiglitazone decreased by 14%, compared to rosiglitazone alone. The median t_{max} of rosiglitazone remained increased by 0.25 hr from 0.75 to 1.0 hr and the arithmetic mean t_{1/2} of rosiglitazone decreased slightly by 0.1 hr from 4.0 to 3.9 hrs following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

Effect of avanafil on desipramine, a CYP2D6 substrate, PK

Avanafil given to subjects who received desipramine had a 1.1-fold increase in AUC_{0-inf}, compared to desipramine alone. C_{max} of desipramine increased by 1.1-fold, compared to desipramine alone. The median t_{max} and the arithmetic mean t_{1/2} of desipramine remained unchanged at 6 and 14 hrs, respectively, following desipramine and avanafil co-administration, compared to desipramine alone.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

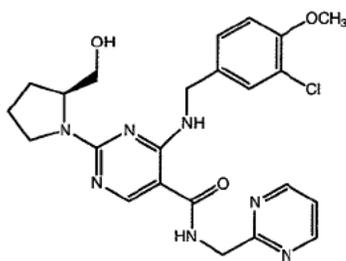
Vivus is seeking approval of avanafil for ED in males. ED is defined as the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual performance. The proposed dose and dosing regimen is 100 mg oral tablet to be taken approximately 30 minutes before sexual activity on an as needed basis. Avanafil should not be taken more than once daily and may be taken with or without food. The

dose can be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability.

ED is considered by the sponsor as a non-life threatening and is associated with the aging process and increases in prevalence in men with diabetes, cardiovascular disease and spinal cord injuries. There are currently four FDA-approved pharmacologic therapies for ED and are all from the same class known as phosphodiesterase type 5 (PDE5) inhibitors. PDE5 inhibitors have shown to help restore penile blood flow and erections in response to sexual stimulation. Currently approved oral PDE5 inhibitors include Viagra (sildenafil), Cialis (tadalafil), Levitra (vardenafil), and Staxyn (sildenafil).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Avanafil has a chemical name of (S)-4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide with a molecular weight of 483.95. The chemical formula is $C_{23}H_{26}ClN_7O_3$. (b) (4)
Avanafil is highly insoluble in water pH 5.88 (<0.1 mg/mL). Solubility of avanafil is higher under acidic conditions (661 µg/mL at pH 3.32) and very low in neutral to alkali conditions (2.6 µg/mL at pH 7.94)



The to-be-marketed formulation of avanafil is an immediate-release, oval, pale yellow tablet containing 50 mg, 100 mg, or 200 mg avanafil drug substance. During the clinical development program, there were two avanafil immediate-release formulations used – Formulation I and Formulation II (b) (4)

The sponsor changed the shape of the tablet from (b) (4) to an oval light-yellow coated tablet. (b) (4)

The early tablets (Formulation I) (b) (4) and were available in 12.5, 25, 50, and 100 mg strengths. Formulation II is an oval, light-yellow coated tablet and is available in 50, 100, and 200 mg strengths. Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and is the proposed to-be-marketed formulation. However, the Phase 3 studies were conducted using multiple units of 50 or 100 mg tablets. The three proposed dosage strengths of Formulation II are produced (b) (4)

The table below summarizes the components and composition of the to-be-marketed avanafil tablets. The sponsor is seeking approval of all three tablet strengths - 50, 100, and 200 mg (Study TA-020).

Components	Composition (mg / tablet)			% Composition
	50 mg	100 mg	200 mg	
Avanafil API	(b) (4)			(b) (4)
Mannitol				
Fumaric acid				
Hydroxypropylcellulose				
Low substituted hydroxypropylcellulose				
(b) (4) calcium carbonate				
Magnesium stearate				
Yellow ferric oxide*				
Total mass (mg / tablet)				
(b) (4)				

The table below summarizes avanafil formulations used during clinical development (eCTD 2.7.1 Summary of Biopharmaceutics Studies)

Study ID	Type of Study	Phase	Avanafil Tablet Strength	Avanafil Doses
Formulation I				
HP-01	PK, food effect, tolerability	1	12.5, 50, 100 mg	12.5, 25, 50, 100, 200, 400, 600 and 800 mg
TA-02	PK, safety single, multi dose	1	50, 100 mg	50, 100 and 200 mg QD
TA-04	Drug-drug interaction (nitrate)	1	100 mg	200 mg
TA-07	PK, BID dosing	1	100 mg	200 mg BID
TA-01	Visual stimulation	2	50, 100 mg	50, 100 and 200 mg
TA-03	Home administration	2	100 mg	200 mg
TA-05	Safety, efficacy	2	12.5, 50, 100 mg	50, 100, 200 and 300 mg
Formulation II				
TA-011	Drug-drug interaction (ritonavir, erythromycin, ketoconazole)	1	50, 100 mg	50 or 200 mg
TA-012	Drug-disease interaction (hepatic)	1	200 mg	200 mg
TA-013	Drug-disease interaction (renal)	1	200 mg	200 mg
TA-014	Elderly vs. young PK, semen PK	1	200 mg	200 mg
TA-015	Drug-drug interaction (alcohol)	1	200 mg	200 mg
TA-016	Drug-drug interaction (warfarin)	1	200 mg	200 mg
TA-017	Drug-drug interaction (alpha blockers)	1	200 mg	200 mg
TA-018	Drug-drug interaction (omeprazole, desipramine, and rosiglitazone)	1	200 mg	200 mg
TA-019	Drug-drug interaction (enalapril, amlodipine)	1	200 mg	200 mg
TA-020	Food effect, bioequivalence, dose proportionality	1	50, 100 mg (Formulation II) 100 mg (Formulation I)	50 or 200 mg
TA-021	Sperm function	1	200 mg	200 mg
TA-140	TQT	1	100 mg	100 and 800 mg
TA-301	Safety, efficacy in generalized ED	3	50 mg	50, 100, 200 mg
TA-302	Safety, efficacy in diabetics with ED	3	100 mg	100 and 200 mg
TA-314	Long term follow up (rollover from TA-301 and TA-302)	3	50, 100, 200 mg	50, 100 and 200 mg
TA-022	Dose equivalence	1	50, 100, 200 mg	200 mg

TA-022 is a Phase I Study conducted to evaluate the dose equivalence between 50, 100, and 200 mg strengths. The study report was submitted after filing of this NDA.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The sponsor is seeking approval to market avanafil for the treatment of ED. Avanafil is a PDE5 inhibitor. It 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 cyclic guanosine monophosphate (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.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical program included 18 Phase I studies, 3 Phase II studies, and 2 Phase III studies. The proposed dosing instruction for avanafil is a starting dose of 100 mg to be taken orally as needed approximately 30 min before sexual activity. The dosing frequency is once per day and with or without food. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg.

In the Phase III study TA-301, the doses were 50 mg, 100 mg, and 200 mg and were administered in multiples of 50 mg tablets. In the second Phase III study TA-302, the doses were 100 and 200 mg and were administered in multiples of 100 mg tablets, Formulation II. In both studies, subjects were instructed to take one dose of avanafil or placebo approximately 30 min prior to initiation of sexual activity. No restrictions were placed on the timing or consumption of food or alcohol.

The supporting Phase II study TA-05 evaluated the safety and efficacy of 50, 100, 200, and 300 mg avanafil, Formulation I. Each dose group received 2 capsules with multiples of 12.5, 50 and 100 mg tablets encapsulated. Subjects were instructed to take one dose of avanafil or placebo approximately 30 min prior to initiation of sexual activity.

The majority of Phase I clinical pharmacology studies evaluating drug-drug interactions, food effect, and intrinsic factors were conducted with a single tablet of 200 mg avanafil, Formulation II.

2.2.2 What are the clinical endpoints measured in clinical pharmacology and clinical studies?

The three co-primary efficacy endpoints for the 12-week pivotal Phase III studies are (1) change from baseline in the percentage of sexual attempts resulting in successful intercourse [Sexual Encounter Profile question 3 (SEP3)]; (2) change from baseline in the percentage of sexual attempts resulting in successful vaginal penetration (SEP2); and (3) change from baseline in the International Index of Erectile Function (IIEF) erectile function domain score. These are the current clinical efficacy endpoints recommended to all sponsors seeking approval for the treatment of ED.

Cialis® (tadalafil) and Levitra® (vardenafil), PDE5 inhibitors, were approved under NDAs 021368 (November 21, 2003) and 021400 (August 19, 2003), respectively. Both Cialis and Levitra were approved with the same clinical efficacy endpoints as those presented in this NDA. The primary endpoints used for the approval of Viagra (sildenafil) on March 27, 1998 under NDA 020895 were different from the current recommendations and were based on two questions from the IIEF. Staxyn (vardenafil) is an orally disintegrating tablet of Levitra and was approved under NDA 200179 (June 17, 2010) based on the clinical findings of Levitra.

In the Phase II proof-of-concept study TA-05, the three efficacy endpoints were similar to those used in Phase III studies and were recorded in the subjects diary.

In clinical pharmacology studies, the endpoints for the majority of studies were PK parameters of avanafil. In some cases such as drug-drug interactions, the endpoints were PK parameters of the interacting drug. For pharmacodynamic studies with alcohol, glyceryl nitrate, alpha-blockers, and antihypertensives, the endpoints were changes in blood pressure and pulse rate. For one study with avanafil and warfarin, the endpoints were INR, PT, platelet aggregation, and PK of warfarin.

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In an open-label study in six healthy male subjects, the sponsor evaluated the metabolism of a single oral suspension dose of 600 mg ¹⁴C-radiolabeled avanafil (Study TA-010). Metabolite profiling was done in human plasma, urine, and feces. Blood, urine, and fecal samples were collected up 168, 216, and 216 hrs after dosing, respectively. Avanafil was extensively metabolized in humans. Fecal excretion was the major route of elimination of radioactivity. After oral dosing of ¹⁴C-radiolabeled avanafil through 216 hrs, 61% of the radioactive dose was recovered in feces and 21% in urine. Recovery of total radioactivity in urine and feces ranged from 85 to 94%.

Unchanged avanafil was the major radioactive component in plasma and accounted for about 37% of total radioactivity within 12 hrs postdose. The major circulating metabolite was M16, an open pyrrolidine ring carboxylic acid avanafil, which accounted for about 11% of the total radioactivity or 29% of unchanged avanafil. M10, a carboxylic acid avanafil and M16 were the major metabolites in feces. M16 was the major metabolite excreted in urine. About 6% of radioactive dose was excreted as unchanged avanafil in fecal samples. Unchanged avanafil was not detected in pooled urine samples.

Metabolism of avanafil is likely completed through phase I metabolism. Phase II metabolism is a minor pathway. Biotransformation of avanafil is likely completed through hydroxylation, oxidation, multiple N-dealkylation reactions, demethylation and glucuronide conjugation. Modification of the pyrrolidine ring is likely to result in the majority of the identified metabolites.

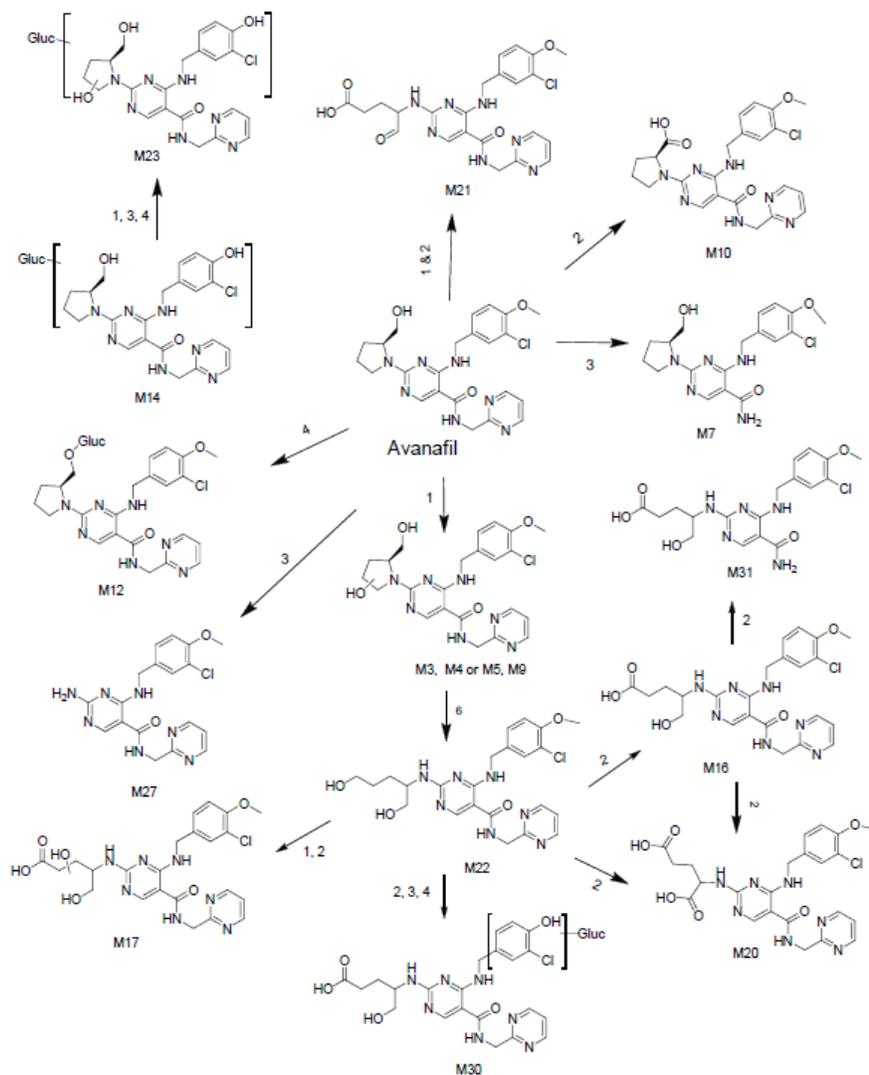
Percent of total radioactivity as avanafil metabolites in pooled plasma, urine, and feces (Study TA-010)

Metabolite ID	[M+H] ⁺ m/z	Retention Time Minutes ^(b)	% of Total Radioactivity														
			FECES 0-120 hour						PLASMA 0-12 hr	URINE 0-24 hour							
			S-1	S-2	S-3	S-4	S-5	S-6	Hamilton Pool	S-1	S-2	S-3	S-4	S-5	S-6		
M30	678	5.96										3.7	3.2	1.6	1.6		
M23	662	10.7				2.8											
M20	530	13.0 (2)			4.7			3.2	4.6		1.8	4.9	2.2	2.5	4.6	4.7	4.8
Unknown-2		11.1 (3)									2.0						
M14	646	14.7									0.6	6.4	5.1	2.8	6.1		
M31	424	15.3	2.6	4.0				2.4	5.4							4.4	2.1
M17	532	16.3	6.6	5.6	8.0			4.9	4.9		2.0	3.6	5.2	3.9	10.3		2.8
M21	514	16.7	4.7									3.4	2.3			5.0	4.0
M16	516	17.1	36.6	29.0	26.0	13.5	32.3	31.4		10.6		47.4	46.6	64.1	53.5	50.8	54.1
Unknown-3	518	18.9				3.4											
M10	498	19.4	19.5	21.9	23.1	12.2	17.2	22.9			2.3	11.8	9.3	10.1	8.7	8.2	11.4
M12	660	19.6 Plasma									1.5						
M22	502	21.8	2.8	6.5	6.7	2.7	5.8	6.6			2.0	6.4	7.8	8.7	6.6	6.0	8.2
M3	500	22.9									1.7						
M27	400	23.6									3.8						
M5 (4)	500	24.5		3.6	6.6	3.8	4.0	2.5			2.0						
M4 (4)	500	24.6									8.4						
M9	500	25.3		1.6	2.5						2.3	2.6	1.7	TA (5)	1.5		
M7	392	26.7									1.1						
Avanafil	484	27.0		5.5	7.1	10.4	10.3				36.7					1.8	

Percent of radioactive dose excreted as avanafil or its metabolites in pooled urine and feces (Study TA-010)

Metabolite ID	[M+H] ⁺ m/z	RT (min)	% Radioactive Dose Excreted															
			FECES 0-120 hour						-	URINE 0-24 hour								
			S1	S2	S3	S4	S5	S6		Mean	S1	S2	S3	S4	S5	S6	Mean	
M30	678	5.96										0.7	0.7	0.3	0.4			0.5
M23	662	10.7					0.6				0.6							
M20	530	13.0			3.3			2.4	3.0		2.9	1.0	0.5	0.5	1.1	0.9	1.0	0.8
M14	646	14.7										1.3	1.1	0.5	1.5			1.1
M31	424	15.3	2.0	2.8				1.8	3.5		2.5					0.9	0.4	0.7
M17	532	16.3	5.0	4.0	5.7			3.7	3.2		4.3	0.7	1.2	0.7	2.5		0.6	1.1
M21	514	16.7	3.5								3.5	0.7	0.5					0.6
M16	516	17.1	27.5	20.6	18.5	3.0	24.4	20.6		19.1	9.5	10.4	11.9	13.1	10.2	11.5		11.1
Unknown-3	518	18.9				0.8					0.8							
M10	498	19.4	14.6	15.6	16.4	2.7	13.0	15.0		12.9	2.4	2.1	1.9	2.1	1.7	2.4		2.1
M22	502	21.8	2.1	4.6	4.8	0.6	4.4	4.3		3.5	1.3	1.7	1.6	1.6	1.2	1.7		1.5
M4/5	500	24.5		2.6	4.7	0.8	3.0	1.6		2.5								
M9	500	25.3		1.1	1.8					1.5	0.5	0.4	TA	0.4				0.4
Avanafil	484	27		3.9	5.0	2.3	7.8			4.8						0.4		0.4
Total			54.7	55.2	60.2	10.8	60.5	51.2		58.9	18.1	18.6	17.4	22.7	15.3	17.6		20.3

The figure below is the proposed metabolite pathways of avanafil in humans (Study TA-010).



1. Hydroxylation; 2. Oxidation; 3. N-dealkylation; 4. Glucuronide conjugation; 5. Demethylation; 6. Pyrrolidine ring opening via N-dealkylation; 7. Dehydrogenation probably via hydroxylation followed by dehydration.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the dose-response relationships for efficacy?

The sponsor submitted data from two Phase III studies conducted in multiple centers in the United States to support the proposed indication, treatment of ED in men. Three doses (50, 100, and 200 mg) were evaluated for safety and efficacy in Study TA-301. Two doses (100 and 200 mg) were evaluated in safety and efficacy in Study TA-302.

The three co-primary efficacy endpoints for the 12-week pivotal Phase III studies are (1) change from baseline in the percentage of sexual attempts resulting in successful intercourse [Sexual Encounter Profile question 3 (SEP3)]; (2) change from baseline in the percentage of sexual attempts resulting in successful vaginal penetration (SEP2); and (3) change from baseline in the International Index of Erectile Function (IIEF) erectile function domain score.

In study TA-301, treatment with avanafil at 50 mg, 100 mg, and 200 mg doses led to statistically significant improvements in SEP3, SEP2, and IIEF erection function domain score compared to placebo. As the dose increased 2-fold from 50 to 100 mg, SEP3, SEP2, and IIEF erectile function domain score increased approximately 2-fold. SEP3 was higher by 13.8%, 29.3% and 30.2% following 50 mg, 100 mg and 200 mg avanafil, respectively, compared to placebo. SEP2 was higher by 11.1%, 20.1% and 22.7% following 50 mg, 100 mg and 200 mg avanafil, respectively, compared to placebo. The change from baseline in the IIEF erectile function domain score was 2.6, 5.5 and 6.7 following 50 mg, 100 mg and 200 mg avanafil, respectively, compared to placebo.

