Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Avanafil

Proprietary Product Name: Spedra

Sponsor: A Menarini Australia Pty Ltd

First Round CER report: 30 January 2015
Second Round CER report: 25 June 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the drug concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the drug concentration-time curve from time zero to the time of the last measurable concentration
$AUC_{0\text{-}tau}$	Area under the drug concentration-time curve over the dosing interval
$AUEC_{0\text{-}t}$	Area under the effect-time curve from time 0 to time t
BID	Twice daily
BMI	Body mass index
cGMP	Cyclic guanosine monophosphate
CL_{int}	Intrinsic metabolic clearance
C_{max}	Maximum observed plasma drug concentration
$C_{max,ss}$	Maximum observed plasma drug concentration at steady-state
CSR	Clinical Study Report
DAE	Discontinuation due to adverse event
DBP	Diastolic blood pressure
EAS	Erection Assessment Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Erectile dysfunction

Abbreviation	Meaning
EF	Erectile function
EOT	End of treatment
FDA	US Food and Drug Administration
GCP	Good clinical practices
HbA1c	Haemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
IC_{50}	Half maximal inhibitory concentration
IIEF	International Index of Erectile Function
INR	International normalized ratio
ITT	Intent to treat
IVRS	Interactive voice response system
LOCF	Last observation carried forward
LS	Least squares
MDCK-WT	Madin-Darby canine kidney wild type
MDR1	Multi-drug resistance gene
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OTC	Over the counter
Papp	Apparent permeability
PD	Pharmacodynamic
PDE5	Phosphodiesterase 5
Pgp	P-glycoprotein
PK	Pharmacokinetic
PT	Prothrombin time
QD	Once daily

Abbreviation	Meaning
QTcB	Bazett-corrected QT
QTcF	Fridericia-corrected QT
QtcI	Individual-corrected QT
RE	Efflux ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SEP	Sexual Encounter Profile
SOC	System organ class
TEAE	Treatment-emergent adverse event t½ Terminal elimination half-life
T_{max}	Time to reach the maximum plasma concentration
VSS	Visual sexual stimulation

1. Introduction

This is a submission to obtain registration for a new chemical entity avanafil tablets (Spedra) with proposed indications for the treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required.

1.1. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

- Spedra (avanafil) 50 mg tablets blister package
- Spedra (avanafil) 100 mg tablets blister package
- Spedra (avanafil) 200 mg tablets blister package

1.2. Dosage and administration

The proposed dosage recommendations are:

Use in adult men:

The recommended dose is 100 mg taken as needed at least 15 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once per day.

Spedra may be taken with or without food.

Use in Older men (≥ 65 years old):

Dose adjustments are not required in older patients. However, it should be considered that comorbidities increase with age.

Patients with Renal impairment:

Dose adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min) - CKD Stage 2 - 3. The pharmacokinetics of Spedra in patients with severe renal disease or on renal dialysis (CKD stage 4 - 5) has not been studied; Spedra is contraindicated in these patients.

Patients with Hepatic impairment:

Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum effective dose and adjust dosage based on tolerance. The pharmacokinetics of Spedra in patients with severe hepatic disease (Child Pugh class C) has not been studied; Spedra is contraindicated in these patients.

Concomitant use of CYP3A4 inhibitors:

In patients receiving concomitant treatment with moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of Spedra should not exceed 100 mg, with an interval of at least 48 hours between doses. Co-administration of Spedra with potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) is contraindicated.

2. Clinical rationale

Erectile dysfunction is a common condition in males aged 40 to 70 years, affecting 30% to 50% of that population. The condition may decrease quality of life for affected males and their partners. The current standard of care is oral treatment with phosphodiesterase 5 (PDE5) inhibitors, a number of which are currently approved for marketing in Australia, including sildenafil, tadalafil and vardenafil.

The sponsor states that 'Avanafil is a new PDE5 inhibitor for oral administration and was developed for its high selectivity for the PDE5 isoenzyme relative to other PDE5 inhibitors. Avanafil is rapidly absorbed following administration, reaching peak plasma concentration between 30 - 45 minutes in the fasted state giving the opportunity for clinical effectiveness as early as 15 minutes after administration.'

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 18 clinical pharmacology studies, including 12 that provided pharmacokinetic data and 9 that provided pharmacodynamic data.
- One population pharmacokinetic analyses.
- Four pivotal efficacy/safety studies.
- Three dose-finding studies.
- One other efficacy/safety study.
- One PSUR.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

The clinical studies all have statements of adherence to, and appear to have adhered to, Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Study HP-01
		Study TA-140
	Multi-dose	Study TA-02
	Mass balance	Study TA-07 Study TA-010
	Bioequivalence† - Single dose	Study TA-020
	Food effect	Study TA-020
	Hepatic impairment	Study TA-012
	Renal impairment	Study TA-013
	Elderly	Study TA-014
PK interactions	Ketoconazole, erythromycin, ritonavir	Study TA-0911
	Warfarin	Study TA-016
	Omeprazole, rosiglitazone, desipramine	Study TA-018
Population PK analyses	Healthy subjects	Study VIVU-RAS-002

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

Sites and mechanisms of absorption

The typical T_{max} for avanafil in the fasted state was 0.75 hours and in the fed state was 2 hours (Study VIVU-RAS-002).

4.2.1.2. Bioavailability

Absolute bioavailability

Absolute bioavailablity data were not provided.

Bioavailability relative to an oral solution or micronised suspension

Data for bioavailability relative to an oral solution or micronised suspension were not provided.

Bioequivalence of clinical trial and market formulations

The formulation used in the Phase III studies is the same as that intended for marketing in Australia.

Bioequivalence of different dosage forms and strengths

The 50 mg, 100 mg and 200 mg tablet strengths are bioequivalent in the fasted state (Table 2). However, absorption was faster with the 50 mg tablet strength compared to the 200 mg tablet strength: median t_{max} 0.5 hours compared to 0.75 hours respectively.

Table 2: Pharmacokinetic results

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

Bioequivalence to relevant registered products

Not applicable.

Influence of food

Compared to the fasted state, food delays absorption and decreases C_{max} for avanafil, but overall exposure is unchanged (Study TA-020, Table 2). In Study TA-020, the mean % ratio (90% CI) fed to fasted for C_{max} was 61.0 (52.57 to 70.79) and for AUC_{0-inf} was 96.20 (88.86 to 104.14). The median (range) t_{max} was 0.75 (0.47 to 2.0) hours for fasted and 2.0 (1.2 to 4.0) hours for fed. In Study HP-01, at the 100 mg dose level, food decreased C_{max} by 25% and median t_{max} increased

from 0.63 hours to 1.73 hours, while there was no significant change in $AUC_{0\text{-}inf}$ (Table 3). The effects of food on C_{max} and T_{max} were confirmed in the population pharmacokinetic study (Study VIVU-RAS-002).

Table 3: Pharmacokinetic results

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 (µg)	Clr (mL/min)
100	Mean	1156.73	0.63	16.69	2909.93	3451.09	6.0	0.037
(Fasted)	SD	128.24	0.25-1.25	16.51	480.60	844.74	4.7	0.035
100	Mean	876.28	1.75	9.15	3632.10	3942.83	9.8	0.048
(Fed)	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	-	-

(1) : Wilcoxon signed rank test

Dose proportionality

There was dose proportionality between a 50 mg and a 200 mg dose in the fasted state (Study TA-020, Table 2). In Study HP-01 there was dose proportionality from 12.5 mg up to 600 mg (Table 4).

Table 4: Pharmacokinetic results for increasing doses

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 (µg)	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	Mean	1156.73	0.63	16.69	2909.93	3451.09	6.0	0.037
(Fasted)	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**

Dose proportionality was maintained during multiple dosing in the 50 mg to 200 mg dose range (Table 5).

Table 5: Dose proportionality

	Plasma TA-1790					
	Treatment A		Treatment B		Treatment C	
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD
Cmax(ug/mL)	0.401	0.136	0.892	0.419	2.181	0.636
Cmin(ug/mL)	0.000	0.000	0.000	0.000	0.000	0.000
Tmax(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
T1/2(hr)	1.28	0.737	1.46	0.785	1.34	0.363
Kel(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
Vz/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
Cmax/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(Cmax/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 = 50 mg TA-1790 QD Administration
Treatment B = 100 mg TA-1790 QD Administration
Treatment C = 200 mg TA-1790 QD Administration

Samples below the quantifiable limit of 1252 (the values reported in this table are plasma concentrations; 0.00626 is the concentration in the preparation that is injected onto the column that has been diluted 20-fold are reported as 0.000.

There was dose proportionality between 100 mg and 800 mg single doses for avanafil, M4 and M6 (Study TA-140). For avanafil the mean (SD) $AUC_{0\text{-}inf}$ for 100 mg was 2657 (1014) ng*hour/mL and for 800 mg was 27879 (11555) ng*hour/mL, and C_{max} was 980 (3430) ng/mL and 6802 (2873) ng/mL respectively. For M4 the mean (SD) $AUC_{0\text{-}inf}$ for 100 mg was 1081 (290) ng*hour/mL and for 800 mg was 9740 (3271) ng*hour/mL, and C_{max} was 248 (77.0) ng/mL and 1521 (506) ng/mL respectively. For M16 the mean (SD) $AUC_{0\text{-}inf}$ for 100 mg was 838 (220) ng*hour/mL and for 800 mg was 8198 (2868) ng*hour/mL, and C_{max} was 359 (120) ng/mL and 2098 (883) ng/mL respectively.

Bioavailability during multiple-dosing

There were no changes in bioavailability noted during multiple daily dosing in the 50 mg to 200 mg dose range (Table 5). There was no accumulation with twice daily dosing of 200 mg over a one week period. Steady state was achieved within 48 hours.

Effect of administration timing

The effect of administration timing was not addressed in the PK studies.

4.2.1.3. Distribution

Volume of distribution

In Study HP-01, the volume of distribution is in the range 47 to 83 L. In Study TA-02 volume of distribution was in the range 89 to 102 L in the dose range 50 g to 200 mg. The volume of distribution increases with body weight (Study VIVU-RAS-002).

Plasma protein binding

Avanafil and its M4 metabolite are highly protein bound: 98.6% to 99.1% and 95.5% to 97.2% respectively (Study TA-012). The M16 metabolite is moderately protein bound: 81.2% to 85.7%. In Study TA-014 avanafil plasma protein binding was approximately 99%.