In study TA-302, treatment with avanafil at 100 mg and 200 mg doses led to statistically significant improvements in SEP3, SEP2, and IIEF erection function domain score, compared to placebo. SEP3 was higher by 15.6% and 16.4% following 100 mg and 200 mg avanafil, respectively, compared to placebo. SEP2 was higher by 9.0% and 11.7% following 100 mg and 200 mg avanafil, respectively, compared to placebo. The change from baseline in the IIEF erectile function domain score was 2.9 and 4.1 following 100 mg and 200 mg avanafil, respectively, compared to placebo.

Change from baseline in percentage of SEP3 and SEP2, and change from baseline in IIEF erectile function domain score between the run-in period and the treatment period – intent-to-treat population (LOCF)

Study Endpoint	LS mean difference (p-value)		
	Avanafil 50 mg	Avanafil 100 mg	Avanafil 200 mg
Study TA-301 (n)	154	157	156
Compare vs. placebo (P-value)			
Change in % of sexual attempts with successful SEP3	13.8% (0.0002)	29.3% (<0.0001)	30.2% (<0.0001)
Change in % of sexual attempts with successful SEP2	11.1% (0.0009)	20.1% (<0.0001)	22.7% (<0.0001)
Change in IIEF EF domain score	2.6 (0.0014)	5.5 (<0.0001)	6.7 (<0.0001)
Dose is Effective vs. placebo? (Yes / No)	Yes	Yes	Yes
Compare vs. Avanafil 50 mg (P-value)			
Change in % of sexual attempts with successful SEP3		15.6% (<0.0001)	16.4% (<0.0001)
Change in % of sexual attempts with successful SEP2		9.0% (0.0064)	11.7% (0.0004)
Change in IIEF EF domain score		2.9 (0.0003)	4.1 (<0.0001)
Dose is Effective vs. Avanafil 50 mg? (Yes / No)		Yes	Yes
Compare vs. Avanafil 100 mg			
Change in % of sexual attempts with successful SEP3			0.8% (0.8198)
Change in % of sexual attempts with successful SEP2			2.6% (0.4221)
Change in IIEF EF domain score			1.2 (0.1366)
Dose is Effective vs. Avanafil 100 mg?(Yes / No)			No
Study TA-302 (n)		126	126
Compare vs. placebo			
Change in % of sexual attempts with successful SEP3		15.2% (<0.0001)	20.4% (<0.0001)
Change in % of sexual attempts with successful SEP2		14.0% (0.0004)	18.4% (<0.0001)
Change in IIEF EF domain score		2.8 (0.0017)	3.6 (<0.0001)
Dose is Effective vs. placebo? (Yes / No)		Yes	Yes
Compare vs. Avanafil 100 mg			
Change in % of sexual attempts with successful SEP3			5.3% (0.1724)
Change in % of sexual attempts with successful SEP2			4.4% (0.2719)
Change in IIEF EF domain score			0.8 (0.3387)
Dose is Effective vs. Avanafil 100 mg?(Yes / No)			No

Source: table from statistical review by Jia Guo, Ph.D.

Subjects were stratified by duration of ED subgroup: subjects who had ED <24 months, subjects who had ED ≥24 months and <60 months, and subjects who had ED ≥60 months at baseline.

The following table summarizes the percentage of sexual attempts between run-in period and treatment period in which the subject was able to maintain an erection sufficient to have successful intercourse (SEP3) (Study 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
<24 months						
Placebo	29	15.6 (19.12)	38.7 (31.67)	23.1 (22.75)	23.3 (5.85)	<0.0001
Avanafil 50 mg	23	10.1 (17.91)	54.3 (35.32)	44.2 (39.74)	40.4 (6.61)	<0.0001
Avanafil 100 mg	22	14.5 (19.28)	53.2 (37.71)	38.7 (31.22)	37.5 (6.72)	<0.0001
Avanafil 200 mg	18	13.3 (22.82)	55.3 (38.41)	41.9 (46.47)	40.2 (7.43)	<0.0001
≥24 months and <60 months						
Placebo	50	11.2 (16.06)	33.7 (36.15)	22.5 (37.29)	19.6 (4.50)	<0.0001
Avanafil 50 mg	52	15.8 (18.73)	53.6 (32.43)	37.8 (29.26)	38.0 (4.37)	<0.0001
Avanafil 100 mg	59	14.8 (19.34)	64.3 (34.62)	49.6 (35.01)	49.7 (4.11)	<0.0001
Avanafil 200 mg	62	13.6 (18.08)	61.2 (35.90)	47.6 (34.51)	47.9 (4.00)	<0.0001
≥60 months						
Placebo	76	12.4 (18.49)	18.1 (25.20)	5.7 (17.78)	6.9 (3.63)	0.0561
Avanafil 50 mg	79	12.9 (18.72)	29.4 (34.62)	16.4 (31.09)	17.5 (3.55)	<0.0001
Avanafil 100 mg	76	13.1 (18.59)	52.5 (36.21)	39.5 (33.35)	40.2 (3.62)	<0.0001
Avanafil 200 mg	76	11.2 (17.94)	54.0 (39.28)	42.8 (34.04)	42.2 (3.61)	<0.0001

The following table summarizes the percentage of sexual attempts between run-in period and treatment period in which the subject was able to insert his penis into his partner's vagina (SEP2) (Study 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
<24 months						
Placebo	29	39.4 (32.56)	59.0 (37.30)	19.6 (22.60)	14.9 (5.24)	0.0045
Avanafil 50 mg	23	48.0 (34.51)	86.1 (21.33)	38.1 (29.73)	37.3 (5.91)	<0.0001
Avanafil 100 mg	22	40.7 (44.04)	70.0 (37.84)	29.3 (33.93)	24.6 (6.03)	<0.0001
Avanafil 200 mg	18	64.4 (30.43)	84.3 (27.96)	19.9 (41.51)	28.6 (6.66)	<0.0001
≥24 months and <60 months						
Placebo	50	58.6 (36.94)	66.3 (36.24)	7.8 (37.77)	13.4 (4.02)	0.0009
Avanafil 50 mg	52	55.6 (35.61)	78.9 (27.57)	23.2 (37.92)	27.9 (3.92)	<0.0001
Avanafil 100 mg	59	50.5 (37.36)	82.1 (25.39)	31.5 (34.51)	33.1 (3.68)	<0.0001
Avanafil 200 mg	62	47.1 (37.65)	81.7 (28.36)	34.6 (36.77)	34.8 (3.58)	<0.0001
≥60 months						
Placebo	76	41.7 (35.85)	43.7 (36.73)	2.0 (30.04)	-0.0 (3.25)	0.9897
Avanafil 50 mg	79	37.9 (36.76)	48.4 (39.41)	10.5 (33.04)	6.2 (3.18)	0.0512
Avanafil 100 mg	76	45.2 (37.35)	68.6 (34.34)	23.4 (36.04)	23.3 (3.24)	<0.0001
Avanafil 200 mg	76	45.4 (39.79)	72.0 (33.97)	26.6 (33.50)	26.1 (3.23)	<0.0001

The following table summarizes the change in IIEF erection function domain score from baseline to end of treatment (Study 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
<24 months						
Placebo	29	13.4 (5.12)	17.6 (7.83)	4.2 (5.75)	4.5 (1.27)	0.0005
Avanafil 50 mg	22	13.5 (4.63)	21.7 (6.28)	8.2 (6.73)	8.4 (1.46)	<0.0001
Avanafil 100 mg	21	13.1 (6.08)	19.4 (8.12)	6.3 (7.15)	6.4 (1.49)	<0.0001
Avanafil 200 mg	18	14.2 (3.75)	23.3 (5.51)	9.1 (6.76)	9.6 (1.61)	<0.0001
≥24 months and <60 months						
Placebo	50	14.2 (5.46)	17.4 (7.37)	3.3 (7.10)	3.8 (0.97)	0.0001
Avanafil 50 mg	52	13.5 (4.80)	21.7 (6.67)	8.1 (7.71)	8.4 (0.95)	<0.0001
Avanafil 100 mg	59	12.9 (4.93)	22.6 (6.68)	9.7 (6.91)	9.7 (0.89)	<0.0001
Avanafil 200 mg	62	13.3 (5.11)	22.9 (7.23)	9.6 (6.54)	9.9 (0.87)	<0.0001
≥60 months						
Placebo	73	10.8 (4.39)	13.0 (7.50)	2.2 (6.09)	1.6 (0.81)	0.0486
Avanafil 50 mg	78	11.8 (5.51)	14.6 (7.68)	2.8 (6.77)	2.6 (0.78)	0.0009
Avanafil 100 mg	76	12.3 (5.57)	20.1 (8.57)	7.8 (8.27)	7.8 (0.79)	<0.0001
Avanafil 200 mg	75	12.0 (5.09)	21.5 (8.54)	9.4 (7.55)	9.2 (0.79)	<0.0001

Final conclusions of efficacy are pending review by Guodong Fang, MD.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The following table is a summary of treatment-emergent adverse events (≥1% of subjects in any treatment group) by system organ class and preferred term (Study 301).

System Organ Class Preferred Term	Placebo (N=161) n (%)	Avanafil 50 mg (N=160) n (%)	Avanafil 100 mg (N=161) n (%)	Avanafil 200 mg (N=162) n (%)	Total (N=644) n (%)
Infections and infestations	11 (6.8)	13 (8.1)	13 (8.1)	19 (11.7)	56 (8.7)
Nasopharyngitis	2 (1.2)	1 (0.6)	2 (1.2)	6 (3.7)	11 (1.7)
Bronchitis	1 (0.6)	3 (1.9)	1 (0.6)	4 (2.5)	9 (1.4)
Upper respiratory tract infection	1 (0.6)	3 (1.9)	2 (1.2)	1 (0.6)	7 (1.1)
Influenza	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.6)
Sinusitis	3 (1.9)	0 (0.0)	1 (0.6)	2 (1.2)	6 (0.9)
Tooth infection	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	3 (0.5)
Nervous system disorders	5 (3.1)	9 (5.6)	17 (10.6)	19 (11.7)	50 (7.8)
Headache	2 (1.2)	7 (4.4)	12 (7.5)	15 (9.3)	36 (5.6)
Dizziness	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	3 (0.5)
Musculoskeletal and connective tissue disorders	6 (3.7)	11 (6.9)	12 (7.5)	8 (4.9)	37 (5.7)
Back pain	1 (0.6)	4 (2.5)	4 (2.5)	3 (1.9)	12 (1.9)
Musculoskeletal pain	0 (0.0)	1 (0.6)	1 (0.6)	2 (1.2)	4 (0.6)
Osteoarthritis	1 (0.6)	0 (0.0)	2 (1.2)	0 (0.0)	3 (0.5)
Pain in extremity	2 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	4 (0.6)
Vascular disorders	1 (0.6)	7 (4.4)	12 (7.5)	6 (3.7)	26 (4.0)
Flushing	0 (0.0)	6 (3.8)	10 (6.2)	6 (3.7)	22 (3.4)
Hypertension	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	3 (0.5)
Gastrointestinal disorders	5 (3.1)	9 (5.6)	9 (5.6)	6 (3.7)	29 (4.5)
Diarrhea	1 (0.6)	1 (0.6)	3 (1.9)	2 (1.2)	7 (1.1)
Constipation	0 (0.0)	3 (1.9)	0 (0.0)	0 (0.0)	3 (0.5)
Stomach discomfort	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (0.3)
Respiratory, thoracic, and mediastinal disorders	4 (2.5)	4 (2.5)	12 (7.5)	8 (4.9)	28 (4.3)
Nasal congestion	2 (1.2)	1 (0.6)	7 (4.3)	3 (1.9)	13 (2.0)
Dyspnea exertional	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	2 (0.3)
Injury, poisoning, and procedural complications	5 (3.1)	3 (1.9)	5 (3.1)	2 (1.2)	15 (2.3)
Skin laceration	0 (0.0)	1 (0.6)	2 (1.2)	0 (0.0)	3 (0.5)
Skin and subcutaneous tissue disorders	1 (0.6)	3 (1.9)	3 (1.9)	3 (1.9)	10 (1.6)
Rash	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.6)	3 (0.5)
Investigations	2 (1.2)	1 (0.6)	3 (1.9)	2 (1.2)	8 (1.2)
Hepatic enzyme increased	1 (0.6)	0 (0.0)	0 (0.0)	2 (1.2)	3 (0.5)

The most frequently reported drug-related treatment-emergent adverse events (TEAEs) by treatment in Study TA-301 are as follows:

	Placebo (N=161) n (%)	Avanafil 50 mg (N=160) n (%)	Avanafil 100 mg (N=161) n (%)	Avanafil 200 mg (N=162) n (%)
Headache	2 (1.2)	7 (4.4)	12 (7.5)	15 (9.3)
Flushing	0 (0.0)	6 (3.8)	10 (6.2)	6 (3.7)
Nasal congestion	2 (1.2)	1 (0.6)	7 (4.3)	3 (1.9)
Back pain	1 (0.6)	4 (2.5)	4 (2.5)	3 (1.9)
Nasopharyngitis	2 (1.2)	1 (0.6)	2 (1.2)	6 (3.7)

Similar to the efficacy outcome, of the three doses evaluated in the Phase III study, the highest frequency of adverse events occurred at the two highest doses (100 and 200 mg), compared to placebo.

Final conclusions of safety are pending review by Guodong Fang, MD.

2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-response?

Yes. The sponsor evaluated the safety and efficacy of various doses (50, 100, 200, and 300 mg) of avanafil in 263 subjects (mean age 56.1; range 32 to 70 yrs) with mild or moderate ED (based on IIEF) in a pivotal Phase II study. The three primary endpoints were: (1) the success rate of the subject's responses to Subject Diary question #6 "Were you able to insert your penis into your partner's vagina?"; (2) the success rate of the subject's response to Subject Diary question #7 "Did your erection last long enough for you to have successful intercourse?"; and (3) erectile function domain score (EFS) of the IIEF questionnaire.

The following figure and tables are from Study TA-05

Figure 2 Penetration Success Rate: Percentage of Attempts Enabling Vaginal Penetration (ITT Population)

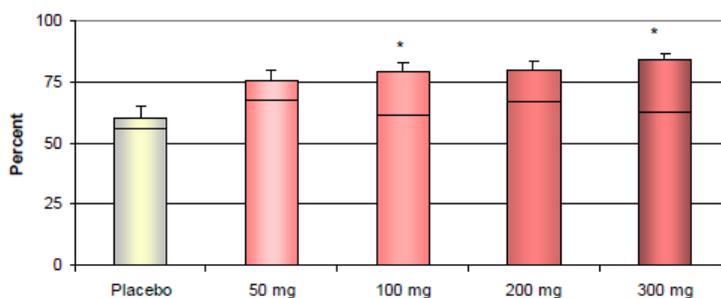
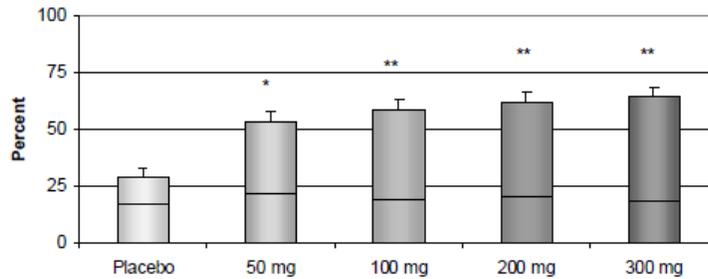


Figure 3 Intercourse Success Rate: Percentage of Attempts With Successful Completion of Intercourse (ITT Population)



* and ** represents statistically significant difference versus placebo with p-value <0.05

Table 7 Overall Erectile Function Domain Score (ITT Population)

	Placebo (N=55)	Avanafil			
		50 mg (N=56)	100 mg (N=60)	200 mg (N=56)	300 mg (N=57)
EFS from IIEF Questionnaire					
Baseline (Run-in)					
Mean (SD)	15.8 (4.0)	16.1 (3.5)	16.2 (4.1)	16.5 (3.8)	16.5 (3.8)
Median	15.0	16.0	16.0	16.0	16.0
Min-Max	11 - 24	11 - 25	11 - 25	11 - 25	11 - 25
Pairwise P-value vs. Placebo ^(I)		0.5243	0.6649	0.3494	0.3064
End of Treatment (LOCF)					
Mean (SD)	16.9 (7.3)	19.4 (7.5)	22.3 (7.0)	22.4 (7.4)	22.5 (7.2)
Median	15.0	21.0	25.0	25.0	25.0
Min-Max	5 - 29	1 - 30	6 - 30	5 - 30	2 - 30
Pairwise P-value vs. Placebo ^(I)		0.0680	<0.0001	0.0001	<0.0001
Change from Baseline (Run-in)					
Mean (SD)	1.1 (6.4)	3.2 (7.6)	6.1 (6.7)	5.9 (7.1)	6.0 (7.9)
Median	0.0	5.0	6.5	7.5	7.0
Min-Max	-12 - 16	-16 - 17	-8 - 19	-17 - 19	-18 - 18
Pairwise P-value vs. Placebo ^(II)		0.0235	0.0001	0.0002	<0.0001

Treatment-emergent adverse events reported by $\geq 2\%$ subjects in the intent-to-treat (ITT) population

Adverse Event	Placebo (N=55) n (%)	Avanafil			
		50 mg (N=56) n (%)	100 mg (N=60) n (%)	200 mg (N=56) n (%)	300 mg (N=57) n (%)
Headache	2 (3.6%)	4 (7.1%)	7 (11.7%)	7 (12.5%)	15 (26.3%)
Nasopharyngitis	2 (3.6%)	1 (1.8%)	3 (5.0%)	2 (3.6%)	2 (3.5%)
Upper Respiratory Tract Infection	0 (0%)	1 (1.8%)	2 (3.3%)	4 (7.1%)	1 (1.8%)
Nasal Congestion	2 (3.6%)	3 (5.4%)	3 (5.0%)	3 (5.4%)	3 (5.3%)
Back Pain	0 (0%)	3 (5.4%)	1 (1.7%)	0 (0%)	2 (3.5%)
Flushing	0 (0%)	1 (1.8%)	3 (5.0%)	3 (5.4%)	4 (7.0%)
Sinusitis	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	2 (3.5%)
Nausea	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)	2 (3.5%)
Pharyngitis Streptococcal	0 (0%)	0 (0%)	2 (3.3%)	0 (0%)	0 (0%)
Upper Respiratory Tract Congestion	0 (0%)	0 (0%)	0 (0%)	2 (3.6%)	0 (0%)
Prostate Examination Abnormal	2 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

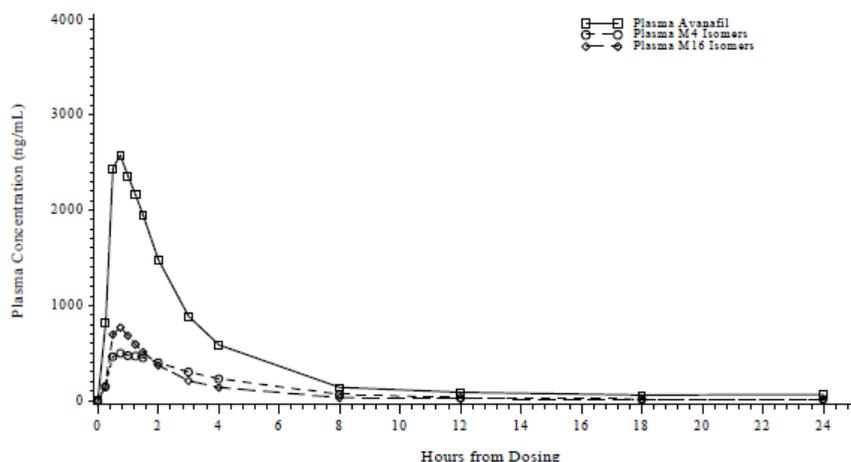
Based on the outcome of this Phase II study, the sponsor selected 50, 100, and 200 mg for their Phase III studies. The 300 mg dose was not included in the Phase III studies as it did not provide additional efficacy benefits and resulted in additional adverse events such as headache and flushing.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of the drug and its major metabolite?

Avanafil is extensively metabolized to various metabolites, mainly by CYP3A4 and to a minor extent by CYP2 enzymes. M4 and M16 are the two major metabolites with a plasma concentration of approximately 23% and 29% of avanafil, respectively. In vitro studies showed that M4 has an inhibitory potency of 18% of avanafil for PDE5 and accounts for approximately 4% of the pharmacological activity of avanafil. M16 was inactive against PDE5.

The following figure is the arithmetic mean plasma avanafil, M4, and M16 concentration vs. time following a single dose of 200 mg avanafil, Formulation II, fasted (Study TA-022)



M4 represents a minor contribution (4%) to the overall pharmacologic activity of avanafil, while M16 is inactive against the PDE5 enzyme; therefore, PK parameters reported in the majority of this review are for the parent drug avanafil only.

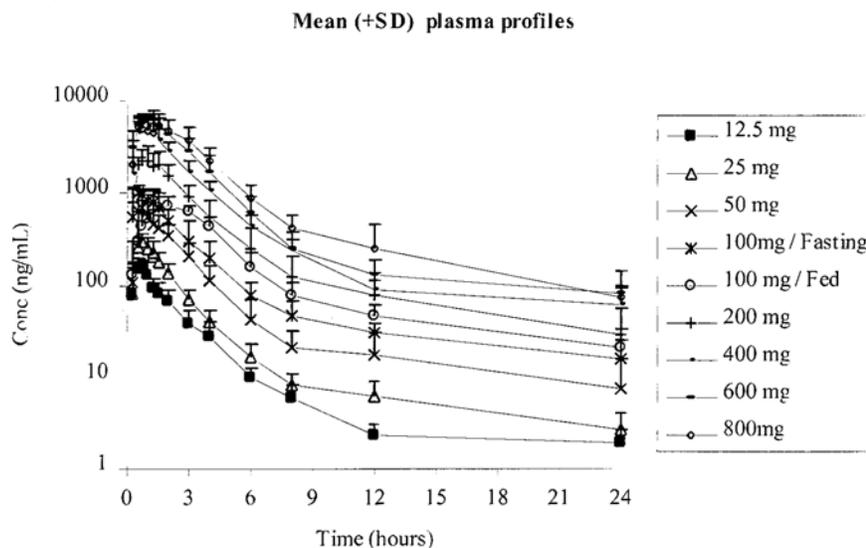
2.2.5.2 What are the single dose and multiple dose PK parameters?

The sponsor developed two formulations during the course of the clinical development program. Formulation II is the to-be-marketed formulation and the one used in the Phase III clinical trials. Single dose and multiple dose PK of the proposed 50 mg, 100 mg, and 200 mg dose strengths were conducted with Formulation I only. Single dose PK of 200 mg avanafil Formulation II was evaluated in a subsequent Phase I study. Formulation I and II were evaluated for relative bioavailability and are bioequivalent. The analytical method used in Study TA-02 was HPLC, not LC-MS/MS as in most other clinical pharmacology studies; therefore, the actual PK parameters are different between early and late Phase I studies.

Single Dose PK of avanafil, Formulation I (Study HP-01)

Single dose PK for Formulation I was characterized in healthy male subjects (Study HP-01). AUC_{0-inf} ranged from 381 to 24457 ng*hr/mL after a single dose of 12.5 to 800 mg and is dose proportional from 12.5 to 600 ng*hr/mL. C_{max} ranged from 166 to 7249 µg/mL after a single dose of 12.5 to 800 mg and is dose proportional from 12.5 to 600 mg. The median T_{max} ranged from 0.63 to 1.25 hr.

The plasma concentration-time profile for these doses are shown in the following figure (Study HP-01).



The following table is a summary of geometric mean (SD) PK parameters of avanafil, Formulation I in plasma following a single dose of avanafil in healthy male subjects (Study HP-01).

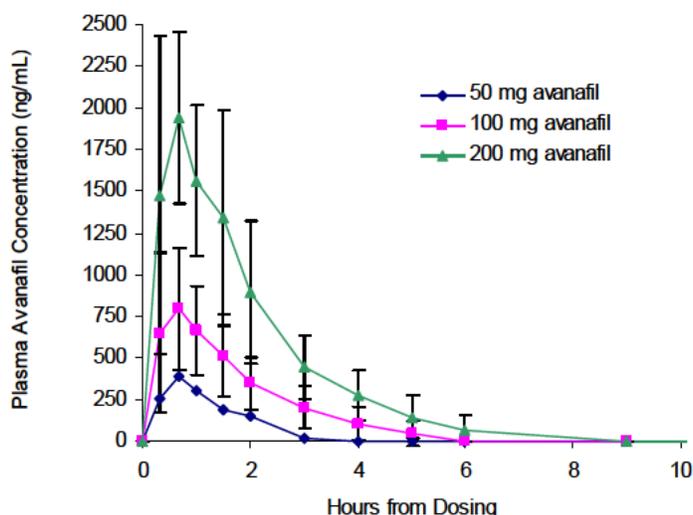
Dose (mg)		C_{max} (ng/mL)	t_{max}^* (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	Ae (μ g)	Clr (mL/min)
12.5	Mean	165.50	0.63	6.02	364.21	380.55	-	-
	SD	38.96	0.25-0.75	5.68	109.99	116.09	-	-
25	Mean	311.75	0.75	9.71	694.08	741.43	-	-
	SD	55.44	0.50-1.00	7.92	134.90	187.48	-	-
50	Mean	732.28	0.75	9.41	1736.39	1885.90	-	-
	SD	383.07	0.50-1.50	5.06	736.06	974.58	-	-
100 (Fasted)	Mean	1156.73	0.63	16.69	2909.93	3451.09	6.0	0.037
	SD	128.24	0.25-1.25	16.51	480.60	844.74	4.7	0.035
200	Mean	2593.67	0.88	8.91	7688.58	8165.07	21.0	0.039
	SD	727.81	0.50-1.00	4.60	2606.78	3104.47	19.2	0.034
400	Mean	5993.67	0.75	19.84	14868.97	17363.12	33.1	0.037
	SD	1380.01	0.75-1.00	28.04	2924.20	6510.88	29.4	0.031
600	Mean	7248.50	0.75	11.78	20715.60	22388.05	62.8	0.051
	SD	987.87	0.50-1.25	5.34	6115.30	6695.51	40.7	0.034
800	Mean	6301.67	1.25	8.29	23481.27	24456.62	67.6	0.046
	SD	1211.59	0.50-1.50	4.78	3940.42	3778.23	70.3	0.048

* median and range

Multiple Dose PK of avanafil, Formulation I (Study TA-02)

Multiple dose PK of avanafil Formulation I was evaluated in healthy male subjects with 50 mg, 100 mg, and 200 mg doses. The 200 mg dose was given as 2 x 100 mg tablets. In healthy male subjects given avanafil (50, 100, or 200 mg) for 14 days, mean maximum avanafil concentrations (t_{max}) were reached between 0.6 and 0.7 hr. At the proposed dose of 100 mg, AUC_{0-t} and C_{max} is 1.6 µg*hr/mL and 0.9 µg/mL, respectively. Accumulation (R) was calculated based on Day 14 AUC_{0-t}/Day 1 AUC_{0-inf} was minimal and ranged from 1.1 to 1.3 for all three doses.

The following is the plasma concentration versus time profiles for avanafil, Formulation I following 14 days of daily doses (data from Study TA-02 replotted by reviewer).



The following table is a summary of mean (SD) pharmacokinetic parameters of avanafil in plasma following 14 daily doses of avanafil in healthy male subjects (Study TA-02).

Pharmacokinetic Parameters	Plasma TA-1790					
	Treatment A		Treatment B		Treatment C	
	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD
C _{max} (ug/mL)	0.401	0.136	0.892	0.419	2.181	0.636
C _{min} (ug/mL)	0.000	0.000	0.000	0.000	0.000	0.000
T _{max} (hr)	0.583	0.208	0.703	0.245	0.723	0.416
AUC(0-tau)(ug*hr/mL)	0.5758	0.1872	1.635	0.7495	4.113	1.504
T _{1/2} (hr)	1.28	0.737	1.46	0.785	1.34	0.363
K _{el} (1/hr)	0.627	0.175	0.615	0.328	0.554	0.154
CL/F(L/hr)	95.86	34.71	72.38	28.30	58.15	33.92
V _z /F(L)	157.8	93.42	147.2	107.1	105.2	44.92
AI	0.743	0.0882	0.961	0.487	1.04	0.321
R	1.28	0.491	1.09	0.608	1.09	0.331
C _{max} /Dose(ug/mL/mg)	0.008	0.003	0.009	0.004	0.011	0.003
AUC(0-tau)/Dose (ug*hr/mL/mg)	0.01152	0.00374	0.01635	0.00749	0.02057	0.00751
ln(C _{max} /Dose)	-4.871	0.3019	-4.843	0.5607	-4.569	0.3535
ln[AUC(0-tau)/Dose]	-4.512	0.3273	-4.202	0.4369	-3.959	0.4372

Treatment A: avanafil 50 mg QD (1 x 50 mg tablet)

Treatment B: avanafil 100 mg QD (1x 100 mg tablet)

Treatment C: avanafil 200 mg QD (2 x 100 mg tablet)

The avanafil showed biphasic elimination. The sponsor reports a half-life of approximately 1.2-1.5 hrs following single and multiple doses of avanafil in Study TA-02. This half-life was mostly based on the first elimination phase. This was also observed

with the study evaluating the effect of CYP3A4 inhibitors (Study TA-011) on avanafil PK. On the other hand, the sponsor reports a half-life of approximately 5 hrs (range 4.5 to 6.4 hrs) following a single 50 to 200 mg avanafil, which was reported in all other clinical pharmacology studies. This half-life was mostly based on second elimination phase. Therefore, the half-life of approximately 5 hrs is the approximate terminal elimination.

Single Dose PK of avanafil, Formulation II (Study TA-022)

Single dose PK of 200 mg avanafil, Formulation II was characterized in healthy young male subjects. Cmax was reached 0.5 to 0.75 hrs in healthy young men given a single 200 mg dose of avanafil, Formulation II. The arithmetic mean half-life of avanafil ranged from 5.0 to 6.4 hrs.

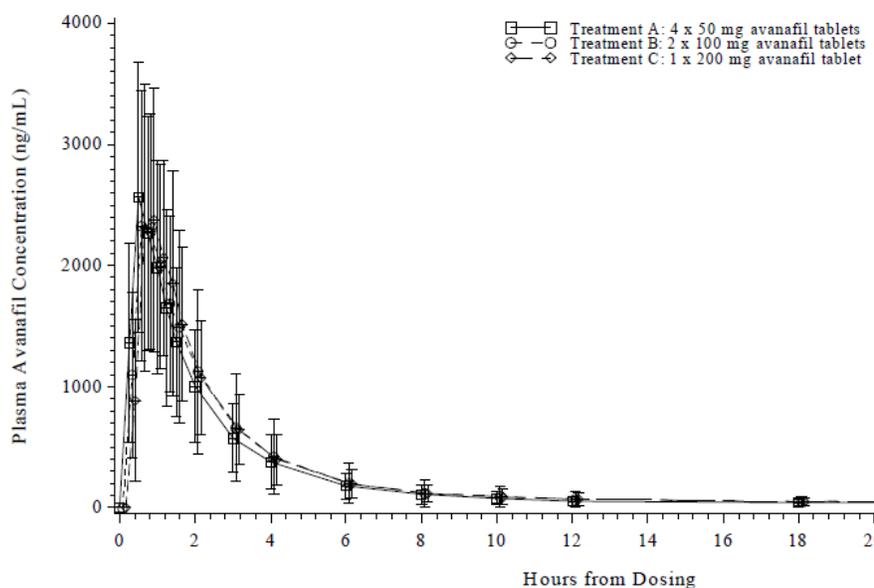
The following table is a summary of PK parameters for avanafil following a single dose 200 mg avanafil, Formulation II, fasted in healthy young male subjects (data from Study TA-022)

PK parameter*	Avanafil Dose		
	4 x 50 mg (N=22)	2 x 100 mg (N=23)	1 x 200 mg (N=22)
AUC0-inf (ng*hr/mL)	6510 (3360)	6990 (4020)	7000 (3050)
AUC0-t (ng*hr/mL)	6000 (2750)	6340 (3440)	6240 (2800)
Cmax (ng/mL)	2660 (1150)	2520 (971)	2620 (61.8)
tmax (hr) ¹	0.5 (0.33, 0.76)	0.5 (0.5, 1.5)	0.75 (0.25, 2.0)
t _{1/2} (hr)	6.4 (3.2)	6.0 (2.9)	5.0 (2.6)
K _{el} (1/hr)	0.16 (0.12)	0.16 (0.10)	0.18 (0.10)

*arithmetic mean (SD)

¹tmax: median and range

The following is the plasma concentration versus time profiles for avanafil, Formulation II following a single 200 mg dose (Study TA-022).



2.2.5.3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to those in patients?

The sponsor did not evaluate PK of avanafil in men with ED. The population evaluated in a PK study that best represents the target population is healthy elderly men. In Study TA-014 the sponsor evaluated the effect of age on the PK of avanafil in a single-center, open-label, non-randomized, two-cohort, single 200 mg dose PK study in healthy young, non-vasectomized (mean age 31.6 years) and healthy elderly subjects (mean age 72.6 years). Subjects were given 1 x 200 mg tablet, Formulation II of avanafil under fasted conditions.

The following table summarizes the PK parameters of avanafil for young and elderly subjects (data from Study TA-014)

PK parameter*	Subjects	
	Young Subjects (N=18)	Elderly Subjects (N=14)
AUC _{0-inf} (ng*hr/mL)	7970 (1960)	8510 (4330)
C _{max} (ng/mL)	2850 (887)	2790 (837)
t _{max} (hr) ¹	0.6 (0.25, 1.0)	0.75 (0.5, 0.8)
t _{1/2} (hr)	6.5 (2.9)	5.6 (3.1)
K _{el} (1/hr)	0.14 (0.10)	0.17 (0.09)

*arithmetic mean (SD)

¹t_{max}: median and range

Mean (SD) C_{max} for avanafil was similar in young and elderly subjects at 2850 (877) ng/mL and 2790 (837), respectively. Mean AUC_{0-inf} for avanafil was 1.07-fold higher in elderly subjects, compared to young subjects.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (renal impairment, hepatic impairment, age, gender, race) influence exposure (PK) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Renal Impairment

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

Mean (SD) AUC_{0-inf} for avanafil was 3.0% and 9.1% lower in subjects with mild renal impairment and moderate renal impairment, respectively, compared to healthy subjects with normal renal function.

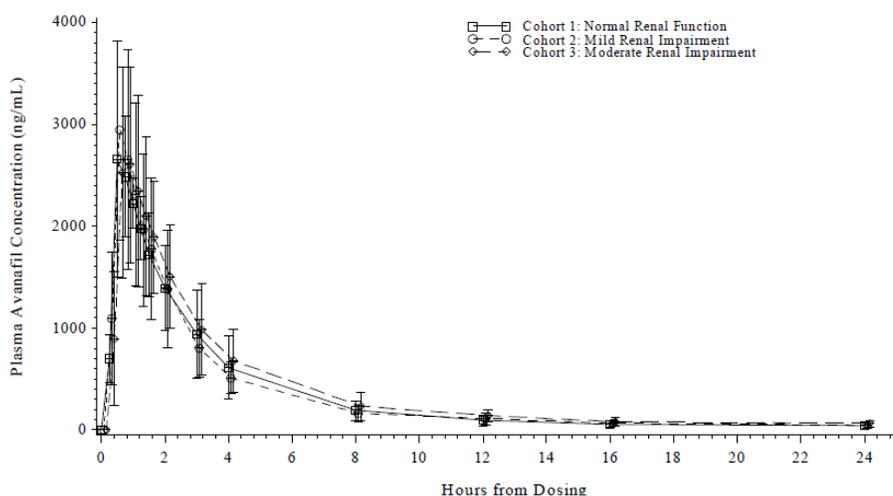
Mean (SD) C_{max} was similar in all three groups: 2870 (1060), 2950 (1090), and 2790 (1010) ng/mL in subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Median t_{max} was similar in all three groups: 0.75, 0.5, and 0.75 hr in subjects with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Mean (SD) t_{1/2} was similar in subjects with normal renal function and mild renal impairment at 6.4 (4.4) and 6.2 (3.0), respectively. However, mean (SD) t_{1/2} was reduced by 1.5 hrs from 6.4 (4.4) to 4.9 (2.2) in subjects with moderate renal impairment, compared to subjects with normal renal function.

Mild and moderate renal impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. AUC_{0-inf} decreased by 3.0% and increased by 9.1% in subjects with mild and moderate renal impairment, respectively. C_{max} increased by 2.8% and decreased by 2.8% in subjects with mild and moderate renal impairment, respectively. In the context of inter-subject variability of approximately 30%, the changes in C_{max} and AUC_{0-inf} of approximately 3-9% are not significant. The sponsor did not evaluate the effect of severe and end stage renal impairment on avanafil PK. No dose adjustment in patients with mild and moderate renal impairment is recommended.

Arithmetic mean (SD) avanafil concentrations vs. time following 200 mg avanafil in subjects with normal renal function, and mild and moderate renal impairment based on CL_{Cr} (Study TA-013).



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-inf} (ng*hr/mL)	8490 (1180)	8240 (2800)	9260 (2920)
C _{max} (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)

¹t_{max}: median and range

Hepatic Impairment

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. The sponsor did not evaluate the effect of severe hepatic impairment on PK of avanafil.

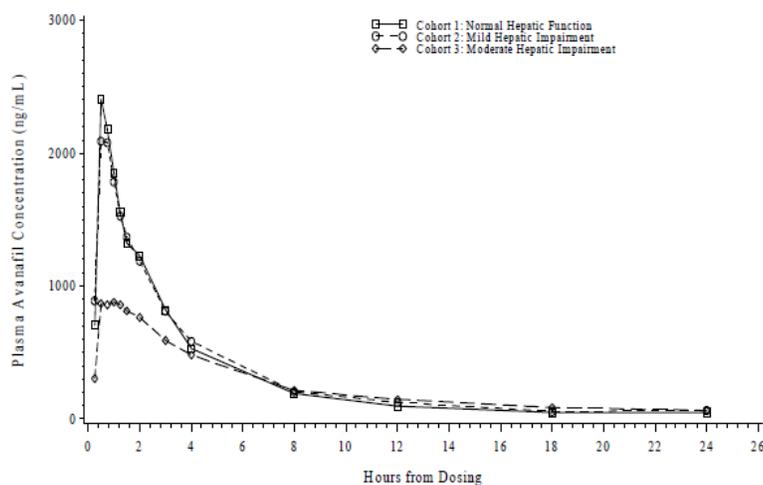
Mild and moderate hepatic impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. Subjects with normal hepatic function and mild hepatic impairment had similar mean C_{max}, AUC_{0-t}, and AUC_{0-inf} for avanafil. In subjects with mild hepatic impairment, mean C_{max}, AUC_{0-t}, and AUC_{0-inf} for avanafil was lower by 2.7%, higher by 7.0%, and higher by 3.8%, respectively. In the context of inter-subject variability of approximately 30%, the change in AUC_{0-inf} of 3.8% and C_{max} of 2.7% in subjects with mild hepatic impairment is not significant.