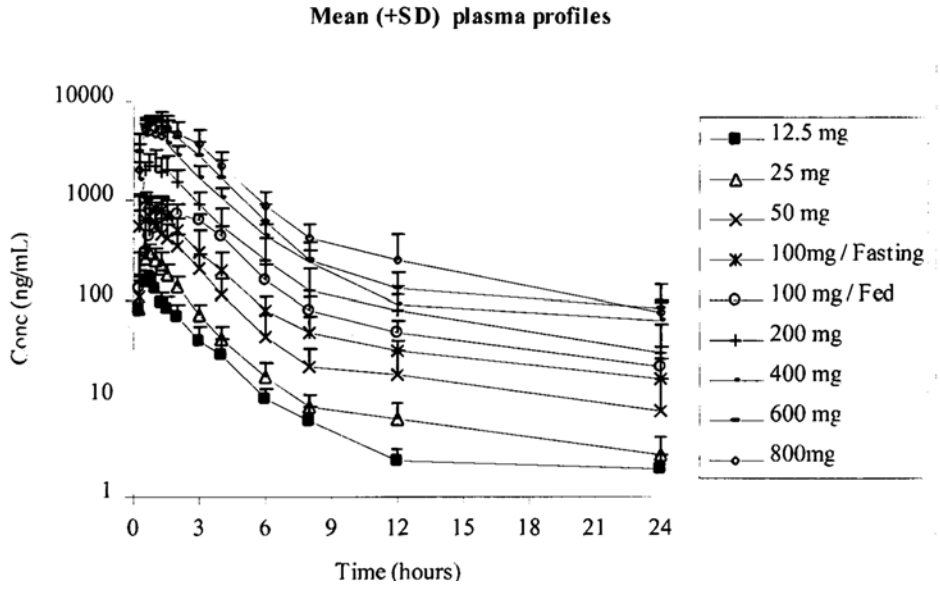
Erythrocyte distribution

Erythrocyte distribution was not described in the data.

Tissue distribution

Following oral dosing, avanafil demonstrates a biexponential elimination pattern, indicating a redistribution phase (Figure 1).

Figure 1: Mean ± SD plasma concentration versus time profiles after single oral administration of avanafil in healthy volunteers (semi-log scale)



The mean avanafil concentration 1 hour post-dose in seminal fluid was 151 ng/mL (Study TA-014, Table 6).

Table 6: Pharmacokientics of avanafil, M4 and M16 isomers

					Cohort B Versus Cohort A	
Pharmacokinetic Parameters	Elderly Subjects	N	Young Subjects	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	.	.

Cohort A: one 200 mg avanafil tablet in male subjects 18 to 45 years of age, inclusive
Cohort B: one 200 mg avanafil tablet in male subjects at least 65 years of age
The data for four subjects (Subjects 11, 15, 18 [Cohort A] and 113 [Cohort B]) were not included in the statistical analysis of $AUC_{0-\infty}$ because the coefficient of determination (R^2 value) for the k_{el} calculation was < 0.8 or the slope was undefined.
[a] C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented as geometric LS means 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 as arithmetic mean ± SD and is presented with two significant figures.
. = Value missing or not reportable.
CI = confidence interval; SD = standard deviation
Parameters were log-transformed prior to analysis. % Mean Ratio = 100*(test/reference)
Source: Tables 14.2.1.3, 14.2.1.4 and 14.2.1.7.2

					Cohort B Versus Cohort A	
Pharmacokinetic Parameters	Elderly Subjects	N	Young Subjects	N	90% CI	% Mean Ratio
C_{max} (ng/mL)[a]	575	14	578	18	(81.48, 121.34)	99.43
AUC_{0-t} (ng*hr/mL)[a]	2730	14	2420	18	(93.11, 136.15)	112.59
AUC_{0-inf} (ng*hr/mL)[a]	2860	13	2760	16	(90.03, 118.45)	103.27
t_{max} (hr)[b]	0.78 (0.50, 2.0)	14	0.76 (0.50, 1.5)	18	.	.
$t_{1/2}$ (hr)[c]	6.9 ± 1.5	13	6.9 ± 1.9	16	.	.

					Cohort B Versus Cohort A	
Pharmacokinetic Parameters	Elderly Subjects	N	Young Subjects	N	90% CI	% Mean Ratio
C_{max} (ng/mL)[a]	1330	14	878	18	(117.34, 194.77)	151.18
AUC_{0-t} (ng*hr/mL)[a]	3950	14	2150	18	(148.71, 226.07)	183.35
AUC_{0-inf} (ng*hr/mL)[a]	4240	11	2500	15	(147.73, 195.26)	169.84
t_{max} (hr)[b]	0.78 (0.55, 1.5)	14	0.57 (0.50, 1.0)	18	.	.
$t_{1/2}$ (hr)[c]	7.2 ± 1.5	11	7.9 ± 2.5	15	.	.

The mean M4 concentration in seminal fluid was 531 ng/mL. The mean M16 concentration in seminal fluid was 588 ng/mL. The mean avanafil, M4 isomers and M16 isomers semen/plasma

concentration ratios were 0.07, 0.83, and 0.74, respectively. There were similar findings in a second study of avanafil and metabolites in seminal fluid (Study TA-021, Table 7).

Table 7: Arithmetic Mean (SD) and Geometric Mean Pharmacokinetic Parameters for Plasma Avanafil, M4, and M16

		Avanafil		M4		M16	
Matrix	Parameter	Arithmetic Mean ± SD (N)	Geometric Mean	Arithmetic Mean ± SD (N)	Geometric Mean	Arithmetic Mean ± SD (N)	Geometric Mean
Plasma	Concentration (ng/mL)	3200 ± 1150	3020	557 ± 150	537	958 ± 308	906
		(17)		(17)		(17)	
Seminal Fluid	Concentration (ng/mL)	185 ± 89.4	168	404 ± 143	377	367 ± 132	339
		(17)		(17)		(17)	
	Volume (mL)	2.81 ± 0.798	2.68	2.81 ± 0.798	2.68	2.81 ± 0.798	2.68
		(17)		(17)		(17)	
	Total Amount (ng)	512 ± 260	449	1100 ± 456	1010	983 ± 352	907
		(17)		(17)		(17)	
	% Dose (%)	0.0002562 ± 0.00013021	0.0002245	.	.	.	.
		(17)		.	.	.	.
Seminal Fluid/Plasma	Concentration Ratio	0.06 ± 0.02	0.06	0.74 ± 0.26	0.70	0.43 ± 0.22	0.37
		(17)		(17)		(17)	

Volume = Estimated total semen sample volume
Total Amount = Concentration x Volume
% Dose = Total Amount / Avanafil Dose *100
Seminal Fluid/Plasma Ratio = Seminal Fluid Concentration / Plasma Concentration
Plasma concentration, seminal fluid concentration and seminal fluid total amount are presented with three significant figures.
Seminal fluid / plasma concentration ratios are presented with two decimals.

4.2.1.4. Metabolism

Interconversion between enantiomers

No data were included in the submission with regard to interconversion between anantomers.

Sites of metabolism and mechanisms/enzyme systems involved

Avanafil is predominantly metabolised in the liver by CYP3A4 and to a lesser extent CYP2C9.

Non-renal clearance

The predominant route of elimination of avanafil is in the faeces.

Metabolites identified in humans

Active metabolites

The M4 metabolite has an in vitro inhibitory potency for PDE5 that is 18% that of the parent (avanafil). The M4 metabolite is predicted to account for approximately 4% of total pharmacological activity. The M16 metabolite is inactive.

Other metabolites

In vitro, avanafil underwent extensive biotransformation in human liver microsomes with at least 11 metabolites identified.

Pharmacokinetics of metabolites

In the dose range 12.5 mg to 800 mg, single dose, plasma concentrations of the primary metabolites were not sufficient to enable the estimation of the PK parameters (Table 4).

Consequences of genetic polymorphism

No pharmacogenetic data were included in the submission.

4.2.1.5. Excretion

Routes and mechanisms of excretion

Apparent clearance (CL/F) is around 60 L/hour (Table 3).

Mass balance studies

In the mass balance study, Study TA-010, mean (CV%) CL/F of unchanged avanafil was 65.86 (14) L/hour and t½ was 12.74 (39) hours. Approximately 21% of the administered dose was excreted in the urine, but only 0.02% as unchanged avanafil. The main urinary metabolite was M16 (an open pyrrolidine ring carboxylic acid avanafil). Approximately 62% of administered dose was recovered in the faeces, primarily in the form of metabolites, the major faecal metabolites being M10 (carboxylic acid avanafil) and M16. In one subject only 46% of the administered dose was recovered in the faeces.

Renal clearance

Renal clearance of unchanged avanafil is in the range 0.037 to 0.051 mL/min in the dose range 12.5 mg to 100 mg (Table 4).

4.2.1.6. Intra- and inter-individual variability of pharmacokinetics

Inter-individual and intra-individual variability of avanafil was acceptable. Volume of distribution increases with weight (Study VIVU-RAS-002). The other factors influencing PK were food and CYP Inhibitors.

4.2.2. Pharmacokinetics in the target population

No PK data in the target population were included in the submission.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

In subjects with mild hepatic impairment, there was no significant difference in exposure to avanafil or the M4 metabolite, but there was a 50% increase in exposure to the M16 metabolite (Study TA-012). For avanafil the % mean ratio (90% CI), mild hepatic impairment/normal, was 99.90 (67.08 to 148.78) for $AUC_{0\text{-}inf}$ and 96.05 (62.61 to 147.34) for C_{max}. For M4 the % mean ratio (90% CI), mild hepatic impairment/normal, was 101.02 (75.92 to 134.41) for $AUC_{0\text{-}inf}$ and 96.89 (61.92 to 151.60) for C_{max}. For M16 the % mean ratio (90% CI), mild hepatic impairment/normal, was 149.91 (102.74 to 218.74) for $AUC_{0\text{-}inf}$ and 137.04 (89.65 to 209.48) for C_{max}. T_{max} and t½ were similar for the two groups.

In subjects with moderate hepatic impairment, avanafil C_{max} was decreased by 60%, % mean ratio (90% CI) 42.68 (27.82 to 65.47), but overall exposure was unchanged, $AUC_{0\text{-}inf}$ % mean ratio (90% CI) 102.53 (67.52 to 155.69). Also for the M4 metabolite C_{max} was decreased by 44%, % mean ratio (90% CI) 46.03 (29.42 to 72.02), but there was no significant change in overall exposure, $AUC_{0\text{-}inf}$ % mean ratio (90% CI) 88.55 (63.94 to 122.62). M16 exposure was similar for the two groups: C_{max} % mean ratio (90% CI) 72.45 (47.40 to 110.75) and for $AUC_{0\text{-}inf}$ 118.48 (78.16 to 179.59). T_{max} and t½ were similar for the two groups.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

In subjects with mild impairment of renal function, in comparison with normal renal function, there was similar exposure to avanafil: C_{max} mean ratio (90% CI), mild renal impairment/normal renal function, 104.02 (73.34 to 147.53) and for $AUC_{0\text{-}inf}$ 88.09 (61.43 to 126.31). There was no significant difference in exposure to the M4 metabolite: mean ratio (90% CI) for C_{max} 116.21 (85.51 to 157.93) and for $AUC_{0\text{-}inf}$ 107.38 (87.42 to 131.90). For the M16 metabolite there was no significant difference for C_{max}: 133.40 (91.76 to 193.93); but $AUC_{0\text{-}inf}$ was increased by 48%: 148.30 (104.44 to 210.57). T_{max} and t½ were similar for the two groups.