Maximum concentration was significantly reduced in subjects with moderate hepatic impairment. On the other hand, systemic exposure in subjects with moderate impairment increased by 11.2%; therefore, moderate hepatic impairment does not significantly impact the total exposure of avanafil. The sponsor did not evaluate the effect of severe hepatic impairment on avanafil PK. Clearance increased slightly – 4.0% and 9.0% in subjects with mild and moderate hepatic impairment, compared with subjects with

normal hepatic function. No dose adjustment in patients with mild and moderate hepatic impairment is recommended.

Mild headache was the most common AE. It was reported a total of 12 times by 11 (46%) of all subjects: 5 with normal hepatic function, 3 with mild hepatic impairment, and 3 with moderate hepatic impairment. Despite the reduction of approximately 51% in C_{max} and 11% increase of AUC_{0-inf} in subjects with moderate hepatic impairment compared to normal hepatic function, the number and percent of subjects reporting AEs were similar in all three cohorts. Therefore, the small changes in avanafil PK in subjects with mild and moderate hepatic impairment do not appear to contribute to additional adverse events.

The following is the geometric mean (SD) avanafil concentrations vs. time profile in subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (Study TA-012).



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

PK parameter*	Normal Hepatic Function (N=8)	Mild Hepatic Impairment (N=8)	Moderate Hepatic Impairment (N=8)
AUC _{0-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)

¹t_{max}: median and range

QT Prolongation

The sponsor evaluated the effect of avanafil on QT prolongation in a randomized, double-blind, 4-arm crossover study. Fifty-seven subjects received avanafil 100 mg, avanafil 800 mg, placebo, and moxifloxacin 400 mg (positive control). The least-squares (LS) mean of

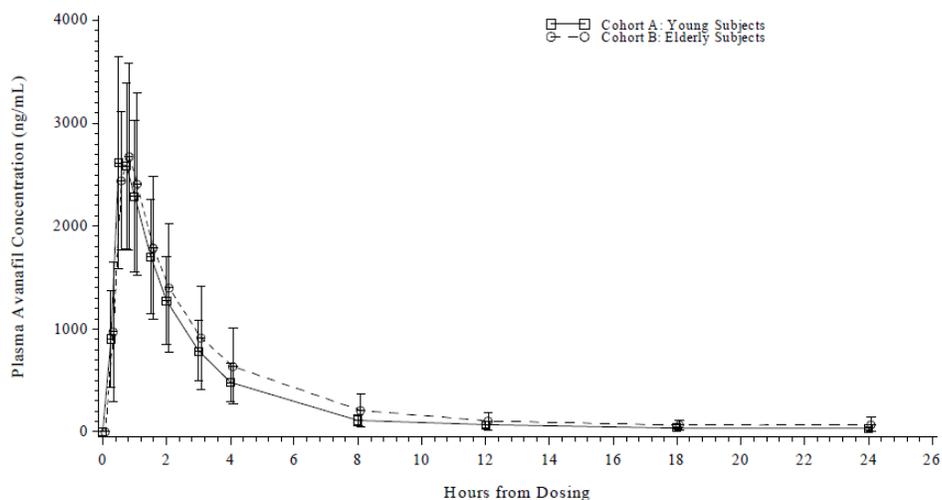
$\Delta\Delta\text{QTcF}$ was 9.4 ms and the 90% CI for $\Delta\Delta\text{QTcF}$ was 7.2 – 11.6 ms. The upper bound of the 90% CI for $\Delta\Delta\text{QTcF}$ exceeded 10 ms (11.6 ms) at one time point for the supratherapeutic dose and therefore failed to exclude a 10 ms increase in QT, the regulatory threshold for regulatory concern.

Interaction with strong CYP3A4 inhibitors such as ketoconazole and ritonavir increased C_{max} by 3.1- and 2.4-fold, respectively, while $\text{AUC}_{0-\text{inf}}$ increased by approximately 13-fold. Renal and hepatic impairment did not significantly increase avanafil concentrations. Supratherapeutic dose of 800 mg avanafil was sufficient to cover the 13-fold increase in avanafil 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. Refer to the QT review by Jeffry Florian for additional information.

Age

The sponsor evaluated the effect of age on the PK of avanafil in a single-center, open-label, non-randomized, two-cohort, single 200 mg dose (1 x 200 mg) PK study in healthy young non-vasectomized (mean age 31.6 years; range 19-43 years) and healthy elderly subjects (mean age 72.6 years; range 65-80 years) (Study TA-014). Subjects were given 1 x 200 mg tablet, Formulation II of avanafil under fasted conditions.

The following figure is the arithmetic mean (SD) plasma **avanafil** concentrations vs. time in young and elderly subjects (Study TA-014).



The following table summarizes the PK parameters of avanafil for young and elderly subjects (data from Study TA-014).

PK parameter*	Young Subjects (N=18)	Elderly Subjects (N=14)
$\text{AUC}_{0-\text{inf}}$ (ng*hr/mL)	7970 (1960)	8510 (4330)
C_{max} (ng/mL)	2850 (887)	2790 (837)
t_{max} (hr) ¹	0.6 (0.25, 1.0)	0.75 (0.5, 0.8)
$t_{1/2}$ (hr)	6.5 (2.9)	5.6 (3.1)
K_{el} (1/hr)	0.14 (0.10)	0.17 (0.09)

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

Mean (SD) C_{max} for avanafil was similar in young and elderly subjects at 2850 (877) ng/mL and 2790 (837), respectively. Mean AUC_{0-inf} for avanafil was 1.07-fold higher in elderly subjects, compared to young subjects.

The geometric LS mean ratio for C_{max}, AUC_{0-t}, and AUC_{0-inf} between elderly and young subjects was 100, 112, and 98%, respectively. The 90% CIs of the mean ratios were 77.5% to 145.5%. The overall differences observed between the elderly and young subjects are not significantly different given the variability observed between subjects.

Headache was the only adverse event reported by > 10% of the subjects in this study, which was reported by 6 of 32 (19%) subjects (4 young subjects and 2 elderly subjects). Other adverse events due to avanafil include dizziness, fatigue, and myalgia, but were reported less frequently. Overall, there is no difference in the incidence or frequency of adverse events related to avanafil between young and elderly subjects.

Race

The majority of subjects in the Phase I clinical pharmacology studies were Caucasian. The sponsor did not evaluate the effect of race on avanafil PK.

2.4 Extrinsic Factors

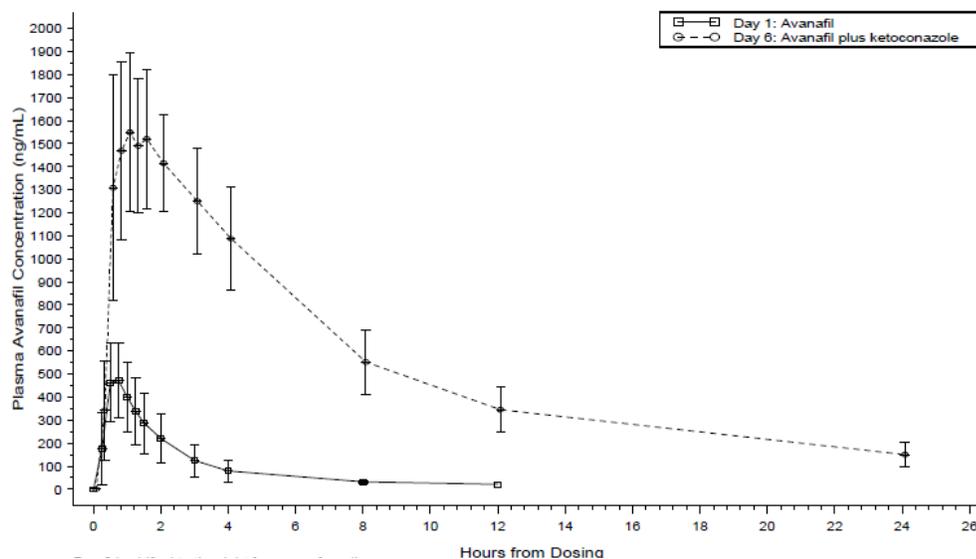
2.4.1 What extrinsic factors (CYP3A4 inhibitors and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Effect of ketoconazole (a strong CYP3A4 inhibitor)

The sponsor evaluated the influence of multiple doses of the potent CYP3A4 inhibitor ketoconazole on the PK of avanafil (Study TA-011). This study was an open-label, randomized, one sequence, three-way parallel study in healthy male subjects. A single 50 mg dose of avanafil was administered with 240 mL of water after ketoconazole 400 mg was given once daily for 5 days.

Mean AUC_{0-inf} and C_{max} of avanafil increased 12.8-fold and 3.1-fold, respectively, when avanafil was co-administered with ketoconazole, compared to avanafil alone. Median t_{max} increased by 0.5 hr from 0.5 to 1.0 hr.

The following figure is the arithmetic mean (SD) plasma avanafil concentrations vs. time profile on Day 1 following 50 mg avanafil and Day 6 following 50 mg avanafil and ketoconazole (Study TA-011).



The following table summarizes the PK parameters of avanafil for subject given 50 mg avanafil and 50 mg avanafil + 400 mg ketoconazole (data from Study TA-011).

PK parameter*	Avanafil (N=15)	Avanafil + Ketoconazole (N=14)
AUC _{0-inf} (ng*hr/mL)	1130 (450)	14500 (2880)
C _{max} (ng/mL)	535 (164)	1660 (328)
t _{max} (hr) ¹	0.5 (0.25, 1.5)	1.0 (0.5, 2.0)
t _{1/2} (hr)	1.8 (1.2)	8.5 (1.3)

*arithmetic mean (SD)

¹t_{max}: median and range

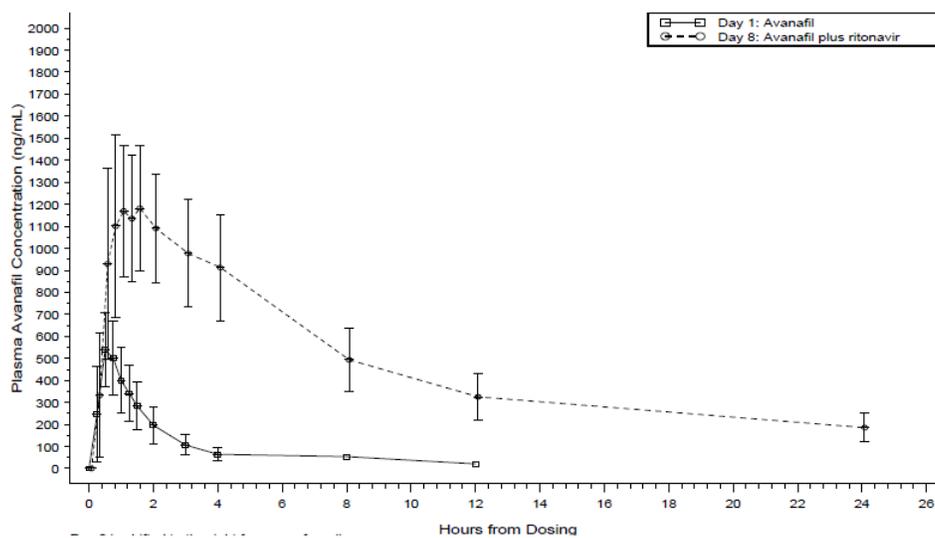
The recommended dose in adults of ketoconazole is a single administration of 200 mg and may be increased to 400 mg once daily. The sponsor anticipated the highest clinical dose of avanafil to be 200 mg; however, the avanafil dose administered in this study was 50 mg. The lower dose selected for this study allowed for a safety margin in the event of a substantial increase in avanafil exposure due to co-administration with a strong CYP3A4 inhibitor. The study design and dose selections for this completed study are acceptable.

Effect of ritonavir (a strong CYP3A4 inhibitor)

The sponsor evaluated the influence of multiple doses of the potent CYP3A4 inhibitor ritonavir on the PK of avanafil (Study TA-011). This study was an open-label, randomized, one sequence, three-way parallel study in healthy male subjects. Ritonavir 300 mg was given twice daily (BID) for 1 day (Day 2), 400 mg BID for 1 day (Day 3), 600 mg BID for 5 days (Days 4-8) and a single 50 mg dose of avanafil on Days 1 & 8.

Mean AUC_{0-inf} and C_{max} of avanafil increased 12.8-fold and 2.4-fold, respectively, when avanafil was co-administered with ritonavir, compared to avanafil alone. Median t_{max} increased by 1.0 hr from 0.5 to 1.5 hrs.

The following figure is the arithmetic mean (SD) plasma avanafil concentrations vs. time profile on Day 1 following 50 mg avanafil and Day 8 following 50 mg avanafil and ritonavir (Study TA-011).



The following table summarizes the PK parameters of avanafil for subject given 50 mg avanafil and 50 mg avanafil + 300 mg ritonavir ((data from Study TA-011).

PK parameter*	Avanafil (N=14)	Avanafil + Ritonavir (N=13)
AUC _{0-inf} (ng*hr/mL)	1050 (434)	13200 (2740)
C _{max} (ng/mL)	568 (165)	1360 (253)
t _{max} (hr) ¹	0.5 (0.25, 0.75)	1.5 (0.5, 3.0)
t _{1/2} (hr)	1.4 (0.53)	8.8 (1.7)

*arithmetic mean (SD)

¹t_{max}: median and range

The sponsor reports an increase in avanafil half-life from 1.8 to 8.5 and from 1.4 to 8.8 hrs following administration of ketoconazole and ritonavir, respectively. This increase in half-life is reported by the sponsor due to a low estimation of half-life for avanafil alone. The estimation of half-life was based on the first elimination phase and, in the study with CYP3A4 inhibitors, was likely due to a deficiency in time points between 12 and 24 hrs. With the exception of the CYP3A4 inhibition study TA-011 and SD/MD PK study TA-02, all other clinical pharmacology studies report an elimination half-life of approximately 5 hrs (range 4.5 to 6.4 hrs) following a single 50 to 200 mg avanafil. Therefore, half-life of avanafil is estimated to increase approximately by 3-4 hrs with administration of a strong CYP3A4 inhibitor.

The recommended dosage in adults of ritonavir is 600 mg twice daily. Treatment-emergent adverse events from ritonavir administration can be reduced with a dose titration scheme such as a starting dose of no less than 300 mg twice daily and increased at 2 to 3 day intervals by 100 mg twice daily. Ritonavir is a mechanism-based CYP3A4 inhibitor. The dose and dosing regimen of ritonavir in this completed drug interaction study is optimized to minimize treatment-emergent adverse events resulting from ritonavir and to achieve a maximum *in vivo* irreversible inhibitory effect of CYP3A4. The

sponsor anticipated the highest clinical dose of avanafil to be 200 mg; however, the avanafil dose administered in this study was 50 mg. The lower dose selected for this study allowed for a safety margin in the event of a substantial increase in avanafil exposure due to co-administration with a strong CYP3A4 inhibitor. The study design and dose selections for this completed study are acceptable.

Concomitant administration of avanafil and a strong CYP3A4 inhibitor increased avanafil exposure by approximately 13-fold. With linear PK, a 50 mg avanafil dose would be equivalent to approximately 650 mg when given with a strong CYP3A4 inhibitor. The maximum dose evaluated in Phase III studies is 200 mg; it is also the highest recommended dose. Therefore, an adjustment in avanafil dose is needed for patients taking a strong CYP3A4 inhibitor. The dose should be reduced to address the 13-fold increase in AUC. Increasing the dosing interval from 24 to 48 hrs can address the increase in half-life and ensure that 4-5 half-lives have elapsed between doses. Assuming the highest approvable dose will be 200 mg, a dose of approximately 15 mg would account for the 13-fold increase in exposure. Considering the inter-subject variability of approximately 30%, non-life threatening adverse event profile, as needed dosing regimen, and manufacturing of another dose strength, an avanafil dose of “no more than 25 mg once every 48 hrs as needed” is recommended for patients taking avanafil with a strong CYP3A4 inhibitor, although it would achieve approximately 63% higher exposure compared to the exposure from 200 mg avanafil alone.

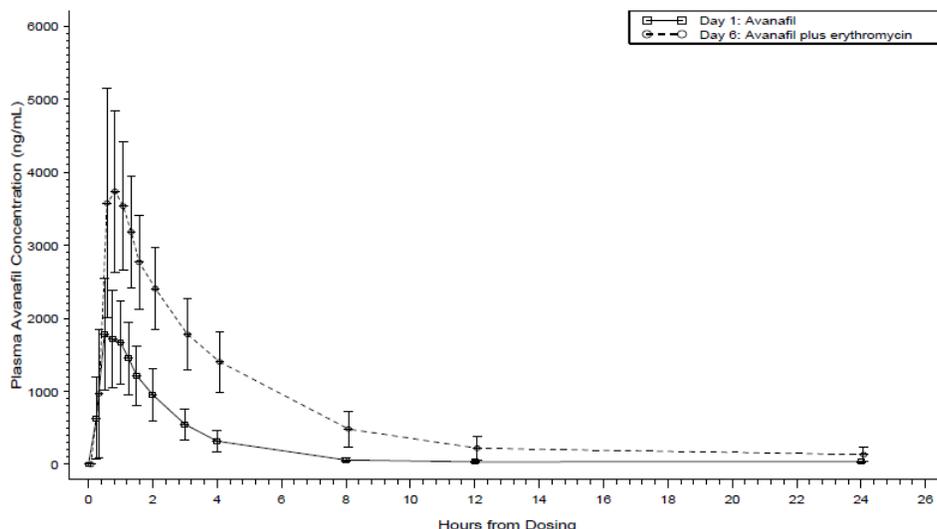
Effect of erythromycin (a moderate CYP3A4 inhibitor)

The sponsor evaluated the influence of multiple doses of the potent CYP3A4 inhibitor ritonavir on the PK of avanafil (Study TA-011). This study was an open-label, randomized, one sequence, three-way parallel study in healthy male subjects. Erythromycin 500 mg was given every 12 hrs for 5 days followed by a single 200 mg dose of avanafil on Days 1 & 6.

Mean AUC_{0-inf} and C_{max} of avanafil increased 3.6-fold and 2-fold, respectively, when avanafil was co-administered with erythromycin, compared to avanafil alone.

Median t_{max} increased by 0.25 hr from 0.5 to 0.75 hr. The sponsor reports an increase in avanafil half-life from 2.4 to 8.1 hrs following administration of erythromycin. This increase in half-life is reported by the sponsor due to a low estimation of half-life for avanafil alone. The estimation of half-life was based on the first elimination phase and, in the study with CYP3A4 inhibitors, was likely due to a deficiency in time points between 12 and 24 hrs. With the exception of the CYP3A4 inhibition study TA-011 and SD/MD PK study TA-02, all other clinical pharmacology studies report an elimination half-life of approximately 5 hrs (range 4.5 to 6.4 hrs) following a single 50 to 200 mg avanafil. Therefore, half-life of avanafil is estimated to increase by approximately 3 hrs with administration of a moderate CYP3A4 inhibitor.

The following figure is the arithmetic mean (SD) plasma avanafil concentrations vs. time profile on Day 1 following 200 mg avanafil and Day 6 following 200 mg avanafil and erythromycin (Study TA-011).



The following table summarizes the PK parameters of avanafil for subject given 200 mg avanafil and 200 mg avanafil + 500 mg erythromycin ((data from Study TA-011).

PK parameter*	Avanafil (N=15)	Avanafil + Erythromycin (N=14)
AUC _{0-inf} (ng*hr/mL)	5120 (1010)	18300 (7430)
C _{max} (ng/mL)	2030 (678)	4230 (1300)
t _{max} (hr) ¹	0.5 (0.5, 1.5)	0.75 (0.5, 1.2)
t _{1/2} (hr)	2.4 (0.4)	8.1 (1.6)

*arithmetic mean (SD)

¹t_{max}: median and range

The sponsor did not evaluate the effect of a mild CYP3A4 inhibitor on avanafil PK. The usual dose of erythromycin in adults is 250 mg four times daily. If twice daily dosage is desired, the recommended dose is 500 mg every 12 hours. Due to the short half-life of 1.5 hrs and as a mechanism-based CYP3A4 inhibitor, erythromycin given over multiple days allows for a maximum in vivo irreversible inhibitory effect of CYP3A4. Therefore, the erythromycin dose and dosing regimen as evaluated by the sponsor is appropriate and optimizes the potential for a drug-drug interaction between avanafil and erythromycin. The sponsor anticipated the highest clinical dose of avanafil to be 200 mg and therefore selected 200 mg dose for this study. The study design and dose selections for this completed study are acceptable.

Patients who take a moderate CYP3A4 inhibitor and avanafil are susceptible to higher systemic concentrations of avanafil. In the scenario evaluated, the 200 mg dose would be equivalent to approximately 720 mg. Assuming the highest approvable dose will be 200 mg, a reduced avanafil dose of approximately 56 mg would account for the 3.6-fold increase in exposure in the presence of a moderate CYP3A4 inhibitor. An avanafil dose of 50 mg once every 24 hrs as needed is recommended for patients taking avanafil with a moderate CYP3A4 inhibitor.

Headache was the most frequent adverse event in subjects given avanafil and a strong or moderate CYP3A4 inhibitor and appeared to double in frequency compared to avanafil

200 mg alone. The total frequency of headache was 57% in all three treatment groups and was similar among the different groups. The total frequency of headache in subjects administered with 200 mg avanafil alone as either 4 x 50 mg, 2 x 200 mg, or 1 x 200 mg (Study TA-022) was 30%.

Effect of alcohol

The sponsor evaluated the pharmacodynamic effects of concomitant administration of 200 mg avanafil and alcohol in a single center, double-blind, randomized, placebo-controlled, three-period, three-way crossover study in young male subjects (Study TA-015).

When comparing avanafil + alcohol and placebo + alcohol, there was no statistically significant effect on the maximum mean supine SBP and systolic AUEC_{0-t}. However, despite the lack of statistical difference between the two treatment groups, there was a significant decrease in the SBP of 3.53 mmHg and systolic AUEC_{0-t} of 12.48 mmHg*hr in subjects given avanafil + alcohol, compared to placebo + alcohol. There were statistically significant changes in the maximum decrease of 4.54 mmHg in DBP and 16.32 mmHg*hr in diastolic AUEC_{0-t}. This trend was also observed with pulse rate - a statistically significant changes in the maximum increase in pulse rate of 9.3 bpm and pulse rate AUEC_{0-t} of 25.07 bpm*hr. Overall, there was an additive hypotensive effect from avanafil treatment with a decrease SBP/DBP of 3.53/4.54 mmHg. (b) (4)

This reviewer disagrees with the proposed labeling based on the available data indicating a decrease in both systolic and diastolic blood pressure and recommends labeling the findings (a decrease SBP/DBP of 3.53/4.54 mmHg) from this alcohol study.

Headache occurred with the same frequency (14%) in subjects given avanafil + alcohol and avanafil + placebo drink, and occurred less frequently (7%) in subjects given placebo + alcohol.

2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Based on *in vitro* study, 10-avanafil-pk-17 using human hepatocytes, the sponsor found that avanafil inhibited CYP2C19, CYP2C8, and CYP2D6 with a Ki of 2.9, 15.2, and 43.9 μ M, respectively. The sponsor indicated that the mean maximum plasma concentration of 200 mg avanafil was about 5.2 μ M, thereby resulting in C_{max}/Ki ratios greater than >0.1.

Avanafil is not a P-gp substrate based upon *in vitro* study 10-avanafil-pgp-01 where the net efflux ratio (RE_(MDR1)/RE_(wt)) was 1.8 and is thus considered negative and does not signal a need for an *in vivo* study. OCP's drug interaction guidance states a net efflux ratio over 2 is considered positive and recommends an *in vivo* study with one or more potent P-gp inhibitors. The net efflux ratio (RE_(MDR1)/RE_(wt)) for digoxin alone and digoxin + avanafil were the same at 9.9 and 9.9, respectively, which indicates avanafil is not a P-gp inhibitor.

2.4.2.2 Is the drug an inhibitor of CYP enzymes?

Data from *in vitro* study, 10-avanafil-pk-22 showed that at 50 μ M avanafil concentration (12 times the 200 mg dose), there was a 6.2% induction of CYP3A4 compared to the

positive control 25 µM rifampicin. This effect observed at high avanafil concentration is insignificant; therefore, no in vivo study to evaluate CYP3A4 induction by avanafil was conducted by the sponsor.

The sponsor has shown in vitro that avanafil moderately inhibits CYP2C19, CYP2C8, and CYP2D6 with Ki values of 2.9, 15.2, and 43.9 µM, respectively. Therefore, the sponsor decided to conduct clinical studies (Study TA-018) to evaluate the effect of a single 200 mg dose of avanafil on the PK of omeprazole (a CYP2C19 substrate), rosiglitazone (a CYP2C8 substrate), and desipramine (a CYP2D6 substrate) in vivo.

Is avanafil a CYP2C19 inhibitor: effect on omeprazole?

Twenty healthy male subjects were administered a single oral dose of 40 mg omeprazole delayed-release capsule once daily for 8 days (Days 1 - 8) then a single oral dose of 200 mg avanafil on Day 8. Subjects were randomized to one of the following treatment groups following an overnight fast of at least 10 hrs:

- Once daily 40 mg oral dose of omeprazole for 7 days (Days 1 - 7)
- Once daily 40 mg oral doses of omeprazole for 8 days plus 200 mg avanafil (Day 8)

Mean AUC_{0-t} and C_{max} of omeprazole increased 1.06-fold and 1.09-fold, respectively, following omeprazole and avanafil co-administration, compared to omeprazole alone.

Median t_{max} of omeprazole remained unchanged at 2.0 hrs. Mean t_{1/2} of omeprazole increased by 0.1 hr from 1.8 to 1.9 hrs following omeprazole and avanafil co-administration, compared to omeprazole alone.

The following table summarizes the PK parameters of omeprazole for subject given omeprazole and omeprazole + avanafil ((data from Study TA-018).

PK parameter*	Omeprazole (N=19)	Omeprazole + Avanafil (N=19)
AUC _{0-t} (ng*hr/mL)	5380 (3290)	5700 (2970)
C _{max} (ng/mL)	1520 (773)	1650 (572)
t _{max} (hr) ¹	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)
t _{1/2} (hr)	1.8 (0.7)	1.9 (0.7)

*arithmetic mean (SD)

¹t_{max}: median and range

Omeprazole is a proton pump inhibitor approved for the treatment of duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease in adults. The recommended starting dose ranges from 20 to 60 mg daily in adults.

Is avanafil a CYP2C8 inhibitor: effect on rosiglitazone?

Twenty healthy male subjects administered a single dose of 8 mg rosiglitazone tablet then a single oral dose of 200 mg avanafil or rosiglitazone alone. The two treatments in this cohort were separated by a washout period of at least 7 days. Subjects were randomized to one of the following treatment groups following an overnight fast of at least 10 hrs:

- A single oral dose of 8 mg rosiglitazone
- A single oral dose of 8 mg rosiglitazone plus a single oral dose of 200 mg avanafil

Mean AUC_{0-inf} of rosiglitazone increased 1.02-fold from 3040 to 3010 ng.hr/mL following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

Mean Cmax of rosiglitazone decreased 14% from 648 to 560 ng/mL following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

Median tmax of rosiglitazone increased 0.25 hr from 0.75 to 1.0 hr. Mean t_{1/2} of rosiglitazone decreased by 0.1 hr from 4.0 to 3.9 hrs following rosiglitazone and avanafil co-administration, compared to rosiglitazone alone.

The following table summarizes the PK parameters of rosiglitazone for subject given rosiglitazone and rosiglitazone + avanafil ((data from Study TA-018)

PK parameter*	Rosiglitazone (N=19)	Rosiglitazone + Avanafil (N=20)
AUC _{0-inf} (ng*hr/mL)	3040 (647)	3100 (691)
Cmax (ng/mL)	648 (181)	560 (167)
tmax (hr) ¹	0.75 (0.5, 4.0)	1.0 (0.5, 4.0)
t _{1/2} (hr)	4.0 (0.75)	3.9 (0.8)

*arithmetic mean (SD)

¹tmax: median and range

Rosiglitazone is a thiazolidinedione antidiabetic agent used to improve glycemic control in adults with type 2 diabetes mellitus. The recommended starting dose is 4 mg daily in divided doses or as a single dose and may increase to 8 mg daily in patients not responding adequately in the initial treatment phase. The adverse events associated with rosiglitazone therapy include cardiac failure and cardiovascular events such as myocardial infarction and cardiovascular death. A study design that includes a single dose of the substrate drug and inhibitor allows for assessment of the most significant changes in rosiglitazone exposure. Though 8 mg rosiglitazone is clinically relevant, a lower dose of 4 mg would be suitable for this study. The sponsor anticipated the highest clinical dose of avanafil to be 200 mg and therefore selected 200 mg dose for this study. The study design and dose selections for this completed study are acceptable.

Is avanafil a CYP2D6 inhibitor: effect on desipramine?

Twenty healthy male subjects were administered a single oral dose of 50 mg desipramine tablet then a single oral dose of 200 mg avanafil or desipramine alone. The avanafil dose was administered 2 hrs after the desipramine administration. The two treatments in this cohort were separated by a washout period of at least 10 days. Subjects were randomized to one of the following treatment groups following an overnight fast of at least 10 hrs:

- A single oral dose of 50 mg desipramine
- A single oral dose of 50 mg desipramine plus a single oral dose of 200 mg avanafil

Mean AUC_{0-inf} and Cmax of desipramine increased 1.06-fold and 1.05-fold, respectively, following desipramine and avanafil co-administration, compared to desipramine alone.

Median tmax of desipramine was unchanged at 6.0 hrs following desipramine and avanafil co-administration and desipramine alone. Mean t_{1/2} of desipramine was unchanged at 14 hrs following desipramine and avanafil co-administration and desipramine alone.

The following table summarizes the PK parameters of desipramine for subject given desipramine and desipramine + avanafil (data from Study TA-018).

PK parameter*	Desipramine (N=19)	Desipramine + Avanafil (N=20)
AUC _{0-inf} (ng*hr/mL)	472 (185)	499 (188)
C _{max} (ng/mL)	19.0 (5.2)	20.0 (6.0)
t _{max} (hr) ¹	6.0 (6.0, 8.0)	6.0 (6.0, 8.0)
t _{1/2} (hr)	14 (3.0)	14 (2.8)

*arithmetic mean (SD)

¹t_{max}: median and range

Desipramine is a tricyclic antidepressant approved for the treatment of depression. The recommended initial dose for adults is 100 to 200 mg per day in divided doses or as a single dose. The recommended initial dose for adolescents and geriatrics is 25 to 100 mg per day in divided doses or as a single dose. Desipramine has cardiovascular, psychiatric, neurological effects such as hypotension, hypertension, hallucinations, numbness, etc. Using a low dose of desipramine such as 50 mg for this drug interaction study provides a margin of safety in the event avanafil inhibits CYP2D6 and results in high systemic concentrations of desipramine. A study design that includes a single dose of the substrate drug and inhibitor allows for assessment of the most significant changes in desipramine exposure. The sponsor anticipated the highest clinical dose of avanafil to be 200 mg and therefore selected 200 mg dose for this study. The study design and dose selections for this completed study are acceptable.

Overall, in vivo results from this PK study showed that avanafil is not an inhibitor of CYP2C19, CYP2C8, and CYP2D6 enzymes. The potential of a single 200 mg dose of avanafil to affect multiple doses of omeprazole, a single dose rosiglitazone or a single dose of desipramine is unlikely. The magnitude of a drug-drug interaction between avanafil and CYP2C19, CYP2C8, and CYP2D6 substrates is unknown in chronic users of avanafil and these CYP substrates.

2.4.2.3. What other co-medications are likely to be administered to the target population?

The target population for avanafil is men with ED who are likely to be middle age and older and prone to having hypertension and benign prostatic hyperplasia (BPH). Medications commonly used to treat hypertension and BPH include nitrates (i.e. glyceryl trinitrate), alpha-adrenergic blockers (i.e. doxazosin and tamsulosin) and angiotensin converting enzyme inhibitors (i.e. enalapril) and calcium channel blockers (i.e. amlodipine). Use of warfarin to regulate the coagulation pathway may be a concern in the ED target population. As such, the sponsor evaluated the effect of avanafil co-administration with the above mentioned drugs as determined by hemodynamic responses and various coagulation parameters.

Glyceryl trinitrate

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, 1, 4, 8, and 12 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.

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 sitting SBP 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 standing SBP were 24.1, 24.8, and 22.7 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The difference between treatment groups and placebo are not statistically different.

The mean maximum decreases from predose to postdose in sitting SDP were 16.7, 17.4, and 14.3 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. The mean maximum decreases from predose to postdose in standing SDP were 21.5, 20.3, and 17.5 mmHg in subjects given avanafil, sildenafil, and placebo, followed by glyceryl trinitrate 0.5 hr later. Only the change in standing DBP with avanafil + glyceryl trinitrate co-administration was statistically different from placebo + glyceryl trinitrate.

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. Only the change in standing pulse rate with sildenafil + glyceryl trinitrate co-administration was statistically different from placebo + glyceryl trinitrate.

Before administration of glyceryl trinitrate, few subjects exhibited decreases in blood pressure. With the administration of glyceryl trinitrate, the number of subjects with symptomatic hypotension increased in subjects who received avanafil, compared to placebo, and was not different from subjects given sildenafil. There was no difference between treatment groups based on the time of administration of avanafil, sildenafil or placebo and glyceryl trinitrate. Overall, the potentiation of hypotension is a concern in patients requiring sublingual glyceryl trinitrate and taking avanafil; therefore, this reviewer recommends avanafil 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 recommends including the corresponding data to convey the decrease in sitting and standing SBP/DBP after administration of avanafil and glyceryl trinitrate separated by 30 min.

Doxazosin and Tamsulosin

The sponsor evaluated the hemodynamic interactions between avanafil and two α -adrenergic blockers, doxazosin and tamsulosin, in middle-aged healthy male subjects in a single center, randomized, double-blind, placebo-controlled, two-way crossover study (Study TA-017).

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 half-life 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 a 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. 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.

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. 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 PD interaction is shown; therefore, the initial dose of 4 mg is preferred over the maximum dose of 8 mg. The design of the 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. Subjects enrolled in this study had a mean age of 46.5 yrs (range 40-61 yrs), which appears to be low and the applicability of these findings may not be relevant to an older ED population with hypertension and BPH. The effect on blood pressure and heart rate can be more significant with frequent use of alpha blockers and avanafil, and in an older ED population.

❖ doxazosin + avanafil

Statistically significant differences were observed in the maximum decrease from baseline in the supine SBP. Maximum decrease in supine SBP was 6.0 mmHg. There was no statistically significant difference in the $AUEC_{0-12}$ for supine SBP between subjects who received avanafil or placebo.

Statistically significant differences were observed in the maximum decrease from baseline in the supine DBP and in the $AUEC_{0-12}$ for supine DBP between subjects who received avanafil or placebo. The maximum decrease in supine DBP and $AUEC_{0-12}$ were 3.6 mmHg and 31.4 mmHg*hr, respectively.

Statistically significant differences were not observed in the maximum decrease from baseline in the supine pulse rate between subjects who received avanafil or placebo. There was a statistically significant increase in the $AUEC_{0-12}$ for supine pulse rate of 45.8 bpm*hr.

The maximum increase in supine pulse rate and $AUEC_{0-12}$ were 7.2 bpm and 44.5 bpm*hr, respectively.

❖ tamsulosin + avanafil

Statistically significant differences were not observed in the maximum decrease from baseline in the supine SBP, the $AUEC_{0-12}$ for supine SBP, or $AUEC_{0-12}$ for supine DBP between subjects who received avanafil or placebo.

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.

Statistically significant differences were observed in the maximum decrease from baseline in the supine pulse rate and AUEC₀₋₁₂ of 4.7 bpm and 40.76 8 bpm*hr, respectively.

Enalapril and Amlodipine

The sponsor evaluated the hemodynamic interactions between avanafil and two anti-hypertensive drugs (enalapril maleate (an ACE inhibitor) and amlodipine (a calcium channel blocker)) in healthy middle-age men in a single center, randomized, double-blind, placebo-controlled, two-way crossover study (Study TA-019).

❖ enalapril + avanafil

A single 200 mg dose of avanafil given to subjects who received 10 mg doses of enalapril twice daily for 11 days had a minor effect on BP and pulse rate. 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.

❖ amlodipine + avanafil

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 and DBP decreased by 1.6 mmHg and 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.

- Amlodipine PK: Mean C_{max} of amlodipine decreased 8.9%, compared to placebo + amlodipine. Mean AUC_{0-t} of amlodipine decreased 3.8%, compared to placebo + amlodipine. Median t_{max} of amlodipine remained unchanged at 8 hrs with a single dose of avanafil + multiple doses of amlodipine and placebo + amlodipine co-administration.
- Avanafil PK: Mean C_{max} and AUC_{0-inf} of avanafil increased 22% and 70%, respectively, compared to avanafil alone. Median t_{max} and mean t_{1/2} of avanafil increased by 0.12 hr from 0.63 to 0.75 hr and by 2.9 hr from 7.0 to 9.9 hrs, respectively, with a single dose of avanafil + multiple doses of amlodipine, compared to avanafil alone.

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. It

appears that increases in C_{max} and AUC_{0-inf} of avanafil of 22% and 70%, respectively, from co-administration with amlodipine did not result in a corresponding increase in adverse events.

Enalapril is an angiotension converting enzyme and is converted to enalaprilat, which is a more potent ACE inhibitor than enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours. The study design incorporating multiple doses of enalapril over 11 days will provide more than 3 half-lives needed to reach steady-state concentrations that would be reflective of patients on enalapril therapy. The usual enalapril dosage range is 10 to 40 per day administered in a single dose or two divided doses. The study design and dose selection for this study is acceptable and reflects the clinical doses and regimen.

Amlodipine is a calcium channel blocker. The recommended initial dose of amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly patients, or patients with hepatic insufficiency impairment may be started on 2.5 mg once daily with this dose of amlodipine added to other antihypertensive therapy. Due to the long terminal elimination half-life of about 30–50 hours, steady-state plasma concentrations of amlodipine are reached after 7 to 8 days of consecutive daily dosing; therefore the study design incorporating 18 days of amlodipine dosing at 5 mg allows for assessment of avanafil interaction with chronic use of amlodipine.