In subjects with moderate impairment of renal function, in comparison with normal renal function, there was similar exposure to avanafil: the mean ratio (90% CI), mild renal impairment/normal renal function, for C_{max} was 99.96 (70.48 to 141.78) and for $AUC_{0\text{-}inf}$ 118.93 (80.86 to 174.92). For M4 there was a similar C_{max} but overall exposure was greater: the mean ratio (90% CI) for C_{max} was 100.29 (73.80 to 136.29) and for $AUC_{0\text{-}inf}$ 135.55 (109.66 to 167.54). Also for M16 there was a similar C_{max} but overall exposure was greater: the mean ratio (90% CI) for C_{max} was 124.69 (85.77 to 181.27) and for $AUC_{0\text{-}inf}$ 235.37 (163.59 to 338.66). T_{max} and t½ were similar for the two groups.

4.2.3.3. Pharmacokinetics according to age

There was no significant difference in PK parameters between healthy young males and healthy elderly males for a 200 mg single dose (Study TA-014, Table 6). The % mean ratio (90% CI) for $AUC_{0\text{-}inf}$ was 98.47 (77.46 to 125.18) % and for C_{max} was 100.38 (80.42 to 125.29) %. There was greater exposure to the M16 metabolite in elderly subjects: % mean ratio (90% CI) for $AUC_{0\text{-}inf}$ was 169.84 (147.73 to 195.26) % and for C_{max} was 151.18 (117.34 to 194.77) %. There was no significant increase in exposure to the M4 metabolite.

4.2.3.4. Pharmacokinetics related to genetic factors

PK in relation to genetic factors was not addressed in the submission.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

The population PK study indicated that CYP Inhibitors result in a clinically significant increase in exposure to avanafil (Study VIVU-RAS-002).

Ketoconazole increased exposure to avanafil thirteen-fold, increased exposure to the M4 metabolite by 20% and decreased exposure to the M16 metabolite by 40%. The % mean ratio, avanafil + ketoconzole/avanafil for $AUC_{0\text{-}t}$ was 1346.85 (1138.27 to 1652.70) for avanafil, 121.42 (104.61 to 140.94) for M4 and 57.18 (47.72 to 68.52) for M16. The mean t½ for avanafil increased from 1.39 hours to 8.50 hours with ketoconazole.

Erythromycin increased exposure to avanafil threefold, increased exposure to the M4 metabolite by 90% and did not significantly alter exposure to the M16 metabolite. The % mean ratio, avanafil + erythromycin/avanafil for $AUC_{0\text{-}t}$ was 348.81 (285.65 to 425.94) for avanafil, 190.02 (161.83 to 223.12) for M4 and 117.42 (98.53 to 139.93) for M16. The mean t½ for avanafil increased from 2.22 hours to 7.81 hours with erythromycin.

Ritonavir increased exposure to avanafil thirteen-fold, decreased exposure to the M4 metabolite by 32% and decreased exposure to the M16 metabolite by 57%. The % mean ratio, avanafil + ritonavir/avanafil for $AUC_{0\text{-}t}$ was 1266.86 (1023.93 to 1567.43) for avanafil, 68.39 (54.90 to 85.91) for M4 and 42.77 (31.42 to 58.23) for M16.

Avanafil did not have any clinically significant effects on exposure to warfarin. Following a 25 mg single dose of warfarin, the % mean ratio (90% CI), warfarin + avanafil/warfarin + placebo, for $AUC_{0\text{-}inf}$ was 100.74 (97.88 to 103.68) for R-warfarin and 102.20 (100.19 to 104.26) for S-warfarin.

Avanafil did not have any clinically significant effects on exposure to omeprazole. Following 40 mg omeprazole, at steady state, there was a 12% increase in AUC and 17% increase in C_{max}: % mean ratio (90% CI), omeprazole + avanafil/omeprazole, for $AUC_{0\text{-}t}$ was 111.91 (103.85 to 120.60) and for C_{max} was 116.73 (99.68 to 136.70).

Avanafil did not have any clinically significant effects on exposure to rosiglitazone. Following 8 mg rosiglitazone, single dose, there was no significant effect on AUC but a 12% decrease in C_{max}: % mean ratio (90% CI), rosiglitazone + avanafil/rosiglitazone, for $AUC_{0\text{-}t}$ was 103.49 (100.41 to 106.66) and for C_{max} was 87.84 (80.40 to 95.97).

Avanafil did not have any clinically significant effects on exposure to desipramine. Following 50 mg desipramine, single dose, there was no significant effect on AUC or C_{max}: % mean ratio (90% CI), desipramine + avanafil/desipramine, for AUC_{0-t} was 104.08 (98.82 to 109.62) and for C_{max} was 103.30 (97.10 to 109.89).

Avanafil did not have any clinically significant effects on exposure to amlodipine (Study TA-019,). Following 5 mg amlodipine, at steady state, there was no significant effect on AUC or C_{max}: % mean ratio (90% CI), amlodipine + avanafil/amlodipine, for AUC_{0-t} was 94.39 (91.24 to 97.64) and for C_{max} was 89.37 (86.21 to 92.65). However, amlodipine increased exposure to avanafil by 60% and increased its t½: % mean ratio (90% CI), amlodipine + avanafil/avanafil, for AUC_{0-t} was 159.87 (135.25 to 188.98) and for C_{max} was 128.48 (101.89 to 162.02); median t½ increased from 6.2 hours to 8.2 hours.

4.2.4.2. Clinical implications of in vitro findings

Membrane permeability studies indicated that avanafil has high passive permeability and is unlikely to have significant interactions with P-glycoprotein. Study 10-AVANAFIL-BCS-01 indicated that avanafil has high passive permeability, and is a modest P-glycoprotein substrate in Caco-2 cells. Study 10-AVANAFIL-PGP-01 indicated avanafil is a weak substrate of P-glycoprotein and there was no clear indication of inhibition of P-glycoprotein.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of avanafil have been adequately characterised. The dosing recommendations in the proposed PI with regard to hepatic impairment, renal impairment, age and drug interactions are supported by the PK data.

However, the PK data indicate that the 50 mg formulation was absorbed more rapidly than the 200 mg formulation; and that food increases T_{max} from 0.75 hours to 2.0 hours. These findings are important because the potential for rapid onset of action would be an advantage for avanafil in comparison with currently available treatments for ED.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 8 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 8: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Secondary Pharmacology	Effect on sperm function	Study TA-014,
		Study TA-021
	Effect on colour vision	Study TA-016
	Effect on QT interval	Study TA-140
PD Interactions	Warfarin	Study TA-016
	Glyceryl trinitrate	Study TA-04

PD Topic	Subtopic	Study ID
	Ethanol	Study TA-015
	Doxazosin, tamsulosin	Study TA-017
	Enalapril, amlodipine	Study TA-019

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by avanafil produces increased levels of cGMP in the corpus cavernosum of the penis. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Avanafil has no effect in the absence of sexual stimulation.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The primary pharmacodynamic effects were not investigated in the clinical pharmacology studies.

5.2.2.2. Secondary pharmacodynamic effects

Following a single dose of avanafil 200 mg, mean sperm motility one hour post dose did not change by ≥ 20% from baseline and there was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress (Study TA-014). Avanafil 200 mg did not affect semen volume, sperm concentration, total sperm count, % normal forms, total motile count, % motility, forward progression, WHO calculated forward progression, or vitality (Study TA-021)

Effects of avanafil on colour vision were assessed in Study TA-016 using the Farnsworth-Munsell 100-Hue test. In combination with warfarin, there was no significant effect of avanafil on the measures of colour vision.

Study TA-140 was a Thorough QT study that explored the effects of avanafil 100 mg and 800 mg on QT interval Table 9). There were no concerns with regard the 100 mg dose level, but for the 800 mg dose level at 3 hours, the upper 90% CI was > 10 (that is, above the boundary for regulatory concern). This issue is discussed further in Safety below.

Table 9: Effect on QT interval

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

[1] Mixed Effects General Linear Model (placebo-adjusted baseline-corrected) is fit for QTc Individual (msec) and includes terms for: treatment, time, a time by treatment interaction and baseline value.
[2] Lower/upper Bound = lower/upper 2-sided 90% (1-sided 95%) ANOVA model based confidence limit.

5.2.3. Time course of pharmacodynamic effects

Time course of effect was addressed in the Phase III studies.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The pharmacokinetic/pharmacodynamic relationships were not investigated in the clinical pharmacology studies.

5.2.5. Genetic-, and age-related differences in pharmacodynamic response

Genetic and age-related differences in pharmacodynamic response were not addressed in the clinical pharmacology studies.

5.2.6. Pharmacodynamic interactions

Avanafil did not have any significant effect on the anticoagulant effects of warfarin. The % mean ratio (90% CI), warfarin + avanafil/warfarin + placebo for INR was 99.08 (90.82 to 107.33) for AUEC0-168 and 95.82 (89.30 to 102.34) for E_{max}. Avanafil had no significant effect on platelet aggregation in combination with warfarin.

There was a clinically significant fall in sitting systolic blood pressure (SBP), of approximately 4 mmHg, when glyceryl trinitrate (GTN) was administered 0.5 hours after avanafil, but not when administered 1 hour or more after avanafil (Study TA-04). The drop in sitting SBP was similar to that observed with sildenafil. There was a similar decrease in standing SBP. There was also an increase in pulse rate of 3 bpm. Symptomatic hypotension was reported following GTN for 28 (27%) with avanafil, 28 (29%) with sildenafil and 12 (12%) with placebo.

Following a single standard drink of ethanol, in subjects treated with avanafil there was a clinically non-significant fall in SBP and DBP of approximately 3 mmHg and rise in pulse rate of 4 bpm. Combining avanafil with ethanol (single standard measure) produced a mean fall in SBP of 3.53 mmHg, a fall in DBP of 4.54 mmHg and a rise in pulse rate of 9.33 bpm.