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). With an increase in maximum concentration and exposure of avanafil of 22% and 70%, respectively, reducing the starting avanafil dose from 100 mg to 50 mg in patients stabilized on an alpha-blocker is a conservative adjustment. This reviewer concurs with the proposal. This reviewer also recommends adding in the label the mean maximum change in standing SBP/DBP following antihypertensive or alpha-blocker therapy with avanafil administration to convey the numerical changes in blood pressure.

The following table summarizes the hemodynamic changes (maximum decreases in BP and maximum increases in pulse rate) from 200 mg avanafil co-administered with commonly used drugs (Studies TA-04, TA-015, TA-017 and TA-019).

	Standing SBP/DBP (mmHg)	Supine SBP/DBP (mmHg)	Standing Pulse Rate (bpm)	Supine Pulse Rate (bpm)
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*
Alcohol + Avanafil	na	14.5/14.6	na	19.3
Alcohol	na	10.9/9.6	na	10.2
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
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

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

Warfarin

The sponsor evaluated the effect of avanafil on the PK and PD of warfarin in healthy young male subjects in a single-center, double-blind, randomized, placebo-controlled, two-way crossover study (Study TA-016). PD was measured as PT, INR, and platelet aggregation.

Multiple doses of avanafil (200 mg daily x 9 days) had essentially no effect on the PK of a single 25 mg dose of warfarin; the PK parameters of R-warfarin and S-warfarin were similar in both treatment groups. Multiple doses of avanafil had essentially no effect on the PD of a single dose of warfarin as determined by INR, PT, and platelet aggregation; the % mean ratios were all approximately 100% (range 96% to 110%) between subjects administered with warfarin + avanafil and warfarin+ placebo.

The following table summarizes the effect of multiple doses avanafil on a single dose of warfarin PD (Study TA-016).

PD parameters	Warfarin + Avanafil (N=23)	Warfarin + Placebo (N=24)
PT (sec), mean max (SD)	23.1 (3.3)	23 (5.6)
INR, mean (SD)	2.2 (0.5)	2.2 (0.5)
Platelet aggregation (%), SD)	75.5 (9.2)	75.5 (7.4)

❖ R-warfarin PK

Following warfarin + placebo administration, mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of R-warfarin were 1870 (252) ng/mL, 100,000 (18,600) ng*hr/mL, and 120 (19.8) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} were 1.0 (0.5, 4.0) hr and 50 (7.7) hr, respectively.

Following warfarin + avanafil administration, mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of R-warfarin were 1840 (283) ng/mL, 101,000 (16,300) ng*hr/mL, and 119 (21.3) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} were 1.5 (0.5, 2.0) hr and 51 (6.8) hr, respectively.

❖ S-warfarin PK

Following warfarin + placebo administration, mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of S-warfarin were 1940 (322) ng/mL, 57,400 (8960) ng*hr/mL, and 208 (35.5) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} were 1.0 (0.5, 2.0) hr and 33 (4.3) hr, respectively.

Following warfarin + avanafil administration, mean (SD) C_{max}, AUC_{0-inf}, and Cl/F of S-warfarin were 1840 (312) ng/mL, 58,300 (9850) ng*hr/mL, and 206 (38.8) mL/hr, respectively. Median (range) t_{max} and mean (SD) t_{1/2} were 1.5 (0.5, 2.0) hr and 34 (4.3) hr, respectively.

The elimination rate constant and clearance of R-warfarin was approximately one-half (0.67 and 0.58, respectively) of S-warfarin. Whereas, half-life and exposure of R-warfarin was approximately slightly less than 2-fold higher (1.5 and 1.7 fold, respectively) than S-warfarin.

The following table summarizes the effect of multiple doses avanafil on a single dose of warfarin PK (Study TA-016).

PK parameter of R-warfarin*	Warfarin + Avanafil (N=23)	Warfarin + Placebo (N=24)	% mean ratio (warfarin + avanafil/warfarin + placebo)
AUC _{0-inf} (ng*hr/mL)	101000 (16300)	100000 (18600)	100.7
C _{max} (ng/mL)	1840 (283)	1870 (252)	98.9
t _{max} (hr) ¹	1.5 (0.5, 1.5)	1.0 (0.5, 4.0)	
t _{1/2} (hr)	51 (6.8)	50 (7.7)	

*arithmetic mean (SD)
¹ median, range

The sponsor proposes to include a statement in the label indicating that there was no significant effect of single 200 mg doses of avanafil on PT and INR of warfarin. This reviewer concurs with the proposed language regarding the effect of avanafil on warfarin.

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

During the clinical development program, there were two avanafil immediate-release formulations used – Formulation I and Formulation II. (b) (4)

(b) (4)
 Formulation I tablets were (b) (4)
 available in 12.5, 25, 50, and 100 mg strengths. Formulation II tablets are oval, light-yellow coated tablet and are available in 50, 100, and 200 mg strengths, (b) (4)

Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and is the proposed to-be-marketed formulation. However, the Phase 3 studies were conducted using multiple units of 50 or 100 mg tablets. The three proposed dosage strengths of Formulation II are produced (b) (4)

The sponsor evaluated the relative bioavailability of Formulation II vs. Formulation I (Study TA-020). Subjects were given 2 x 100 mg under fasted conditions. The mean (SD) for C_{max} was 2920 (911) and 3080 (1040) ng/mL for Formulation II and I, respectively. The mean (SD) for AUC_{0-inf} was 8490 (3060) and 8140 (2820) ng*hr/mL for

Formulation II and I, respectively. Based on the above data and statistical comparisons presented in the following table, formulation changes did not change the rate and extent of avanafil absorption. The two formulations are found to be bioequivalence by this reviewer.

The following table summarizes the statistical comparison of geometric least squares means of avanafil PK following 2 x 100 mg tablets Formulation II, fasted (Treatment A) versus 2 x 100 mg tablet Formulation I, fasted (Study TA-020).

Pharmacokinetic Parameters	Treatment A ^a	N	Treatment C ^a	N	90% CI	% Mean Ratio
C _{max} (ng/mL)	2760	23	2920	23	(81.44, 109.65)	94.50
AUC _{0-t} (ng*hr/mL)	7660	23	7450	23	(94.24, 112.27)	102.86
AUC _{0-inf} (ng*hr/mL)	8310	17	7800	17	(97.78, 116.13)	106.56

2.5.2 What data support or do not support a waiver of in vivo BE data?

The three proposed dosage strengths of Formulation II are produced (b) (4). (b) (4) The sponsor evaluated the relative bioavailability of Formulation I and Formulation II (TA-020) with 2 x 100 mg tablets. The sponsor has requested a waiver to study the 50 and 200 mg tablets based on the dissolution data and use of a (b) (4) to prepare all three tablet strengths. Dissolution data is being reviewed by ONDQA Reviewer.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The sponsor evaluated the effect of food on avanafil PK (TA-020). This was a single-center, open-label, randomized, four-way crossover study in healthy young men. Subjects fasted at least 10 hrs prior to treatment and at least 4 hrs following dosing. Subjects began to eat a standardized high fat (800 to 1000 total calories with 150 calories from protein, 250 calories from carbohydrates, and 500-600 calories from fat) breakfast 30±5 min prior to dosing in the Fed group. Subjects were given 200 mg avanafil (2 x 100 mg) under fed (Treatment B) and fasted (Treatment A) conditions.

Mean (SD) for C_{max} was 1760 (526) and 2920 (911) ng/mL under fed and fasted conditions, respectively. Food reduced the mean C_{max} by approximately 40%. Mean (SD) for AUC_{0-t} was 8070 (2560) and 8060 (2630) ng*hr/mL under fed and fasted conditions, respectively. The arithmetic mean (SD) for AUC_{0-inf} was 8360 (2380) and 8490 (3060) ng*hr/mL under fed and fasted conditions, respectively. Food had essentially no effect on the extent of avanafil absorption as both AUC_{0-t} and AUC_{0-inf} remained relatively unchanged.

The following table summarizes the arithmetic mean of avanafil PK parameters and statistical comparison following 2x100 mg tablets Formulation II, under fed and fasted conditions (Study TA-020).

PK Parameters	Fed (N=23)	Fasted (N=23)	% mean ratio (Fed/Fasted)	90% CI
C _{max} (ng/mL)	1760 (526)	2920 (911)	61.0	(52.6, 70.8)

AUC0-t (ng*hr/mL)	8070 (2560)	8060 (2630)	100.7	(92.3, 110.0)
AUC0-inf (ng*hr/mL)	8360 (2830)	8490 (3060)	96.2	(88.9, 104.1)
Tmax (hr)	2.0 (1.2, 4.0)	0.75 (0.5, 2.0)		
t_{1/2} (hr)	4.5 (1.9)	5.1 (2.9)		

Patients in the Phase III studies were instructed to take avanafil without regard to food intake. In the proposed product label, the sponsor states that avanafil may be taken with or without food. This reviewer concurs with the proposed dosing instruction based on the Phase III study design and outcome of the food effect study.

2.6 BIOANALYTICAL METHODS

The sponsor used LC-MS/MS for the majority of clinical pharmacology studies and validated the method for the determination of avanafil (TA-1790), M4 and M16 in human plasma. The method was validated for precision, accuracy, specificity, and recovery; the results are acceptable (Reports p862 & CP005301). The sponsor met the Agency's recommended acceptance criteria of <20% for precision (CV%) and within +20% for accuracy at the lower limit of quantitation and <15% or within +15% at all concentrations. There were 8 calibration standards with concentrations 1, 1.8, 3, 10, 30, 90, 210, and 250 ng/mL. There were QC samples at 4 different concentrations: 60.0 ng/mL, 300 ng/mL, 3000 ng/mL, and 10000 ng/mL for avanafil and 15.0 ng/mL, 75.0 ng/mL, 750 ng/mL, and 2500 ng/mL for M4 stereoisomers and M16 stereoisomers.

3 DETAILED LABELING RECOMMENDATIONS

Detailed labeling recommendations will be incorporated into DRUP's proposed label.

4 APPENDIX

4.1 OFFICE OF CLINICAL PHARMACOLOGY FILING REVIEW

NDA Number: 202276

Applicant: Vivus

Stamp Date: June 29, 2011

Drug Name: Avanafil

NDA Type: Original

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			n/a Formulation II is the TBM product and was used in the entire Phase 3 program, as well as in most ClinPharm studies.
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			n/a
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			n/a
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			n/a
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology	X		

	section of the label?			
General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES___

The following will be Clinical Pharmacology review issues to be conveyed to the Sponsor:

- The Phase 3 studies were conducted using multiple units of either 50 or 100 mg tablets. How the data from studies using 50 and 100 mg tablets can be extrapolated to support the safety and efficacy of the higher dose strength (200 mg tablets). Refer to the pre-NDA meeting on October 20, 2011 regarding the lack of dose proportionality of the to-be-marketed formulation.
- The effect of p-glycoprotein (P-gp) was not studied based on the in vitro study results. Potential effects of avanafil on a P-gp substrate or P-gp inhibition on avanafil PK.
- (b) (4)
- The demonstration of safety and recommended starting dose in the elderly population (≥ 65 yo).
- The impact of severe renal impairment and End Stage Renal Disease on avanafil PK was not studied. Use of avanafil in these patients
- The impact of severe hepatic impairment on avanafil PK was not studied. Use of avanafil in these patients.
- The effect of a mild CYP3A4 inhibitor on avanafil PK was not studied. Use of avanafil in patients taking a mild, moderate and strong CYP3A4 inhibitor.
- Drug interaction studies conducted with a single dose can be extrapolated to multiple dose use (i.e. Study TA-018 with rosiglitazone and desipramine).

Information Request

- Submit the renal impairment study results based on the new classification scheme of renal impairment as described in FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010).
- Provide justification how drug interaction studies conducted with a single dose (i.e. Study TA-018 with rosiglitazone and desipramine) can be extrapolated to multiple dose use.

LaiMing Lee

Reviewing Clinical Pharmacologist

August 10, 2011

Date

Myong-Jin Kim

Team Leader/Supervisor

Date

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology Filing Memo

NDA: 202276
Compound: Avanafil
Sponsor: Vivus Inc.

Submission Date: June 29, 2011
Filing Review Date: July 20, 2011
Reviewer: LaiMing Lee, Ph.D.

Avanafil (also referred to as TA-1790) is developed by Vivus for the treatment of erectile dysfunction (ED). Avanafil is a phosphodiesterase 5 (PDE5) inhibitor, which increases penile blood flow and erection in response to sexual stimulation.

Avanafil is a solid, oval, pale yellow immediate-release (IR) oral tablet and is intended to be used on an as needed basis. The proposed dosing regimen is one 100 mg tablet 30 minutes prior to initiation of sexual activity and no more than once daily. The Sponsor states that avanafil (b) (4) and can be taken without regard to food intake. The dose may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability. The Sponsor is seeking approval for 50, 100, and 200 mg tablets.

The clinical program includes 17 Phase 1 studies, 3 Phase 2 studies, and 4 Phase 3 studies. There were 7 in vitro studies evaluating the metabolism of avanafil and potential for drug-drug interactions.

Below is a table summarizing avanafil formulations used in clinical studies:

Study ID	Type of Study	Phase	Avanafil Tablet Strength	Avanafil Doses
Formulation I				
HP-01	PK, food effect, tolerability	1	12.5, 50, 100 mg	12.5, 25, 50, 100, 200, 400, 600 and 800 mg
TA-02	PK, safety single, multi dose	1	50, 100 mg	50, 100 and 200 mg QD
TA-04	Drug-drug interaction (nitrate)	1	100 mg	200 mg
TA-07	PK, BID dosing	1	100 mg	200 mg BID
TA-01	Visual stimulation	2	50, 100 mg	50, 100 and 200 mg
TA-03	Home administration	2	100 mg	200 mg
TA-05	Safety, efficacy	2	12.5, 50, 100 mg	50, 100, 200 and 300 mg
Formulation II				
TA-011	Drug-drug interaction (ritonavir, erythromycin, ketoconazole)	1	50, 100 mg	50 or 200 mg
TA-012	Drug-disease interaction (hepatic)	1	200 mg	200 mg
TA-013	Drug-disease interaction (renal)	1	200 mg	200 mg
TA-014	Elderly vs. young PK, semen PK	1	200 mg	200 mg
TA-015	Drug-drug interaction (alcohol)	1	200 mg	200 mg
TA-016	Drug-drug interaction (warfarin)	1	200 mg	200 mg
TA-017	Drug-drug interaction (alpha blockers)	1	200 mg	200 mg
TA-018	Drug-drug interaction (omeprazole, desipramine, and rosiglitazone)	1	200 mg	200 mg
TA-019	Drug-drug interaction (enalapril, amlodipine)	1	200 mg	200 mg
TA-020	Food effect, bioequivalence, dose proportionality	1	50, 100 mg (Formulation II) 100 mg (Formulation I)	50 or 200 mg
TA-021	Sperm function	1	200 mg	200 mg
TA-140	TQT	1	100 mg	100 and 800 mg
TA-301	Safety, efficacy in generalized ED	3	50 mg	50, 100, 200 mg
TA-302	Safety, efficacy in diabetics with ED	3	100 mg	100 and 200 mg
TA-314	Long term follow up (rollover from TA-301 and TA-302)	3	50, 100, 200 mg	50, 100 and 200 mg

There were two avanafil IR tablet formulations (Formulations I and II) used in the avanafil clinical development program. [REDACTED] (b) (4)

[REDACTED] The early tablets (Formulation I) were formulated as 12.5, 25, 50, and 100 mg strengths. Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and is the proposed to-be-marketed formulation. However, it should be noted that the Phase 3 studies were conducted using multiple units of 50 or 100 mg tablets. The Sponsor states that the three proposed dosage strengths of Formulation II are produced [REDACTED] (b) (4). The Sponsor conducted a bioequivalence study with 2 x 100 mg tablets to evaluate the to-be-marketed formulation (Formulation II) and the early formulation (Formulation I). The Sponsor claims that the Formulations I and II are bioequivalent (Study TA-020).

The Sponsor states that systemic exposure AUC_{0-inf} of avanafil Formulation I is dose proportional from 12.5 to 800 mg following single ascending dosing (Study HP-01) and from 50 to 200 mg following multiple dosing (Study TA-02). However, as noted by Chongwoo Yu's preNDA review (DAARTS 12/03/2010) and in the Sponsor's conclusion of Study TA-020, 1 x 50 mg and 2 x 100 mg doses of Formulation II were not dose proportional. Additionally, the estimated half-life appeared to be dose dependent (i.e. 2.5 hr at 50 mg vs. 4.4 hr at 200 mg).

Phase 3 Clinical Studies

The following is a brief description of the three completed Phase 3 clinical studies: TA-301 in the general ED population, TA-302 in diabetic men, and TA-314 long term safety and tolerability.

TA-301 was a randomized, double-blind, placebo-controlled, multicenter study in adult male subjects with mild to severe ED. 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 ratio to one of the following treatments: placebo, avanafil 50 mg, 100 mg, or 200 mg. During the treatment period, subjects were instructed to take one dose of study drug approximately 30 minutes prior to initiation of sexual activity. No restrictions were placed on the timing or consumption of food or alcohol.

TA-302 was a randomized, double-blind, placebo-controlled, multicenter study in adult male subjects with mild to severe ED and type 1 or type 2 diabetes. 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 ratio to one of the following treatments: placebo, avanafil 100 mg, or 200 mg. During the treatment period, subjects were instructed to take one dose of study drug approximately 30 minutes prior to initiation of sexual activity. No restrictions were placed on the timing or consumption of food or alcohol.

TA-314 was an open-label extension study in adult male subjects with mild to severe ED who had completed TA-301 or TA-302. The study was planned with a 52-week treatment period.

Phase 2 Clinical Studies

The following is a brief description of the three Phase 2 clinical studies:

TA-01 was a single-blind, randomized, crossover study in adult male subjects who had a subjective complaint of mild or mild-to-moderate ED. Subjects received in-clinic doses of placebo, sildenafil (50 mg), and avanafil (50 mg, 100 mg, and 200 mg) in a random sequence. Subjects were connected to the RigiScan monitor continuously from 0.5 hour pre-dosing until 2.5 hours post-dosing to measure penile rigidity and tumescence. Visual sexual stimulation (video) was presented during three 20-minute periods beginning at 20 minutes post-dose and concluding at 120 minutes post-dose.

TA-03 was a double-blind, randomized, crossover study in adult male subjects with a subjective complaint of ED. Subjects were treated with avanafil 200 mg or sildenafil 100 mg in random order during treatment periods 1 and 2 and were instructed to initiate sexual activity within 5-10 minutes after dosing. During treatment period 3, all subjects were treated with avanafil 200 mg and were instructed to wait for 2 hours before initiating sexual activity. Each treatment period was 3-4 weeks in duration.

TA-05 was a randomized, double-blind, parallel-design, placebo-controlled, multicenter study in adult male subjects with a subjective complaint of mild to moderate ED. 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 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.

Phase 1 Clinical Pharmacology Studies

The following is a brief description of the seventeen Phase 1 Clinical Pharmacology studies:

HP-01 (single ascending dose, first-in-human) was an ascending single-dose, randomized, placebo-controlled, double-blind study in healthy male subjects, which evaluated safety and tolerability and compared the PK profiles of 8 avanafil doses under fasted condition. HP-01 also assessed the effect of food on the PK profile of 100 mg avanafil formulation I in a crossover design.