In subjects treated with doxazosin, the addition of avanafil 200 mg resulted in a mean decrease in standing DBP of 6.42 bpm and an increase in pulse rate of 7.21 bpm. There was a decrease in supine SBP of 6.00 mmHg and DBP of 5.58 mmHg, with an increase in pulse rate of 3.75 bpm. In

combination, three subjects had standing SBP < 85 mmHg, one had standing SBP decrease > 30 mmHg, two had DBP < 45 mmHg and four had decrease in standing DBP > 20 mmHg.

In subjects treated with tamsulosin, the addition of avanafil 200 mg resulted in a mean decrease in standing DBP of 3.70 bpm and an increase in pulse rate of 2.46 bpm. There was a decrease in supine SBP of 3.13 mmHg and DBP of 3.33 mmHg, with an increase in pulse rate of 4.67 bpm. In combination, two subjects had standing SBP < 85 mmHg, one had standing SBP decrease > 30 mmHg, two had DBP < 45 mmHg and four had decrease in standing DBP > 20 mmHg. One subject had decrease in supine DBP > 20 mmHg.

In subjects treated with enalapril, the addition of avanafil 200 mg did not result in any significant change in standing vital signs. There was a decrease in supine SBP of 1.75 mmHg and DBP of 3.46 mmHg, with an increase in pulse rate of 0.96 bpm. One subject each had decrease in supine SBP > 30 mmHg, supine DBP < 45 mmHg and decrease in supine DBP > 20 mmHg.

In subjects treated with amlodipine, the addition of avanafil 200 mg did not result in any clinically significant change in standing vital signs. There was a decrease in supine SBP of 1.18 mmHg and DBP of 1.47 mmHg, with an increase in pulse rate of 1.00 bpm. One subject had a decrease in supine DBP > 20 mmHg.

5.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic data addressed the issues of disturbance of colour vision, effects on sperm function and QT prolongation. There was no effect on colour vision or sperm function. The data on QTc prolongation were equivocal.

Avanafil did not interact with ethanol or amlodipine. However, in combination with glyceryl trinitrate, enalapril or alpha blockers there were decreases in blood pressure that may be clinically significant.

6. Dosage selection for the pivotal studies

6.1. Study TA-01

Study TA-01 was a single blind, randomised, crossover, dose finding study of avanafil in conjunction with visual sexual stimulation (VSS) in subjects with erectile dysfunction. The study was conducted at 8 centres in the US from March 2002 to August 2002. The study included male subjects, 35 to 70 years of age, with a ≥ 6-month history of mild-to-moderate ED; who were not using androgen therapy that had not been stable for 3 months or other prohibited therapies; with no history of chronic blood pressure < 90/50 mmHg or > 170/100 mmHg or recent stroke or myocardial infarction; and with no significant medical condition or social problem that would interfere with study evaluations or otherwise contraindicate study participation. The study treatments were:

1. Avanafil: at 50 mg, 100 mg or 200 mg. These dose groups were recruited sequentially
2. Placebo
3. Sildenafil 50 mg

The study treatments were administered as three single doses on separate days in a random sequence. The primary outcome measure was measured using the RigiScan. The reporters were blinded to treatment allocation. The outcome measures were:

- Time to ≥ 60% rigidity (tip and base):
- Duration of ≥ 60% rigidity (tip and base)

- Maximum rigidity (tip and base)
- Tumescent Activity Units - TAU (tip and base)
- Rigidity Activity Units – RAU (tip and base)
- Responses to the 5-point Erection Assessment Scale (EAS)

The safety outcome measures were vital signs and adverse events.

There were 297 subjects screened, and 83 were randomised and received study drug: 27 were treated with avanafil 50 mg, 28 with 100 mg, and 28 with 200 mg. One subject did not complete. All subjects were male, and the age range was 26 to 70 years. ED was organic for 50 (60.2%) subjects, psychological for 7 (8.4%) and mixed for 26 (31.3%). Race was Caucasian for 56 (67.5%) subjects and Black for 20 (24.1%).

For the efficacy outcome measures:

- Time to ≥ 60% rigidity (tip and base) decreased with increasing dose up to the 200 mg dose level with similar results to sildenafil, and improved compared to placebo (Table 10 and Table 11).
- Duration of ≥ 60% rigidity (tip and base) increased with increasing dose up to the 200 mg dose level, with similar effect to sildenafil at the 100 mg and 200 mg dose levels (Table 12 and Table 13).
- Maximum rigidity (tip and base) increased to the 200 mg dose level, was greater than placebo at all dose levels and was greater than sildenafil at the 200 mg dose level (Table 14).

Table 10: Summary of Cumulative Time to ≥ 60% Rigidity

	Cumulative Time to ≥ 60% Rigidity Mean (median)[1] (minutes)	
	Tip	Base
Group 1:		
Placebo	19.6 (60)	16.1 (44.0)
Sildenafil	19.3 (47.5)	16.4 (39.0)
50 mg Avanafil	19.5 (44.0)	18.2 (28.0)
Group 2:		
Placebo	18.0 (49.5)	26.5 (49.0)
Sildenafil	13.7 (37.5)*	22.4 (42.0)
100 mg Avanafil	16.2 (33.5)*	19.3 (35.0)
Group 3:		
Placebo	18.9 (44.0)	19.7 (32.0)
Sildenafil	17.8 (26.5)	15.4 (24.0)
200 mg Avanafil	14.4 (24.0)*	17.0 (20.5)*

Source: Section 14.2, Tables 7.1 and 7.2

[1] Mean (Efficacy Subjects) calculated using only those subjects in the efficacy population who achieved ≥ 60% rigidity; Median (Efficacy Subjects) calculated using all efficacy subjects. Subjects not achieving ≥ 60% rigidity are given scores of 20+ for individual time intervals.

*$p < 0.05$: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test where those subjects who did not achieve ≥ 60% rigidity are given the highest rank.

Pairwise comparisons between individual treatment groups were considered significant (indicated with *) only if overall tests showed significant differences among treatment groups.

Table 11: Summary of Time to ≥ 60% Rigidity

	Time to ≥ 60% Rigidity Mean (median) (minutes)					
Interval	**20 – 40 minutes**		**60 – 80 minutes**		**100 – 120 minutes**	
	Tip	Base	Tip	Base	Tip	Base
Group 1:						
Placebo	8.5 (20+)	5.1 (20+)	9.3 (20+)	7.1 (14.0)	5.9 (20+)	7.0 (20+)
Sildenafil	9.4 (20+)	6.9 (20+)	7.0 (19.5)	6.6 (8.0)	8.2 (20+)	5.5 (15.5)
50 mg Avanafil	6.2 (8.5)*	6.0 (5.5)*†	5.6 (10.0)	5.5 (6.0)	10.8 (20+)	7.6 (13.0)
Group 2:						
Placebo	6.9 (20+)	8.2 (20+)	13.4 (20+)	10.1 (20+)	6.0 (20+)	8.0 (20+)
Sildenafil	7.8 (13.5)*	8.7 (14.0)	5.4 (11.5)*	6.8 (19.0)	5.4 (7.0)	8.0 (13.0)*
100 mg Avanafil	5.6 (9.0)*	6.4 (10.5)*	6.2 (7.5)*	7.8 (11.0)*	7.1 (12.5)	7.4 (20+)
Group 3:						
Placebo	6.2 (7.0)	5.4 (6.0)	6.0 (20+)	6.6 (9.5)	8.8 (20+)	8.5 (12.5)
Sildenafil	8.1 (14.5)	5.8 (6.0)	5.4 (5.5)*	4.5 (5.0)	5.4 (5.0)*	5.2 (6.0)*
200 mg Avanafil	4.3 (5.0)	5.8 (5.0)*†	5.4 (4.0)*	4.8 (4.0)*	7.0 (7.0)*	6.9 (5.5)*

Source: Section 14.2, Tables 7.1 and 7.2

[1] Mean (Efficacy Subjects) calculated using only those subjects in the efficacy population who achieved ≥ 60% rigidity; Median (Efficacy Subjects) calculated using all efficacy subjects. Subjects not achieving ≥ 60% rigidity are given scores of 20+ for individual time intervals.

*p < 0.05: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test where those subjects who did not achieve ≥ 60% rigidity are given the highest rank.

†p < 0.05: Pairwise p-value test (versus sildenafil) by Wilcoxon Signed Rank test where those subjects who did not achieve ≥ 60% rigidity are given the highest rank.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

Table 12: Summary of Cumulative Duration of ≥ 60% Rigidity

	Cumulative Duration of ≥ 60% Rigidity Mean (median)[1] (minutes)	
	Tip	Base
Group 1:		
Placebo	3.3 (0.0)	6.4 (1.0)
Sildenafil	6.8 (1.0)	12.0 (2.5)
50 mg Avanafil	6.3 (1.0)	13.9 (7.0)
Group 2:		
Placebo	4.4 (1.0)	3.3 (1.0)
Sildenafil	16.2 (13.0)*	14.2 (6.0)*
100 mg Avanafil	15.3 (8.0)*	10.2 (7.0)*
Group 3:		
Placebo	8.4 (1.5)	9.1 (5.5)
Sildenafil	18.3 (17.0)*	20.4 (19.0)*
200 mg Avanafil	21.3 (19.5)*	23.3 (21.5)*

Source: Section 14.2, Tables 8.1 and 8.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*p < 0.05: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test. Pairwise comparisons between individual treatment groups were considered significant (indicated with *) only if overall tests showed significant differences among treatment groups.

Table 13: Summary of Duration of ≥ 60% Rigidity

	Duration of ≥ 60% Rigidity Mean (median)[1] (minutes)					
Time Interval	**20–40 minutes**		**60–80 minutes**		**100–120 minutes**	
	Tip	Base	Tip	Base	Tip	Base
Group 1:						
Placebo	1.0 (0.0)	2.7 (0.0)	1.0 (0.0)	1.9 (0.0)	1.3 (0.0)	1.8 (0.0)
Sildenafil	2.3 (0.0)	3.9 (0.0)	2.7 (0.0)	4.9 (2.0)*	1.7 (0.0)	3.2 (0.0)
50 mg Avanafil	3.2 (1.0)	6.0 (4.0)*	2.2 (0.0)	4.9 (2.0)*	0.9 (0.0)	3.0 (0.0)
Group 2:						
Placebo	1.4 (0.0)	1.2 (0.0)	0.6 (0.0)	0.9 (0.0)	2.5 (0.0)	1.3 (0.0)
Sildenafil	4.0 (2.0)*	4.3 (1.0)	5.4 (3.0)*	4.7 (0.0)*	6.7 (3.0)*	5.2 (1.0)*
100 mg Avanafil	6.2 (3.0)*†	5.2 (2.0)	5.0 (2.0)*	3.0 (1.0)*	4.5 (2.0)	2.3 (0.0)†
Group 3:						
Placebo	3.6 (1.0)	3.9 (3.0)	2.6 (0.0)	3.1 (1.5)	2.3 (0.0)	2.2 (1.0)
Sildenafil	4.4 (1.5)	5.5 (3.0)	6.7 (6.0)*	7.2 (7.5)*	7.3 (6.5)*	7.7 (7.5)*
200 mg Avanafil	8.5 (8.5)*†	9.5 (10.5)*†	7.5 (6.5)*	7.5 (7.0)*	5.2 (2.0)*	6.3 (3.5)*

Source: Section 14.2, Tables 8.1 and 8.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*$p < 0.05$: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test.

†$p < 0.05$: Pairwise p-value test for differences between sildenafil and avanafil by Wilcoxon Signed Rank test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

Table 14: Summary of Maximum Penile Rigidity

	Maximum Rigidity Mean (median)[1]					
Time Interval	**20–40 minutes**		**60–80 minutes**		**100–120 minutes**	
	Tip	Base	Tip	Base	Tip	Base
Group 1:						
Placebo	39.4 (28.0)	48.7 (57.0)	37.0 (45.0)	49.2 (62.0)	32.6 (13.0)	39.6 (44.0)
Sildenafil	41.7 (24.5)	53.8 (57.5)	49.5 (60.5)	58.1 (68.0)	40.7 (41.5)	54.5 (60.0)*
50 mg Avanafil	57.3 (67.0)	70.9 (75.0)*†	54.0 (53.0)	63.9 (73.0)	32.0 (18.0)	57.4 (60.0)*
Group 2:						
Placebo	31.2 (20.5)	39.3 (49.5)	37.1 (34.0)	37.6 (45.5)	44.0 (39.0)	42.6 (51.0)
Sildenafil	55.6 (69.0)*	58.3 (67.0)	60.1 (73.0)*	56.8 (62.0)*	60.8 (76.0)	62.6 (66.0)
100 mg Avanafil	66.4 (75.0)*	61.3 (71.0)*	63.2 (76.0)	58.5 (67.0)	56.8 (67.0)	49.0 (56.0)
Group 3:						
Placebo	60.9 (73.0)	63.1 (75.0)	43.3 (44.5)	56.8 (73.0)	45.0 (47.5)	53.7 (69.0)
Sildenafil	55.3 (71.0)	64.7 (75.0)	64.0 (71.0)	68.1 (79.0)	67.6 (79.0)*	70.5 (78.0)*
200 mg Avanafil	68.1 (77.0)	80.6 (84.0)	70.0 (80.0)	76.1 (76.0)	65.9 (76.0)*	76.7 (81.5)*

Source: Section 14.2, Tables 9.1 and 9.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*$p < 0.05$: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test.

†$p < 0.05$: Pairwise p-value test for differences between sildenafil and avanafil by Wilcoxon Signed Rank test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

- Tumescent Activity Units - TAU (tip and base) increased with increasing dose up to the 200 mg dose level, with greater effect than placebo at all dose levels and with similar effect to sildenafil at the 100 mg and 200 mg dose levels (Table 15 and Table 16).
- Rigidity Activity Units – RAU (tip and base) increased with increasing dose up to the 200 mg dose level, with greater effect than placebo at all dose levels and with similar effect to sildenafil at the 100 mg and 200 mg dose levels (Table 17 and Table 18).
- Responses to the 5-point Erection Assessment Scale (EAS) was greater than placebo and sildenafil at the 40 minute time point for all dose levels, with increasing effect with dose up

to the 200 mg dose level (Table 19). There was similar effect for avanafil 200 mg and sildenafil 50 mg at the 80 minute and 120 minute time points.

Table 15: Summary of Cumulative Tumescent Activity Units (TAU)

	Cumulative Tumescent Activity Units (TAU) Mean (median)[1] (minutes)	
	Tip	Base
Group 1:		
Placebo	2.7 (1.0)	5.7 (2.0)
Sildenafil	5.8 (2.0)	9.1 (8.0)
50 mg Avanafil	7.5 (6.0)*	13.3 (12.0)*
Group 2:		
Placebo	2.6 (1.0)	4.1 (2.5)
Sildenafil	8.4 (6.5)*	10.4 (8.0)*
100 mg Avanafil	7.0 (5.0)*	8.2 (7.0)*
Group 3:		
Placebo	5.3 (2.0)	6.4 (4.0)
Sildenafil	9.6 (8.5)*	13.3 (9.5)*
200 mg Avanafil	13.1 (10.0)*†	15.1 (17.0)*

Source: Section 14.2, Tables 10.1 and 10.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*p < 0.05: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test.

†p < 0.05: Pairwise p-value test for differences between sildenafil and avanafil by Wilcoxon Signed Rank test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

Table 16: Tumescent Activity Units (TAU) During each Post-dosing Time Window

	Tumescent Activity Units (TAU) Mean (median)[1]					
Time Interval	**20–40 minutes**		**60–80 minutes**		**100–120 minutes**	
	Tip	Base	Tip	Base	Tip	Base
Group 1:						
Placebo	0.9 (0.0)	2.2 (0.5)	0.7 (0.0)	2.0 (0.0)	1.2 (0.0)	1.7 (0.0)
Sildenafil	2.1 (0.5)	3.1 (1.5)	2.4 (1.0)	3.8 (3.0)	1.4 (0.0)	2.5 (2.0)
50 mg Avanafil	3.8 (3.0)	6.2 (5.0)*†	2.4 (2.0)*	4.4 (4.0)*	1.3 (1.0)	2.8 (2.0)
Group 2:						
Placebo	1.1 (0.0)	2.2 (0.0)	0.4 (0.0)	0.5 (0.0)	1.2 (0.0)	1.5 (0.0)
Sildenafil	1.8 (1.0)	2.7 (2.0)	2.2 (1.0)*	2.7 (2.0)*	4.7 (2.0)*	5.3 (3.5)*
100 mg Avanafil	3.5 (3.0)*	4.1 (4.0)	2.0 (0.5)*	2.3 (1.5)*	1.5 (0.0)†	2.0 (0.0)†
Group 3:						
Placebo	2.4 (1.0)	2.7 (2.0)	1.5 (0.0)	2.0 (0.0)	1.4 (0.0)	1.6 (0.0)
Sildenafil	2.8 (2.0)	4.5 (3.0)*	3.3 (3.5)*	4.6 (4.0)*	3.9 (3.5)*	4.8 (4.5)*
200 mg Avanafil	5.4 (5.0)*†	6.1 (6.0)*	5.2 (5.0)*†	5.7 (5.0)*	3.6 (2.0)*	4.6 (5.5)*

Source: Section 14.1, Tables 10.1 and 10.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*p < 0.05: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test.

†p < 0.05: Pairwise p-value test for differences between sildenafil and avanafil by Wilcoxon Signed Rank test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

Table 17: Summary of Cumulative Rigidity Activity Units (RAU)

	Cumulative Rigidity Activity Units (RAU) Mean (median)[1] (minutes)	
	Tip	Base
Group 1:		
Placebo	4.7 (4.0)	13.4 (11.5)
Sildenafil	11.4 (4.0)	17.8 (15.0)
50 mg Avanafil	14.8 (14.0)	24.7 (22.5)*
Group 2:		
Placebo	7.1 (5.0)	10.3 (8.5)
Sildenafil	16.3 (10.0)	20.0 (17.0)
100 mg Avanafil	16.1 (14.0)*	18.5 (17.0)*
Group 3:		
Placebo	11.7 (6.0)	14.6 (11.0)
Sildenafil	20.3 (20.5)*	26.2 (23.5)*
200 mg Avanafil	22.5 (17.0)*	28.9 (27.0)*

Source: Section 14.2, Tables 11.1 and 11.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*p < 0.05: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test.

†p < 0.05: Pairwise p-value test for differences between sildenafil and avanafil by Wilcoxon Signed Rank test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

Table 18: Rigidity Activity Units (RAU) During each Post-dosing Time Window

	Rigidity Activity Units (RAU) Mean (median)[1]					
Time Interval	**20 – 40 minutes**		**60 – 80 minutes**		**100 – 120 minutes**	
	Tip	Base	Tip	Base	Tip	Base
Group 1:						
Placebo	1.8 (1.5)	6.5 (7.0)	2.2 (2.0)	7.1 (6.5)	2.7 (3.0)	4.9 (5.0)
Sildenafil	4.8 (1.0)	6.8 (5.0)	5.1 (3.0)	8.1 (8.0)	3.3 (1.0)	5.7 (5.0)
50 mg Avanafil	8.3 (8.0)	11.9 (9.0)*	4.8 (4.5)	8.2 (8.0)	2.4 (2.0)	6.3 (4.0)
Group 2:						
Placebo	4.4 (4.0)	6.8 (5.5)	2.2 (1.0)	4.3 (5.0)	4.6 (2.0)	5.3 (6.0)
Sildenafil	4.7 (5.0)	7.0 (6.0)	6.8 (7.0)	8.3 (9.0)	9.9 (5.0)	11.1 (8.0)
100 mg Avanafil	8.8 (8.5)*	10.6 (9.0)	5.4 (4.0)	6.3 (6.0)	5.7 (5.0)	5.8 (6.0)
Group 3:						
Placebo	5.4 (5.0)	7.6 (6.5)	6.1 (5.5)	7.4 (8.0)	5.3 (3.0)	5.5 (4.5)
Sildenafil	8.7 (8.0)*	12.1 (10.0)*	8.5 (8.0)	10.8 (11.0)*	8.8 (10.0)*	10.9 (11.0)*
200 mg Avanafil	10.3 (11.0)*	12.0 (11.5)*	8.8 (9.0)	11.6 (9.5)*†	6.5 (5.0)	9.2 (8.5)

Source: Section 14.2, Tables 11.1 and 11.2

[1] Mean (Efficacy Subjects); median (All Treated Subjects).

*p < 0.05: Pairwise p-values test for differences between active treatments and placebo by Wilcoxon Signed Rank test.