Following a single dose of up to 800 mg avanafil, median T_{max} was reached between 0.5 to 1.25 hours. The Sponsor states that the PK of avanafil appeared linear and the AUC_{0-inf} increased in a dose proportional manner over the dose range of 12.5 to 800 mg, while C_{max} increased in a dose proportional manner over the dose range of 12.5 to 600 mg.

TA-02 (multiple dose, once daily) was a single- and multiple-dose, randomized, placebo-controlled, double-blind, parallel study in healthy male subjects, which evaluated safety and tolerability and compared the PK profiles of avanafil 50 mg, 100 mg, and 200 mg given once daily for 14 days.

Following single dosing, dose proportionality was observed for AUC_{0-inf} of avanafil and was slightly more than dose proportional for C_{max}. Following multiple dosing (14 days), it appears as though there was dose proportionality for C_{max}, but not for AUC_{0-tau} (AUC_{0-inf} not reported).

TA-04 (nitrate interaction) was a randomized, placebo-controlled, double-blind, 3-way crossover study to assess the hemodynamic effects to a single dose of 0.4 mg sublingual glyceryl trinitrate (Nitrostat®) in healthy male subjects receiving 200 mg avanafil, 100 mg sildenafil or placebo. Subjects were divided among five study groups, with the study group being determined by the time interval (12 hrs, 8 hrs, 4 hrs, 1 hr and 30 min) between treatment with study drug and nitrate administration.

The Sponsor concludes both avanafil and sildenafil potentiated the hypotensive effect of nitrates. Overall, 11 (12%) subjects with placebo, 15 (15%) subjects with avanafil and 28 (29%) subjects with sildenafil had clinically significant drops in standing systolic blood pressure (≥ 30 mmHg) after nitrate administration.

The Sponsor states administration of avanafil to patients who use any form of organic nitrate is contraindicated due to the potentiation of hypotension. They advise patients taking avanafil wait at least 12 hours after the last dose of avanafil before nitrate administration is considered, and advised close medical supervision with appropriate hemodynamic monitoring.

TA-07 (multiple dose BID) was a non-randomized, open-label study in healthy male subjects, which assessed the single dose and steady-state (7 days) PK of avanafil 200 mg (2x100 mg tablets) following twice daily dosing.

The Sponsor states that following oral administration, the single dose and steady state T_{max} of avanafil were similar at 0.5 hr and that avanafil PK was linear and stationary over the multiple dosing regimens.

TA-010 (mass balance) was a single-dose, non-randomized, open-label, mass balance study in six healthy young male subjects, which assessed the absorption, distribution, metabolism, and excretion of 600 mg avanafil labeled with ¹⁴C given as a suspension.

The major metabolite is an open pyrrolidine ring carboxylic acid avanafil (M16) and monohydroxy avanafil (M4), which accounted for about 10.6% and 8.4% of the total radioactivity or 29% and 23% of the circulating concentration of unchanged avanafil, respectively. The mean recovery of administered radioactivity was approximately 62% in feces and 21% in urine. Fecal excretion was the major route of elimination of radioactivity and little or no total radioactivity was detected in blood and plasma after 10 hrs. Unchanged avanafil was not detected in pooled urine samples. Avanafil was extensively metabolized via phase 1 metabolism. The proposed major routes of biotransformation are hydroxylation, multiple N-dealkylation, demethylation and glucuronide conjugation.

TA-011 (CYP3A inhibitor interaction) was a randomized, open-label, parallel-group, one-sequence crossover study in healthy male subjects, which assessed the single-dose PK of avanafil when co-administered with ketoconazole, erythromycin, or ritonavir.

Group 1: ketoconazole 400 mg QD for 5 days (Days 2 to 6) plus a single dose of avanafil 50 mg on Days 1 and 6; Group 2: erythromycin 500 mg every 12 hours for 5 days (Days 2 to 6) plus a single dose of avanafil 200 mg on Days 1 and 6; Group 3: ritonavir 300 mg BID for 1 day (Day 2, 400 mg BID for 1 day (Day 3), and 600 mg BID for 5 days (Day 4 to 8) plus a single dose of avanafil 50 mg on Days 1 and 8.

The Sponsor states that strong CYP3A4 inhibitors such as ketoconazole and ritonavir increased the geometric LS mean C_{max} and AUC_{0-inf} of avanafil to approximately 3-fold and 14-fold, respectively. The Sponsor recommends (b) (4) for patients taking a potent CYP3A4 inhibitor. Co-administration of avanafil with a moderate CYP3A4 inhibitor erythromycin increased C_{max} and AUC_{0-inf} to approximately 2-fold and 3-fold, respectively. (b) (4)

No mild CYP3A4 inhibitor was evaluated.

TA-012 (hepatic impairment) was a single dose (200 mg), non-randomized, open-label, parallel-group, matched-control study which assessed the PK of avanafil in male subjects (age 45-69 years) with normal hepatic function and male subjects with mild or moderate hepatic impairment.

The Sponsor states that mild hepatic impairment (Child-Pugh Class A) had no effect on the PK of avanafil. The AUC_{0-inf} of avanafil in patients with moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy subjects and avanafil C_{max} was up to 57% lower in patients with moderate hepatic impairment compared to subjects with normal hepatic function. The Sponsor indicates no dose adjustment is required in patients with mild or moderate hepatic impairment, and use in patients with severe hepatic impairment is not recommended. No study in patients with severe hepatic impairment was conducted.

TA-013 (renal impairment) was a single dose (200 mg), non-randomized, open-label, parallel-group, matched-control study which assessed the PK of avanafil in male subjects with normal renal function and male subjects with mild or moderate ($\text{CrCl} \geq 30$ to < 50 mL/min) renal impairment. Age range was 52 to 78 years.

The Sponsor defined mild renal impairment as those subjects with a $\text{CrCl} \geq 50$ to < 80 mL/min. According to FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010), patients with mild renal impairment are those with eGFR or CL_{cr} between 60 and 89 mL/min/1.73 m² or mL/min, respectively. The Sponsor claims that, compared to subjects with normal renal function, mild or moderate renal impairment had little influence on the maximum and systemic exposure of avanafil with the 90% CIs of the mean ratios of C_{max} and AUC_{0-inf} contained 100%. C_{max} % mean ratio for avanafil was 104.02 and 99.96 for subjects with mild and moderate renal impairment, respectively. AUC_{0-inf} % mean ratio for avanafil was 88.09 and 118.93 for subjects with mild and moderate renal impairment, respectively.

The Sponsor indicates no dose adjustment is required in patients with mild or moderate renal impairment, and use in patients with severe renal impairment or end stage renal disease (ESRD) is not recommended. No studies in patients with severe renal impairment or ESRD on hemodialysis were conducted.

TA-014 (age and sperm function) 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 43 yo, while the subjects in the elderly group were 65-80 yo. Avanafil semen exposure and the acute effect of avanafil on sperm function in healthy, young male subjects were also evaluated.

The Sponsor claims the following: avanafil was highly bound to plasma protein 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 $< 0.0002\%$ of the 200 mg administered; mean sperm motility did not change by $> 20\%$ from baseline and there was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress.

According to the Sponsor, following a single oral dose of avanafil 200 mg, systemic exposures to avanafil, M4 and M16 were generally comparable in elderly and young subjects. However, there appears to be a slightly greater exposure of M16 in the elderly, compared to avanafil and M4.

TA-015 (alcohol interaction) was a single dose (200 mg), randomized, double-blind, placebo-controlled, 3-way crossover study in healthy male subjects (age 22 to 44 yrs), which assessed the hemodynamic interactions of avanafil and alcohol.

Treatment A: a single oral dose of 200 mg avanafil tablet plus an oral dose of alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kg of BW)

Treatment B: a single oral dose of placebo tablet plus an oral dose of alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kg of BW)

Treatment C: a single oral dose of 200 mg avanafil plus an oral dose of placebo drink mixed with fruit juice.

According to the Sponsor, alcohol administered at a dose of 0.5 g/kg is equivalent to approximately 3 oz of 80-proof vodka in a 70 kg male. There appears to be small potentiation of hypotensive effects due to avanafil co-administered with alcohol. In the proposed label, the Sponsor advises patients to be

aware that both alcohol and avanafil act as (b) (4) vasodilators. (b) (4)

TA-016 (warfarin interaction) was a randomized, double-blind, placebo-controlled, 2-way crossover study in healthy male subjects, which assessed the effects of daily avanafil dosing (200 mg for 9 days) on the PK and pharmacodynamics (prothrombin time (PT) and international normalized ratio (INR) of a single dose (25 mg) of warfarin.

Based on the 90% CI of the geometric LS mean ratios for warfarin C_{max}, AUC_{0-t}, and AUC_{0-inf} falling within 90% to 125%, there appears to be no alteration in warfarin PK with avanafil co-administration. PT and INR also appear to be unchanged in the presence of avanafil.

TA-017 (α -adrenergic blocker interaction) was a randomized, double-blind, placebo-controlled, 2-cohort, 2-period crossover study which assessed the effects of the co-administration of 200 mg avanafil on the hemodynamic effects of doxazosin (1 to 8 mg daily for 11 days) or tamsulosin (0.4 mg daily for 11 days) in healthy, middle-aged (40 to 61 yo) male subjects.

The Sponsor states there were statistically significant differences in the maximum decrease from baseline in supine SBP, standing DBP, and supine DBP and the maximum increase from baseline in standing pulse rate, following co-administration of doxazosin and avanafil, compared to doxazosin and placebo.

The Sponsor states there were statistically significant differences in the maximum decrease from baseline in supine DBP and the maximum increase from baseline in supine pulse rate were observed following co-administration of tamsulosin and avanafil, compared with tamsulosin and placebo.

The Sponsor advises caution when avanafil is co-administered with alpha-blockers. Patients should be stable on α -blocker therapy prior to initiating treatment with avanafil, and avanafil should be initiated at the lowest 50 mg dose.

TA-018 (Effects of avanafil on CYP2C and CYP2D6)

Omeprazole (CYP2C19 substrate): Subjects received oral doses of omeprazole 40 mg QD for 8 days (Days 1 to 8) plus a single oral dose of avanafil 200 mg on Day 8. Co-administration of avanafil and omeprazole did not appear to significantly alter omeprazole AUC_{0-tau} (4940 vs. 4420 ng.hr/mL). C_{max} of omeprazole was slightly higher at 16.7% when avanafil was co administered.

Rosiglitazone (CYP2C8 substrate): Subjects were randomized to receive a single oral dose of rosiglitazone 8 mg or a single oral dose of rosiglitazone 8 mg plus a single oral dose of avanafil 200 mg. Co-administration of rosiglitazone and avanafil did not affect the systemic exposure (AUC_{0-inf} or AUC_{0-t}) of rosiglitazone; however, C_{max} of rosiglitazone was slightly lowered.

Desipramine (CYP2D6 substrate): Subjects were randomized to receive a single oral dose of desipramine 50 mg or a single oral dose of desipramine 50 mg plus a single oral dose of avanafil 200 mg. Co-administration of desipramine and avanafil did not affect the systemic exposure (AUC_{0-inf} or AUC_{0-t}) or maximum exposure of desipramine.

TA-019 (enalapril or amlodipine) was a randomized, double-blind, placebo-controlled, 2-cohort crossover study in healthy male subjects, which assessed the PK and hemodynamic effects of the

co-administration of avanafil (200 mg) with enalapril (10 mg twice daily for 11 days) or amlodipine (5 mg once daily for 18 days).

The Sponsor states that a single dose of avanafil 200 mg co administered with enalapril caused a mean maximum change in SBP of -1.75/-3.46 mmHg compared to placebo. Single doses of avanafil 200 mg co-administered with amlodipine caused a mean maximum change in SBP of -1.18/+1.47 mmHg compared to placebo. They claim no statistically significant difference in the maximum change from baseline in standing SBP (primary endpoint) was observed following co-administration of avanafil with enalapril or amlodipine compared to placebo.

TA-020 (food effect, bioavailability, dose proportionality) was a single-dose, randomized, open-label, 4-period, crossover study in healthy male subjects, which assessed the effect of food on the PK of avanafil (2x100 mg Formulation II tablets), the relative bioavailability of two avanafil tablet formulations (2x100 mg Formulation I vs. 2x100 mg Formulation II), and the dose proportionality of avanafil (1x50 mg vs. 2x100 mg Formulation II).

The Sponsor states that systemic exposures (AUC_{0-inf}) to avanafil in the presence of high fat meal were considered of minimal clinical significance. Avanafil t_{max} was delayed by 1.25 hrs from 0.75 to 2.0 hrs, while C_{max} was reduced by 39% in the presence of a high fat meal. The Sponsor proposes avanafil may be taken without regard to food intake.

The increases in T_{max} and AUC_{0-inf} to avanafil between 50 and 200 mg doses under fasted conditions were shown to be slightly greater than dose proportional. The Sponsor states the lack of dose proportionality is likely due to the insufficient detectable concentration vs. time points during the elimination phase following the 50 mg dose.

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 avanafil on sperm function in healthy, young male subjects.

TA-140 (thorough QTc) was a single dose (100 or 800 mg), randomized, blinded, placebo- and active-controlled crossover thorough QT study in healthy male subjects (mean age: 28 years).

Following a single oral dose administration of avanafil, at dose levels of 100 mg or 800 mg, C_{max}, AUC_{0-t}, and AUC_{0-inf} increased approximately dose proportionally by 6.9, 10.8, and 10.5 fold, respectively, with an 8 fold increase in dose level from 100 mg to 800 mg. The time-matched analysis for the QTcI data revealed that all time points had a placebo and baseline corrected result less than 10 msec for the upper CI, except for the 3 hour time point for the 800 mg dose of avanafil, which reached 10.2 msec.

In Vitro Studies

10-AVANAFIL-BCS-01 and 10-AVANAFIL-PGP-01

In Caco-2 monolayers, the apical to basolateral apparent permeability (P_{app}) of avanafil was determined to be 44.6×10^{-6} cm/sec, while the basolateral to apical P_{app} was 73.4×10^{-6} cm/sec. With an efflux ratio (R_E) less than 2, the Sponsor states that avanafil is a weak substrate of P-glycoprotein transporter (P-gp). Based on studies in multi-drug resistance gene and Madin-Darby canine kidney wild type cells, the Sponsor estimated R_E (R_{E(MDR1)}/R_{E(MDCK-WT)}) to be 1.8, which is lower than the suggested value of 2 according to OCP's drug interaction guidance on assessing whether a drug molecule is a P-gp substrate. Based on the in vitro study results, the Sponsor determined that in vivo studies to assess the effect of P-gp inhibition on avanafil PK or the effect of avanafil on P-gp substrates such as digoxin were not necessary.

10-AVANAFIL-PK-12 (protein binding)

The extent of avanafil binding to plasma proteins was determined by ultrafiltration in human plasma over a concentration range of 0.3 to 3.0 mcg/mL. At 0.3 mcg/mL, mean unbound fraction of avanafil was ~1%. The Sponsor states protein binding was reversible and did not appear to be saturable over the concentration range studied. Avanafil was 99% bound to albumin, 43% to γ -globulin, and 66% to α -glycoprotein.

10-AVANAFIL-PK-15, 10-AVANAFIL-PK-16 and 10-AVANAFIL-PK-17

Metabolism of avanafil by CYP450s was evaluated *in vitro* using immunoinhibition and recombinant human CYP450s. The Sponsor states the formation of major metabolites of avanafil was catalyzed primarily by CYP3A4, with a minor contribution by CYP2C.

Based on *in vitro* results obtained from human liver microsomes, the Sponsor determined that there was a low potential for drug interactions with substrates of CYP1A1/2, 2A6, 2E1 and 2B6; a likely potential for drug interaction with substrates of 2C19; and possible interaction with substrates of CYP3A4, 2D6 and 2C8/9.

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/s/

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Office of Clinical Pharmacology Filing Memo

NDA: 202276
Compound: Avanafil
Sponsor: Vivus Inc.

Submission Date: June 29, 2011
Filing Review Date: July 20, 2011
Reviewer: LaiMing Lee, Ph.D.

Avanafil (also referred to as TA-1790) is developed by Vivus for the treatment of erectile dysfunction (ED). Avanafil is a phosphodiesterase 5 (PDE5) inhibitor, which increases penile blood flow and erection in response to sexual stimulation.

Avanafil is a solid, oval, pale yellow immediate-release (IR) oral tablet and is intended to be used on an as needed basis. The proposed dosing regimen is one 100 mg tablet 30 minutes prior to initiation of sexual activity and no more than once daily. The Sponsor states that avanafil (b) (4) and can be taken without regard to food intake. The dose may be increased to 200 mg or decreased to 50 mg based on efficacy and/or tolerability. The Sponsor is seeking approval for 50, 100, and 200 mg tablets.

The clinical program includes 17 Phase 1 studies, 3 Phase 2 studies, and 4 Phase 3 studies. There were 7 in vitro studies evaluating the metabolism of avanafil and potential for drug-drug interactions.

Below is a table summarizing avanafil formulations used in clinical studies:

Study ID	Type of Study	Phase	Avanafil Tablet Strength	Avanafil Doses
Formulation I				
HP-01	PK, food effect, tolerability	1	12.5, 50, 100 mg	12.5, 25, 50, 100, 200, 400, 600 and 800 mg
TA-02	PK, safety single, multi dose	1	50, 100 mg	50, 100 and 200 mg QD
TA-04	Drug-drug interaction (nitrate)	1	100 mg	200 mg
TA-07	PK, BID dosing	1	100 mg	200 mg BID
TA-01	Visual stimulation	2	50, 100 mg	50, 100 and 200 mg
TA-03	Home administration	2	100 mg	200 mg
TA-05	Safety, efficacy	2	12.5, 50, 100 mg	50, 100, 200 and 300 mg
Formulation II				
TA-011	Drug-drug interaction (ritonavir, erythromycin, ketoconazole)	1	50, 100 mg	50 or 200 mg
TA-012	Drug-disease interaction (hepatic)	1	200 mg	200 mg
TA-013	Drug-disease interaction (renal)	1	200 mg	200 mg
TA-014	Elderly vs. young PK, semen PK	1	200 mg	200 mg
TA-015	Drug-drug interaction (alcohol)	1	200 mg	200 mg
TA-016	Drug-drug interaction (warfarin)	1	200 mg	200 mg
TA-017	Drug-drug interaction (alpha blockers)	1	200 mg	200 mg
TA-018	Drug-drug interaction (omeprazole, desipramine, and rosiglitazone)	1	200 mg	200 mg
TA-019	Drug-drug interaction (enalapril, amlodipine)	1	200 mg	200 mg
TA-020	Food effect, bioequivalence, dose proportionality	1	50, 100 mg (Formulation II) 100 mg (Formulation I)	50 or 200 mg
TA-021	Sperm function	1	200 mg	200 mg
TA-140	TQT	1	100 mg	100 and 800 mg
TA-301	Safety, efficacy in generalized ED	3	50 mg	50, 100, 200 mg
TA-302	Safety, efficacy in diabetics with ED	3	100 mg	100 and 200 mg
TA-314	Long term follow up (rollover from TA-301 and TA-302)	3	50, 100, 200 mg	50, 100 and 200 mg

There were two avanafil IR tablet formulations (Formulations I and II) used in the avanafil clinical development program. (b) (4)

The early tablets (Formulation I) were formulated as 12.5, 25, 50, and 100 mg strengths. Formulation II was used in the entire Phase 3 program, as well as in most of the clinical pharmacology studies, and is the proposed to-be-marketed formulation. However, it should be noted that the Phase 3 studies were conducted using multiple units of 50 or 100 mg tablets. The Sponsor states that the three proposed dosage strengths of Formulation II are produced (b) (4)

(b) (4) The Sponsor conducted a bioequivalence study with 2 x 100 mg tablets to evaluate the to-be-marketed formulation (Formulation II) and the early formulation (Formulation I). The Sponsor claims that the Formulations I and II are bioequivalent (Study TA-020).

The Sponsor states that systemic exposure AUC_{0-inf} of avanafil Formulation I is dose proportional from 12.5 to 800 mg following single ascending dosing (Study HP-01) and from 50 to 200 mg following multiple dosing (Study TA-02). However, as noted by Chongwoo Yu's preNDA review (DAARTS 12/03/2010) and in the Sponsor's conclusion of Study TA-020, 1 x 50 mg and 2 x 100 mg doses of Formulation II were not dose proportional. Additionally, the estimated half-life appeared to be dose dependent (i.e. 2.5 hr at 50 mg vs. 4.4 hr at 200 mg).

Phase 3 Clinical Studies

The following is a brief description of the three completed Phase 3 clinical studies: TA-301 in the general ED population, TA-302 in diabetic men, and TA-314 long term safety and tolerability.

TA-301 was a randomized, double-blind, placebo-controlled, multicenter study in adult male subjects with mild to severe ED. 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 ratio to one of the following treatments: placebo, avanafil 50 mg, 100 mg, or 200 mg. During the treatment period, subjects were instructed to take one dose of study drug approximately 30 minutes prior to initiation of sexual activity. No restrictions were placed on the timing or consumption of food or alcohol.

TA-302 was a randomized, double-blind, placebo-controlled, multicenter study in adult male subjects with mild to severe ED and type 1 or type 2 diabetes. 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 ratio to one of the following treatments: placebo, avanafil 100 mg, or 200 mg. During the treatment period, subjects were instructed to take one dose of study drug approximately 30 minutes prior to initiation of sexual activity. No restrictions were placed on the timing or consumption of food or alcohol.

TA-314 was an open-label extension study in adult male subjects with mild to severe ED who had completed TA-301 or TA-302. The study was planned with a 52-week treatment period.

Phase 2 Clinical Studies

The following is a brief description of the three Phase 2 clinical studies:

TA-01 was a single-blind, randomized, crossover study in adult male subjects who had a subjective complaint of mild or mild-to-moderate ED. Subjects received in-clinic doses of placebo, sildenafil (50 mg), and avanafil (50 mg, 100 mg, and 200 mg) in a random sequence. Subjects were connected to the RigiScan monitor continuously from 0.5 hour pre-dosing until 2.5 hours post-dosing to measure penile rigidity and tumescence. Visual sexual stimulation (video) was presented during three 20-minute periods beginning at 20 minutes post-dose and concluding at 120 minutes post-dose.

TA-03 was a double-blind, randomized, crossover study in adult male subjects with a subjective complaint of ED. Subjects were treated with avanafil 200 mg or sildenafil 100 mg in random order during treatment periods 1 and 2 and were instructed to initiate sexual activity within 5-10 minutes after dosing. During treatment period 3, all subjects were treated with avanafil 200 mg and were instructed to wait for 2 hours before initiating sexual activity. Each treatment period was 3-4 weeks in duration.

TA-05 was a randomized, double-blind, parallel-design, placebo-controlled, multicenter study in adult male subjects with a subjective complaint of mild to moderate ED. 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 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.

Phase 1 Clinical Pharmacology Studies

The following is a brief description of the seventeen Phase 1 Clinical Pharmacology studies:

HP-01 (single ascending dose, first-in-human) was an ascending single-dose, randomized, placebo-controlled, double-blind study in healthy male subjects, which evaluated safety and tolerability and compared the PK profiles of 8 avanafil doses under fasted condition. HP-01 also assessed the effect of food on the PK profile of 100 mg avanafil formulation I in a crossover design.

Following a single dose of up to 800 mg avanafil, median T_{max} was reached between 0.5 to 1.25 hours. The Sponsor states that the PK of avanafil appeared linear and the AUC_{0-inf} increased in a dose proportional manner over the dose range of 12.5 to 800 mg, while C_{max} increased in a dose proportional manner over the dose range of 12.5 to 600 mg.

TA-02 (multiple dose, once daily) was a single- and multiple-dose, randomized, placebo-controlled, double-blind, parallel study in healthy male subjects, which evaluated safety and tolerability and compared the PK profiles of avanafil 50 mg, 100 mg, and 200 mg given once daily for 14 days.

Following single dosing, dose proportionality was observed for AUC_{0-inf} of avanafil and was slightly more than dose proportional for C_{max}. Following multiple dosing (14 days), it appears as though there was dose proportionality for C_{max}, but not for AUC_{0-tau} (AUC_{0-inf} not reported).

TA-04 (nitrate interaction) was a randomized, placebo-controlled, double-blind, 3-way crossover study to assess the hemodynamic effects to a single dose of 0.4 mg sublingual glyceryl trinitrate (Nitrostat®) in healthy male subjects receiving 200 mg avanafil, 100 mg sildenafil or placebo. Subjects were divided among five study groups, with the study group being determined by the time interval (12 hrs, 8 hrs, 4 hrs, 1 hr and 30 min) between treatment with study drug and nitrate administration.

The Sponsor concludes both avanafil and sildenafil potentiated the hypotensive effect of nitrates. Overall, 11 (12%) subjects with placebo, 15 (15%) subjects with avanafil and 28 (29%) subjects with sildenafil had clinically significant drops in standing systolic blood pressure (≥ 30 mmHg) after nitrate administration.

The Sponsor states administration of avanafil to patients who use any form of organic nitrate is contraindicated due to the potentiation of hypotension. They advise patients taking avanafil wait at least 12 hours after the last dose of avanafil before nitrate administration is considered, and advised close medical supervision with appropriate hemodynamic monitoring.

TA-07 (multiple dose BID) was a non-randomized, open-label study in healthy male subjects, which assessed the single dose and steady-state (7 days) PK of avanafil 200 mg (2x100 mg tablets) following twice daily dosing.

The Sponsor states that following oral administration, the single dose and steady state T_{max} of avanafil were similar at 0.5 hr and that avanafil PK was linear and stationary over the multiple dosing regimens.

TA-010 (mass balance) was a single-dose, non-randomized, open-label, mass balance study in six healthy young male subjects, which assessed the absorption, distribution, metabolism, and excretion of 600 mg avanafil labeled with ¹⁴C given as a suspension.

The major metabolite is an open pyrrolidine ring carboxylic acid avanafil (M16) and monohydroxy avanafil (M4), which accounted for about 10.6% and 8.4% of the total radioactivity or 29% and 23% of the circulating concentration of unchanged avanafil, respectively. The mean recovery of administered radioactivity was approximately 62% in feces and 21% in urine. Fecal excretion was the major route of elimination of radioactivity and little or no total radioactivity was detected in blood and plasma after 10 hrs. Unchanged avanafil was not detected in pooled urine samples. Avanafil was extensively metabolized via phase 1 metabolism. The proposed major routes of biotransformation are hydroxylation, multiple N-dealkylation, demethylation and glucuronide conjugation.

TA-011 (CYP3A inhibitor interaction) was a randomized, open-label, parallel-group, one-sequence crossover study in healthy male subjects, which assessed the single-dose PK of avanafil when co-administered with ketoconazole, erythromycin, or ritonavir.

Group 1: ketoconazole 400 mg QD for 5 days (Days 2 to 6) plus a single dose of avanafil 50 mg on Days 1 and 6; Group 2: erythromycin 500 mg every 12 hours for 5 days (Days 2 to 6) plus a single dose of avanafil 200 mg on Days 1 and 6; Group 3: ritonavir 300 mg BID for 1 day (Day 2, 400 mg BID for 1 day (Day 3), and 600 mg BID for 5 days (Day 4 to 8) plus a single dose of avanafil 50 mg on Days 1 and 8.

The Sponsor states that strong CYP3A4 inhibitors such as ketoconazole and ritonavir increased the geometric LS mean C_{max} and AUC_{0-inf} of avanafil to approximately 3-fold and 14-fold, respectively. The Sponsor recommends the dose to be adjusted to 50 mg every 48 hrs for patients taking a potent CYP3A4 inhibitor. Co-administration of avanafil with a moderate CYP3A4 inhibitor erythromycin increased C_{max} and AUC_{0-inf} to approximately 2-fold and 3-fold, respectively. (b) (4)

No mild CYP3A4 inhibitor was evaluated.

TA-012 (hepatic impairment) was a single dose (200 mg), non-randomized, open-label, parallel-group, matched-control study which assessed the PK of avanafil in male subjects (age 45-69 years) with normal hepatic function and male subjects with mild or moderate hepatic impairment.

The Sponsor states that mild hepatic impairment (Child-Pugh Class A) had no effect on the PK of avanafil. The AUC_{0-inf} of avanafil in patients with moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy subjects and avanafil C_{max} was up to 57% lower in patients with moderate hepatic impairment compared to subjects with normal hepatic function. The Sponsor indicates no dose adjustment is required in patients with mild or moderate hepatic impairment, and use in patients with severe hepatic impairment is not recommended. No study in patients with severe hepatic impairment was conducted.

TA-013 (renal impairment) was a single dose (200 mg), non-randomized, open-label, parallel-group, matched-control study which assessed the PK of avanafil in male subjects with normal renal function and male subjects with mild or moderate (CrCl \geq 30 to <50 mL/min) renal impairment. Age range was 52 to 78 years.

The Sponsor defined mild renal impairment as those subjects with a CrCl ≥ 50 to < 80 mL/min. According to FDA's Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010), patients with mild renal impairment are those with eGFR or CLcr between 60 and 89 mL/min/1.73 m² or mL/min, respectively. The Sponsor claims that, compared to subjects with normal renal function, mild or moderate renal impairment had little influence on the maximum and systemic exposure of avanafil with the 90% CIs of the mean ratios of Cmax and AUC0-inf contained 100%. Cmax % mean ratio for avanafil was 104.02 and 99.96 for subjects with mild and moderate renal impairment, respectively. AUC0-inf % mean ratio for avanafil was 88.09 and 118.93 for subjects with mild and moderate renal impairment, respectively.

The Sponsor indicates no dose adjustment is required in patients with mild or moderate renal impairment, and use in patients with severe renal impairment or end stage renal disease (ESRD) is not recommended. No studies in patients with severe renal impairment or ESRD on hemodialysis were conducted.

TA-014 (age and sperm function) 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 43 yo, while the subjects in the elderly group were 65-80 yo. Avanafil semen exposure and the acute effect of avanafil on sperm function in healthy, young male subjects were also evaluated.

The Sponsor claims the following: avanafil was highly bound to plasma protein 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 $< 0.0002\%$ of the 200 mg administered; mean sperm motility did not change by $> 20\%$ from baseline and there was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress.

(b) (4)
However, there appears to be a slightly greater exposure of M16 in the elderly, compared to avanafil and M4.

TA-015 (alcohol interaction) was a single dose (200 mg), randomized, double-blind, placebo-controlled, 3-way crossover study in healthy male subjects (age 22 to 44 yrs), which assessed the hemodynamic interactions of avanafil and alcohol.

Treatment A: a single oral dose of 200 mg avanafil tablet plus an oral dose of alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kg of BW)

Treatment B: a single oral dose of placebo tablet plus an oral dose of alcohol drink mixed with fruit juice (0.5 g of absolute ethanol per kg of BW)

Treatment C: a single oral dose of 200 mg avanafil plus an oral dose of placebo drink mixed with fruit juice.

According to the Sponsor, alcohol administered at a dose of 0.5 g/kg is equivalent to approximately 3 oz of 80-proof vodka in a 70 kg male. There appears to be small potentiation of hypotensive effects due to avanafil co-administered with alcohol. In the proposed label, the Sponsor advises patients to be aware that both alcohol and avanafil act as (b) (4) vasodilators, (b) (4)

TA-016 (warfarin interaction) was a randomized, double-blind, placebo-controlled, 2-way crossover study in healthy male subjects, which assessed the effects of daily avanafil dosing (200 mg for 9 days) on the PK and pharmacodynamics (prothrombin time (PT) and international normalized ratio (INR) of a single dose (25 mg) of warfarin.

Based on the 90% CI of the geometric LS mean ratios for warfarin C_{max}, AUC_{0-t}, and AUC_{0-inf} falling within 90% to 125%, there appears to be no alteration in warfarin PK with avanafil co-administration. PT and INR also appear to be unchanged in the presence of avanafil.

TA-017 (α -adrenergic blocker interaction) was a randomized, double-blind, placebo-controlled, 2-cohort, 2-period crossover study which assessed the effects of the co-administration of 200 mg avanafil on the hemodynamic effects of doxazosin (1 to 8 mg daily for 11 days) or tamsulosin (0.4 mg daily for 11 days) in healthy, middle-aged (40 to 61 yo) male subjects.

The Sponsor states there were statistically significant differences in the maximum decrease from baseline in supine SBP, standing DBP, and supine DBP and the maximum increase from baseline in standing pulse rate, following co-administration of doxazosin and avanafil, compared to doxazosin and placebo.

The Sponsor states there were statistically significant differences in the maximum decrease from baseline in supine DBP and the maximum increase from baseline in supine pulse rate were observed following co-administration of tamsulosin and avanafil, compared with tamsulosin and placebo.

The Sponsor advises caution when avanafil is co-administered with alpha-blockers. Patients should be stable on α -blocker therapy prior to initiating treatment with avanafil, and avanafil should be initiated at the lowest 50 mg dose.

TA-018 (Effects of avanafil on CYP2C and CYP2D6)

Omeprazole (CYP2C19 substrate): Subjects received oral doses of omeprazole 40 mg QD for 8 days (Days 1 to 8) plus a single oral dose of avanafil 200 mg on Day 8. Co-administration of avanafil and omeprazole did not appear to significantly alter omeprazole AUC_{0-tau} (4940 vs. 4420 ng.hr/mL). C_{max} of omeprazole was slightly higher at 16.7% when avanafil was co administered.

Rosiglitazone (CYP2C8 substrate): Subjects were randomized to receive a single oral dose of rosiglitazone 8 mg or a single oral dose of rosiglitazone 8 mg plus a single oral dose of avanafil 200 mg. Co-administration of rosiglitazone and avanafil did not affect the systemic exposure (AUC_{0-inf} or AUC_{0-t}) of rosiglitazone; however, C_{max} of rosiglitazone was slightly lowered.

Desipramine (CYP2D6 substrate): Subjects were randomized to receive a single oral dose of desipramine 50 mg or a single oral dose of desipramine 50 mg plus a single oral dose of avanafil 200 mg. Co-administration of desipramine and avanafil did not affect the systemic exposure (AUC_{0-inf} or AUC_{0-t}) or maximum exposure of desipramine.

TA-019 (enalapril or amlodipine) was a randomized, double-blind, placebo-controlled, 2-cohort crossover study in healthy male subjects, which assessed the PK and hemodynamic effects of the co-administration of avanafil (200 mg) with enalapril (10 mg twice daily for 11 days) or amlodipine (5 mg once daily for 18 days).

The Sponsor states that a single dose of avanafil 200 mg co administered with enalapril caused a mean maximum change in SBP of -1.75/-3.46 mmHg compared to placebo. Single doses of avanafil 200 mg co-administered with amlodipine caused a mean maximum change in SBP of -1.18/+1.47 mmHg compared to placebo. They claim no statistically significant difference in the maximum change from baseline in standing SBP (primary endpoint) was observed following co-administration of avanafil with enalapril or amlodipine compared to placebo.

TA-020 (food effect, bioavailability, dose proportionality) was a single-dose, randomized, open-label, 4-period, crossover study in healthy male subjects, which assessed the effect of food on the PK of avanafil (2x100 mg Formulation II tablets), the relative bioavailability of two avanafil tablet formulations (2x100 mg Formulation I vs. 2x100 mg Formulation II), and the dose proportionality of avanafil (1x50 mg vs. 2x100 mg Formulation II).

The Sponsor states that systemic exposures (AUC_{0-inf}) to avanafil in the presence of high fat meal were considered of minimal clinical significance. Avanafil t_{max} was delayed by 1.25 hrs from 0.75 to 2.0 hrs, while C_{max} was reduced by 39% in the presence of a high fat meal. The Sponsor proposes avanafil may be taken without regard to food intake.

The increases in T_{max} and AUC_{0-inf} to avanafil between 50 and 200 mg doses under fasted conditions were shown to be slightly greater than dose proportional. The Sponsor states the lack of dose proportionality is likely due to the insufficient detectable concentration vs. time points during the elimination phase following the 50 mg dose.

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 avanafil on sperm function in healthy, young male subjects.

TA-140 (thorough QTc) was a single dose (100 or 800 mg), randomized, blinded, placebo- and active-controlled crossover thorough QT study in healthy male subjects (mean age: 28 years).

Following a single oral dose administration of avanafil, at dose levels of 100 mg or 800 mg, C_{max}, AUC_{0-t}, and AUC_{0-inf} increased approximately dose proportionally by 6.9, 10.8, and 10.5 fold, respectively, with an 8 fold increase in dose level from 100 mg to 800 mg. The time-matched analysis for the QTcI data revealed that all time points had a placebo and baseline corrected result less than 10 msec for the upper CI, except for the 3 hour time point for the 800 mg dose of avanafil, which reached 10.2 msec.

In Vitro Studies

10-AVANAFIL-BCS-01 and 10-AVANAFIL-PGP-01

In Caco-2 monolayers, the apical to basolateral apparent permeability (P_{app}) of avanafil was determined to be 44.6×10^{-6} cm/sec, while the basolateral to apical P_{app} was 73.4×10^{-6} cm/sec. With an efflux ratio (R_E) less than 2, the Sponsor states that avanafil is a weak substrate of P-glycoprotein transporter (P-gp). Based on studies in multi-drug resistance gene and Madin-Darby canine kidney wild type cells, the Sponsor estimated R_E (R_{E(MDR1)}/R_{E(MDCK-WT)}) to be 1.8, which is lower than the suggested value of 2 according to OCP's drug interaction guidance on assessing whether a drug molecule is a P-gp substrate. Based on the in vitro study results, the Sponsor determined that in vivo studies to assess the effect of P-gp inhibition on avanafil PK or the effect of avanafil on P-gp substrates such as digoxin were not necessary.

10-AVANAFIL-PK-12 (protein binding)

The extent of avanafil binding to plasma proteins was determined by ultrafiltration in human plasma over a concentration range of 0.3 to 3.0 mcg/mL. At 0.3 mcg/mL, mean unbound fraction of avanafil was ~1%. The Sponsor states protein binding was reversible and did not appear to be saturable over the concentration range studied. Avanafil was 99% bound to albumin, 43% to γ -globulin, and 66% to α -glycoprotein.

10-AVANAFIL-PK-15, 10-AVANAFIL-PK-16 and 10-AVANAFIL-PK-17

Metabolism of avanafil by CYP450s was evaluated in vitro using immunoinhibition and recombinant human CYP450s. The Sponsor states the formation of major metabolites of avanafil was catalyzed primarily by CYP3A4, with a minor contribution by CYP2C.

Based on *in vitro* results obtained from human liver microsomes, the Sponsor determined that there was a low potential for drug interactions with substrates of CYP1A1/2, 2A6, 2E1 and 2B6; a likely potential for drug interaction with substrates of 2C19; and possible interaction with substrates of CYP3A4, 2D6 and 2C8/9.

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/s/

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08/29/2011

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