†p < 0.05: Pairwise p-value test for differences between sildenafil and avanafil by Wilcoxon Signed Rank test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

Table 19: Erection Assessment Scale: Number (%) of Subjects with EAS Ratings of ≥ 3 (Full Penile Enlargement) or ≥ 4 (Erection Sufficient for Intercourse) at the Completion of Each Post-dosing Time Window

	Subjects with EAS ≥ 3 (number [%])			Subjects with EAS ≥ 4 (number [%])		
	40 minute	80 minute	120 minute	40 minute	80 minute	120 minute
Group 1:						
Placebo	10 (38%)	16 (62%)	16 (62%)	7 (27%)	7 (27%)	9 (35%)
Sildenafil	16 (62%)	20 (77%)	19 (73%)	13 (50%)	16 (62%)*	11 (42%)
50 mg Avanafil	21 (81%)*	19 (73%)	16 (62%)	12 (46%)	11 (42%)	11 (42%)
Group 2:						
Placebo	7 (27%)	8 (31%)	11 (42%)	3 (12%)	4 (15%)	3 (12%)
Sildenafil	16 (62%)*	18 (69%)*	19 (73%)	11 (42%)*	12 (46%)*	14 (54%)*
100 mg Avanafil	19 (73%)*	19 (73%)*	15 (58%)	10 (38%)*	11 (42%)*	9 (35%)*
Group 3:						
Placebo	15 (54%)	15 (54%)	14 (50%)	8 (29%)	12 (43%)	8 (29%)
Sildenafil	18 (64%)	22 (79%)*	24 (86%)*	14 (50%)	18 (64%)	22 (79%)*
200 mg Avanafil	27 (96%)*†	23 (82%)*	23 (82%)*	21 (75%)*	21 (75%)*	18 (64%)*

Source: Section 14.2, Tables 12.2, 12.3, and 12.4

*$p < 0.05$: Pairwise p-values test for differences between active treatments and placebo by chi-square test.

†Pairwise p-value test for differences between sildenafil and avanafil by chi-square test.

Pairwise comparisons between individual treatment groups were considered significant (indicated with * or †) only if overall tests showed significant differences among treatment groups.

6.2. Study TA-03

Study TA-03 (Module 5, Section 5.3.5.1) was a double blind, randomised, three-way crossover study to evaluate efficacy, onset of effect and duration of effect of avanafil 200 mg at home in subject with mild to moderate ED. The study was conducted at 3 centres in the US from July 2003 to January 2004. The study included males, 35 to 70 years of age, with a ≥ 3-month history of unsatisfactory sexual intercourse due to mild to moderate ED; in a monogamous, heterosexual relationship for ≥ 3 months; not using androgen therapy that had not been stable for 3 months; with no history of chronic high or low blood pressure defined as < 90/50 or > 170/100 mmHg or recent stroke, myocardial infarction, or life-threatening arrhythmia; and with no significant medical condition or social problem that would interfere with study evaluations or otherwise contraindicate study participation. The study treatments were 6 individual doses of each of avanafil 200 mg 5 to 10 minutes prior to intercourse, avanafil 200 mg 2 hours prior to intercourse, and sildenafil 5 to 10 minutes prior to intercourse. There were no significant differences between the treatments in penetration success rate (Table 20). Intercourse success rate was lower with avanafil at 5 to 10 minutes compared to the other two treatments. There was no significant difference between the treatments in time from dosing to achieving erection sufficient for intercourse. There was no significant difference between the groups in the Global Assessment Questionnaire or the Erectile Function Domain score.

Table 20: Penetration Success Rate, Intercourse Success Rate, and Time from Dosing to Achieving an Erection Sufficient for Intercourse (EE Population)

	Avanafil 5 to 10 min (N = 43)	Sildenafil 5 to 10 min (N = 43)	Avanafil 2 hours (N = 42)	P-value
Penetration Success Rate[1]				
Mean (SD)	0.79 (0.28)	0.85 (0.27)	0.88 (0.25)	0.2538[3]
Median	1.00	1.00	1.00	
Min – Max	0 – 1.00	0 – 1.00	0 – 1.00	
Intercourse Success Rate[2]				
Mean (SD)	0.56 (0.37)	0.69 (0.32)	0.75 (0.32)	0.0172[3]
Median	0.60	0.80	0.83	
Min – Max	0 – 1.00	0 – 1.00	0 – 1.00	
Time from Dosing to Achieving Erection Sufficient for Intercourse (#6)				
Reported Values Only[4]				
N	43	41	42	
Mean (SD)	19.2 (11.4)	20.8 (12.5)	50.4 (48.4)	
Median	17.5	20.0	28.8	
Min – Max	1.0 – 60.0	5.0 – 60.0	2.0 – 180.0	
Including Imputed Values[5]				
N	43	43	42	
Mean (SD)	27.2 (20.0)	24.8 (17.7)	57.0 (52.6)	0.3770[3]
Median	20.0	20.00	37.5	
Min – Max	1.0 – 70.0	5.0 – 70.0	3.0 – 180.00	

Source: Section 14.2, Table 4.1

Min = minimum; Max = maximum; SD = standard deviation.

[1] Penetration Success Rate: proportion of erections enabling vaginal penetration (Diary Question #7)

[2] Intercourse Success Rate: proportion of erections lasting long enough for successful intercourse (Diary Question #8)

[3] P-values compare avanafil and sildenafil 5 to 10 minutes after dosing treatments and are determined using paired t-test.

[4] For each subject, the median duration value was calculated for each treatment using only values from those attempts in which a time to first erection sufficient for intercourse was reported.

[5] For each subject, the median duration value was calculated for each treatment using values from all attempts at intercourse. Missing values were assigned a numeric value of 70 minutes during Treatment Periods 1 and 2, and 180 minutes during Treatment Period 3.

6.3. Study TA-05

Study TA-05 was a double blind, randomised, parallel group, dose finding study to evaluate the safety and efficacy of avanafil for the treatment of mild to moderate ED. The study was conducted at 22 centres in the US from April 2004 to May 2005. The study included Males 35 to 70 years of age, with a ≥ 6-month history of mild to moderate ED that did not result from spinal cord injury, diabetes, or radical prostatectomy; in a monogamous, heterosexual relationship for the 3 months; with no history of chronic blood pressure < 90/50 or > 170/100 mmHg or recent stroke, myocardial infarction, or life-threatening arrhythmia; and with no significant medical condition or social problem that would interfere with study evaluations or otherwise contraindicate study participation. The study treatments were: avanafil 50 mg, avanafil 100 mg, avanafil 200 mg, avanafil 300 mg and placebo. At least 6 doses of study drug to be taken 30 minutes prior to initiating sexual activity over a 12 week period. Subjects were randomised to treatment group. The outcome measures were: successful penetration, successful intercourse, and the Erectile Function Domain score (EFS) from the IIEF Questionnaire.

A total of 460 subjects were screened, 371 entered run-in period, and 295 were randomised: 57 to 50 mg, 61 to 100 mg, 59 to 200 mg, 59 to 300 mg and 59 to placebo. Of the randomised subjects 284 (96.3%) were included in ITT population. The age range was 32 to 70 years, 243 (85.6%) were Caucasian and 29 (10.2%) were Black; for 36 (65.5%) the ED was of organic aetiology, four (7.3%) psychological, and 15 (27.3%) mixed. There was a higher proportion of subjects with mixed aetiology in the 100 mg and 200 mg groups. Erectile Function Domain scores were similar at baseline and end of run-in.

Penetration success rate increased with increasing dose, and was statistically significant compared with placebo at the 100 mg and 300 mg dose levels (Table 21).

Table 21: Penetration Success Rate and Intercourse Success Rate (ITT Population)

	Placebo (N=55)	Avanafil 50 mg (N=56)	Avanafil 100 mg (N=60)	Avanafil 200 mg (N=56)	Avanafil 300 mg (N=57)
Penetration Success Rate: percent of erections enabling vaginal penetration (#6)					
Baseline (Run-in)					
Mean (SD)	56.3 (36.0)	67.8 (29.7)	61.7 (34.7)	66.8 (31.0)	62.8 (32.6)
Median	60.0	75.0	70.8	75.0	66.7
Min-Max	0 - 100	0 - 100	0 - 100	0 - 100	0 - 100
Pairwise P-value vs. Placebo [1]		0.1076	0.4250	0.1251	0.3589
During Treatment					
Mean (SD)	60.5 (36.6)	76.1 (30.0)	79.2 (26.5)	79.8 (27.9)	83.7 (20.5)
Median	69.2	83.3	88.6	93.5	92.3
Min-Max	0 - 100	0 - 100	0 - 100	0 - 100	8 - 100
Pairwise P-value vs. Placebo [1]		0.0330	0.0070	0.0039	0.0009
Change from Baseline (Run-in)					
Mean (SD)	4.2 (35.8)	8.4 (31.2)	17.5 (30.5)	13.0 (34.1)	20.9 (33.8)
Median	0.0	0.0	10.9	10.0	20.0
Min-Max	-67 - 100	-46 - 83	-50 - 81	-94 - 94	-92 - 92
Pairwise P-value vs. Placebo [1]		0.4504	0.0298	0.1113	0.0069
Intercourse Success Rate: percent of erections lasting long enough for successful intercourse (#7)					
Baseline (Run-in)					
Mean (SD)	16.9 (19.6)	21.2 (19.6)	19.0 (20.4)	20.4 (18.9)	18.1 (20.1)
Median	0.0	25.0	18.3	20.0	0.0
Min-Max	0 - 50	0 - 50	0 - 50	0 - 50	0 - 50
Pairwise P-value vs. Placebo [1]		0.2359	0.5662	0.3068	0.7779
During Treatment					
Mean (SD)	28.9 (30.2)	53.4 (33.9)	58.6 (33.6)	62.1 (33.0)	64.3 (32.3)
Median	22.2	66.7	64.5	70.3	71.4
Min-Max	0 - 100	0 - 100	0 - 100	0 - 100	0 - 100
Pairwise P-value vs. Placebo [1]		0.0002	< 0.0001	< 0.0001	< 0.0001
Change from Baseline (Run-in)					
Mean (SD)	12.1 (29.9)	32.2 (33.8)	39.6 (34.7)	41.7 (33.6)	46.1 (34.3)
Median	5.6	36.6	44.4	45.0	48.2
Min-Max	-50 - 86	-40 - 83	-29 - 100	-20 - 100	-50 - 100
Pairwise P-value vs. Placebo [1]		0.0020	< 0.0001	< 0.0001	< 0.0001

Source: Section 14.2, Tables 7.1.1 and 7.2.1

Min = minimum; Max = maximum; SD = standard deviation.

[1] Pairwise p-values compare placebo and specific level of avanafil using CMH correlation statistic and modified ridit scores.

Intercourse success rate also increased with dose up to the 300 mg dose level, and was significantly greater than placebo at all dose levels. There was an improvement in Overall Erectile Function Domain score relative to placebo at all dose levels, but there was a plateau in effect from the 100 mg dose level (Table 22).

Table 22: 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 [1]		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 [1]		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 [1]		0.0235	0.0001	0.0002	<0.0001

Source: Section 14.2, Table 7.3.1.

IIEF = International Index of Erectile Function; LOCF = last-observation-carried-forward; Min = minimum; Max = maximum; SD = standard deviation.

For EFS, missing values for the end-of-treatment score are imputed using the LOCF.

[1] Pairwise p-values compare placebo and specific level of AVANAFIL using CMH correlation statistic and modified ridit scores.

There were similar improvements in: percent of erections that achieved some enlargement, percent of times satisfied with erection and percent of times satisfied with sexual experience (Table 23). There were improvements in the Erectile Function Scores from the IIEF Questionnaire, for all the dose levels, that appeared to plateau at the 100 mg dose level (Table 24). The Global Assessment Question responses improved with increasing dose, and were significantly improved compared to placebo at all dose levels (Table 25).

Table 23: Summary of Secondary Subject Diary Parameters During the Treatment Period (ITT Population)

During Treatment Parameter	Placebo (N=55)	Avanafil			
		50 mg (N=56)	100 mg (N=60)	200 mg (N=56)	300 mg (N=57)
Percent of Erections That Achieved Some Enlargement (#5)					
Mean (SD)	80.5 (24.7)	87.1 (21.7)	94.0 (13.4)	92.5 (14.2)	92.8 (14.9)
Median	91.7	100	100	100	100
Min-Max	0 - 100	17 - 100	18 - 100	40 - 100	25 - 100
Pairwise P-value vs. Placebo [1]		0.1135	0.0010	0.0049	0.0034
Percent of Times Satisfied with Erection (#8)					
Mean (SD)	16.5 (23.0)	33.0 (33.7)	46.2 (36.3)	50.2 (30.8)	52.7 (33.8)
Median	0.0	19.4	40.0	50.0	60.0
Min-Max	0 - 71	0 - 100	0 - 100	0 - 100	0 - 100
Pairwise P-value vs. Placebo [1]		0.0033	<0.0001	<0.0001	<0.0001
Percent of Times Satisfied with Sexual Experience (#9)					
Mean (SD)	23.7 (31.6)	38.7 (31.9)	50.4 (34.7)	55.8 (32.1)	54.4 (34.3)
Median	5.6	38.2	52.8	56.9	55.6
Min-Max	0 - 100	0 - 100	0 - 100	0 - 100	0 - 100
Pairwise P-value vs. Placebo [1]		0.0082	<0.0001	<0.0001	<0.0001

Source: Section 14.2, Tables 8.1.1, 8.2.1, and 8.3.1.

Min = minimum; Max = maximum; SD = standard deviation.

For each diary endpoint, a subject is assigned a percentage based on that subject's responses to that endpoint.

[1] Pairwise p-values compare placebo and specific level of avanafil using CMH correlation statistic and modified ridit scores..

Table 24: Erectile Function Scores from IIEF Questionnaire: Change From Baseline (Run-in) Pairwise P-value vs. Placebo (ITT Population)

IIEF Questions (1-5 and 15) [1]		Avanafil 50 mg (N=56)	Avanafil 100 mg (N=60)	Avanafil 200 mg (N=56)	Avanafil 300 mg (N=57)
#1 Frequency of Erections					
Month 1	Mean	0.4	0.3	0.5	0.6
	p-value	0.0160	0.0901	0.0161	0.0008
Month 2	Mean	0.4	0.5	0.5	0.6
	p-value	0.0059	0.0039	0.0005	<0.0001
Month 3	Mean	0.2	0.6	0.5	0.7
	p-value	0.0476	0.0066	0.0056	0.0001
#2 Hard Enough for Penetration					
Month 1	Mean	0.6	0.6	0.9	1.3
	p-value	0.0009	0.0011	<0.0001	<0.0001
Month 2	Mean	0.5	0.7	0.8	1.3
	p-value	0.0063	0.0003	0.0001	<0.0001
Month 3	Mean	0.3	0.9	0.9	1.1
	p-value	0.1156	0.0035	0.0048	0.0001
#3 Able to Penetrate					
Month 1	Mean	0.8	0.7	0.8	1.2
	p-value	0.0008	0.0019	0.0007	<0.0001
Month 2	Mean	0.7	1.0	0.7	1.2
	p-value	0.0037	<0.0001	0.0013	<0.0001
Month 3	Mean	0.6	1.0	0.8	0.9
	p-value	0.1500	0.0055	0.0306	0.0199
#4 Maintain Erection					
Month 1	Mean	1.1	0.9	1.4	1.3
	p-value	<0.0001	0.0002	<0.0001	<0.0001
Month 2	Mean	0.9	1.2	1.4	1.2
	p-value	0.0022	<0.0001	<0.0001	<0.0001
Month 3	Mean	0.8	1.4	1.6	1.3
	p-value	0.0448	<0.0001	<0.0001	0.0005
#5 Difficulty Maintaining Erection					
Month 1	Mean	0.8	0.8	1.1	1.1
	p-value	0.0022	0.0048	<0.0001	<0.0001
Month 2	Mean	0.8	1.0	1.0	1.1
	p-value	0.0354	0.0081	0.0026	0.0010
Month 3	Mean	0.5	1.2	1.2	1.1
	p-value	0.5852	0.0028	0.0019	0.0048
#15 Confidence Maintaining Erection					
Month 1	Mean	0.8	0.8	1.0	1.0
	p-value	0.0013	0.0003	<0.0001	<0.0001
Month 2	Mean	0.7	0.8	0.9	0.9
	p-value	0.0045	0.0007	0.0005	0.0005
Month 3	Mean	0.8	1.1	1.0	0.9
	p-value	0.0531	0.0004	0.0059	0.0025

Source: Section 14.2, Tables 9.2.1, 9.3.1, 9.4.1, 9.5.1, 9.6.1, and 9.7.1.

[1] Mean change from Baseline (Run-in); Change from Baseline (Run-in) pairwise p-values compare placebo and specific level of avanafil using CMH correlation statistic and modified ridit scores.

Table 25: Global Assessment Question (ITT Population)

Global Assessment Question	Placebo (N=55)	Avanafil 50 mg (N=56)	Avanafil 100 mg (N=60)	Avanafil 200 mg (N=56)	Avanafil 300 mg (N=57)
Has Treatment Improved Erections?					
Yes	9 (16.4%)	23 (41.1%)	40 (66.7%)	38 (67.9%)	43 (75.4%)
No	40 (72.7%)	31 (55.4%)	17 (28.3%)	17 (30.4%)	13 (22.8%)
Missing	6 (10.9%)	2 (3.6%)	3 (5.0%)	1 (1.8%)	1 (1.8%)
Pairwise P-value vs. Placebo[1]	-	0.0080	< 0.0001	< 0.0001	< 0.0001

Source: Section 14.2, Table 10.1.

[1] Pairwise p-values compared placebo and specific level of avanafil using a Chi-square test.

6.4. Evaluator's overall conclusions on the dose finding studies

The dose finding studies were most supportive of the 100 mg dose level. The 300 mg dose level did not offer any advantage over the 200 mg dose level. The sponsor was justified in taking the 50 mg, 100 mg and 200 mg dose levels through to further development.

7. Clinical efficacy

7.1. Erectile dysfunction

7.1.1. Pivotal efficacy studies

7.1.1.1. Study TA-301

Study design, objectives, locations and dates

Study TA-301 (Module 5, Section 5.3.5.1) double blind randomised placebo controlled efficacy and safety study of avanafil in subjects with mild to severe ED. The study was conducted at 42 centres in the US from November 2008 to August 2009.

Inclusion and exclusion criteria

The inclusion criteria included:

- Males ≥ 18 years of age
- History of mild to severe ED of at least 6 months duration, as evidenced by a history of inability to achieve vaginal penetration on at least 50% of attempts at sexual intercourse without the use of medical therapy
- In a monogamous, heterosexual relationship for at least 3 months
- Agreement to make at least 4 attempts at intercourse per month
- Agreement not to use any other treatments for ED (including prescription or over-the-counter medications, herbal or naturopathic products, manual techniques, vacuum pumps, constriction devices, experimental techniques, psychological counseling, etc.) during the study

The exclusion criteria included:

- Allergy or hypersensitivity to avanafil, sildenafil, vardenafil, tadalafil, or any of the components of these drug products
- History of dose-limiting adverse effects during therapy with a PDE5 inhibitor or history of consistent treatment failure with other PDE5 inhibitors for the treatment of ED
- Current or expected use of organic nitrates at any time during the study
- Anti-androgen therapy within 90 days of randomization or at any time during the study
- Use of trazodone, ketoconazole, erythromycin, cimetidine, or any other prescription or over-the-counter drugs known to inhibit the activity of CYP3A4 within 28 days prior to randomization or at any time during the study
- Androgen replacement therapy that had not been stable for at least 3 months
- Initiation or change in dose of any alpha-adrenergic antagonist (alpha blocker) within 14 days prior to randomization
- Erectile dysfunction as a result of spinal cord injury or radical prostatectomy
- Untreated hypogonadism or serum total testosterone < 325 ng/dL (early morning collection)
- History of or predisposition to priapism (such as sickle cell disease, blood dyscrasias, or multiple myeloma)
- Any penile implant

- Prostate specific antigen > 4 ng/mL, other evidence of prostate cancer, or previous radical prostatectomy
- History of any malignancy (except basal cell carcinoma or squamous cell carcinoma of the skin successfully treated by curative excision)
- History of type 1 or type 2 diabetes, history of use of any antidiabetic medication, haemoglobin A1c (HbA1c) > 6.5%, and/or fasting blood glucose ≥ 126 mg/dL (7 mmol/L)
- Uncontrolled hypertension as evidenced by SBP > 170 mmHg or DBP > 100 mmHg at screening
- Hypotension as evidenced by SBP < 90 mmHg or DBP < 50 mmHg at screening
- Orthostatic hypotension as evidenced by a reduction of 20 mmHg or more in SBP, a reduction of 10 mmHg or more in DBP, or evidence of cerebral hypoperfusion upon standing from a seated position
- Myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization within the past 6 months
- Unstable angina, angina with sexual intercourse, or congestive heart failure (greater than New York Heart Association Class II)
- History or electrocardiogram (ECG) evidence of any high-risk arrhythmia or ECG judged by the investigator to be clinically significant
- Hypertrophic, obstructive, or other clinically significant cardiomyopathy, or moderate or severe cardiac valvular disease
- AST or ALT > 2 x ULN or other evidence of significant hepatic impairment
- Serum creatinine > 2.5 mg/dL (221 mmol/L), estimated creatinine clearance < 60 mL/min (Cockcroft-Gault), on dialysis, or history of renal transplantation
- History of retinitis pigmentosa or non-arteritic anterior ischemic optic neuropathy
- Positive test for sexually transmitted diseases (syphilis, gonorrhea, or chlamydia)
- Positive test for human immunodeficiency virus, hepatitis C virus antibodies, and/or hepatitis B surface antigen
- Clinically evident penile lesions, abrasions, anatomical deformities such as penile fibrosis, Peyronie's disease, urinary tract or bladder infection, or sexually transmissible disease that the investigator deemed to be clinically significant
- Use of any prescription, over-the-counter, herbal, naturopathic, or male enhancement treatment or device for erectile dysfunction other than study drug within 28 days prior to randomization or at any time during the study
- Participation in another investigational study (drug or device) within 30 days of screening or at any time during the study
- History of drug, alcohol, or substance abuse in the past 12 months, positive urine drug screen, or positive breath alcohol test at screening
- History of bipolar disorder or psychosis, more than one lifetime episode of major depression, current depression of moderate or greater severity, or antidepressant use that had not been stable for at least 3 months
- Sexual partner who was < 18 years of age, nursing, known to be pregnant at screening, wished to become pregnant during the study period, had dyspareunia, and/or had any other

gynecological problems or major medical conditions that would limit participation in sexual intercourse

- History or evidence (through physical examination or laboratory tests) of any clinically significant medical, psychiatric, social, or other condition that, in the opinion of the investigator, would have contraindicated sexual activity or the administration of study drug, affected compliance, interfered with study evaluations, limited study participation, or confounded the interpretation of study results

The randomisation criteria were:

- A 50% or greater failure rate in maintaining an erection long enough to allow successful intercourse as recorded in the subject diary during the run-in period
- An IIEF erectile function domain score of 5 to 25, inclusive
- Documentation of at least 4 attempts at sexual intercourse during the run-in period

Study treatments

The study treatments were:

1. Avanafil 1 x 50 mg tablet
2. Avanafil 2 x 50 mg tablet
3. Avanafil 4 x 50 mg tablet
4. Placebo

All treatments were administered as four tablets, avanafil or placebo, 30 minutes prior to the initiation of sexual activity. No more than two doses of study drug were allowed in a 24 hour period.

Efficacy variables and outcomes

The primary efficacy outcome measures were:

- Change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to maintain an erection of sufficient duration to have successful intercourse (subject diary question 5, also referred to as Sexual Encounter Profile [SEP]3)
- Change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which the subject was able to insert his penis into his partner's vagina (subject diary question 4, also referred to as SEP2)
- Change in IIEF erectile function domain score from baseline to end of the 12-week treatment period.

The secondary efficacy outcome measures were:

- Changes in IIEF domain scores and individual responses from baseline to Week 4, Week 8, Week 12, and end of the 12-week treatment period
- Changes in the percentages of successful or satisfied responses to secondary subject diary questions between the run-in period and the 12-week treatment period
- Responses to the Global Assessment Question on treatment effect and the Future Use Question at Week 12.

The other efficacy outcome measures were the following:

- Number and percentage of successful or satisfied responses to subject diary questions by time interval between dose administration and sexual attempt (≤ 15 minutes, > 15 minutes

and ≤ 30 minutes, > 30 minutes and ≤ 45 minutes, > 45 minutes and ≤ 60 minutes, > 60 minutes and ≤ 120 minutes, > 120 minutes and ≤ 240 minutes, > 240 minutes and ≤ 360 minutes, and > 360 minutes)

- Number and percentage of subjects with an improvement in IIEF erectile function domain score from baseline to end of treatment
- Number and percentage of subjects with a normalized IIEF erectile function domain score (score ≥ 26) at the end of treatment
- Number of successful attempts at sexual activity (based on subject diary question 5, also referred to as SEP3)
- Mean number of attempts at sexual activity per week

The safety outcome measures were AEs, clinical laboratory evaluations, vital signs, physical examinations, and ECGs.

The schedule of study procedures was summarised.

Randomisation and blinding methods

Subjects were randomised in the ratio of 1:1:1:1 by IVRS. Blinding was maintained by using placebo tablets identical to the active treatment.

Analysis populations

The ITT population was used for the analyses of efficacy and included all subjects who were randomised, took at least one dose of study drug and had at least one post-dose efficacy assessment. The safety population included all subjects who took at least one dose of study drug and had safety data available.

Sample size

The sample size calculation was based on all three primary efficacy outcome measures. A sample size of 150 subjects in each group would provide the following power:

- Successful penetration: using a SD of 32 for the change in percentage of subjects, there was > 90% power to detect a 13% difference
- Successful intercourse: using a SD of 33 for the change in percentage of subjects, there was > 90% power to detect a 13% difference
- IIEF erectile function domain score: using a SD of 7.0 for the change in IIEF erectile function domain score, there was 90% power to detect a mean difference of 3 points

Statistical methods

ANCOVA models included baseline erectile dysfunction severity category and baseline values of the dependent variable as covariates. Missing data for the primary efficacy outcome measures were imputed using last observation carried forward (LOCF). Multiplicity was addressed by using a hierarchical approach to hypothesis testing, starting with the highest dose group.

Participant flow

There were 1509 subjects enrolled in the study, and 646 were randomised: 161 to avanafil 50 mg, 161 to 100 mg, 162 to 200 mg and 162 to placebo (Table 26). A total of 550 (85.1%) subjects completed the study: 131 (81.4%) in the avanafil 50 mg group, 141 (87.6%) in the 100 mg, 141 (87.0%) in the 200 mg and 137 (84.6%) in the placebo. Only 17 (2.6%) subjects discontinued because of an adverse event.

Table 26: Subject Disposition – All Enrolled Subjects

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

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

Major protocol violations/deviations

There were no protocol deviations that lead to exclusion form the analysis populations.

Baseline data

The age range was 23 to 88 years, and there were 144 (22.3%) subjects aged ≥ 65 years. The treatment groups were similar in most demographic characteristics. However, there were fewer Black subjects in the avanafil 200 mg group. There were 233 (36.2%) subjects with a history of hypertension and 61 (9.5%) with a history of coronary artery disease. The mean (SD) time from ingestion to initiation of sexual activity was 58.0 (68.43) minutes. Concomitant antihypertensives were taken by 187 (29.0%) subjects, antidepressants by 49 (7.6%) and alpha blockers by 38 (5.9%).

Results for the primary efficacy outcome

- Successful penetration: All the avanafil treatment groups were superior to placebo, and the 100 mg and 200 mg groups were superior to 50 mg. The mean (SD) change from baseline in % successful penetration was 7.1 (32.07) % for placebo, 18.9 (35.51) % for avanafil 50 mg, 27.3 (35.17) % for 100 mg and 29.0 (35.90) % for 200 mg.
- Successful intercourse: All the avanafil treatment groups were superior to placebo, and the 100 mg and 200 mg groups were superior to 50 mg. The mean (SD) change from baseline in % successful intercourse was 14.4 (27.63) % for placebo, 27.8 (33.86) % for avanafil 50 mg, 43.2 (33.86) % for 100 mg and 44.6 (35.67) % for 200 mg.
- The change in IIEF Erectile Function Domain Score was greater in all the avanafil treatment groups compared to placebo, and the 100 mg and 200 mg groups were superior to 50 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 2.9 (6.38) for placebo, 5.4 (7.54) for avanafil 50 mg, 8.3 (7.67) for 100 mg and 9.5 (7.03) % for 200 mg.

Results for other efficacy outcomes

- The change in IIEF Sexual Desire Domain Score was greater in all the avanafil treatment groups compared to placebo.
- The change in IIEF Orgasmic Function Domain Score was greater in all the avanafil treatment groups compared to placebo.

- The change in IIEF Intercourse Satisfaction Domain Score was greater in all the avanafil treatment groups compared to placebo.
- The change in IIEF Overall Satisfaction Domain Score was greater in all the avanafil treatment groups compared to placebo.
- Ability to achieve an erection improved compared to placebo in all the treatment groups compared to placebo.
- Satisfaction with erection increased compared to placebo with all the treatment groups.
- The global response was improved compared to placebo in all the treatment groups.
- The percentage of subjects who would use the treatment again was 26.6% for placebo, 45.1% for 50 mg, 58.5% for 100 mg and 67.1% for 200 mg.
- The increase in the proportion of successful intercourse was from ≥ 15 minutes after ingestion (Table 27)

Table 27: Summary of Attempts in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse by Time Interval (SEP3) – Intent-to-Treat Population

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

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

There was no difference in effect by age group or Race. However, for subjects in the severe group for Baseline Erectile Dysfunction severity, and those with longer duration of ED, there was less effect for the avanafil 50 mg dose for successful penetration (Table 28 and Table 29).

Table 28: Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which the Subject Was Able to Insert His Penis Into His Partner's Vagina (SEP2) – Intent-to-Treat Population – Baseline Erectile Dysfunction Severity Subgroups

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Mild						
Placebo	55	62.8 (33.76)	66.8 (34.28)	4.0 (30.71)	13.1 (3.96)	0.0010
Avanafil 50 mg	55	66.7 (34.13)	79.8 (28.34)	13.1 (38.78)	24.5 (3.98)	<0.0001
Avanafil 100 mg	54	63.0 (39.41)	82.6 (27.02)	19.6 (36.11)	28.8 (4.00)	<0.0001
Avanafil 200 mg	53	62.0 (36.94)	81.3 (29.25)	19.3 (32.32)	28.0 (4.03)	<0.0001
Moderate						
Placebo	49	57.5 (33.13)	63.6 (34.60)	6.2 (39.64)	12.3 (4.17)	0.0033
Avanafil 50 mg	48	50.4 (31.37)	69.9 (32.96)	19.5 (29.24)	21.6 (4.19)	<0.0001
Avanafil 100 mg	51	58.5 (32.68)	80.8 (26.78)	22.3 (27.22)	29.0 (4.09)	<0.0001
Avanafil 200 mg	52	59.1 (33.43)	87.6 (20.22)	28.4 (35.78)	35.5 (4.05)	<0.0001
Severe						
Placebo	51	19.0 (24.47)	30.4 (34.07)	11.5 (24.70)	-4.3 (4.19)	0.3025
Avanafil 50 mg	51	17.7 (25.26)	42.4 (39.52)	24.6 (36.88)	8.2 (4.20)	0.0525
Avanafil 100 mg	52	17.9 (23.39)	58.0 (36.57)	40.1 (38.05)	23.7 (4.16)	<0.0001
Avanafil 200 mg	51	23.0 (31.52)	62.6 (37.55)	39.7 (37.24)	26.2 (4.16)	<0.0001

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

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

Table 29: Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which the Subject Was Able to Insert His Penis Into His Partner's Vagina (SEP2) – Intent-to-Treat Population – Duration of Erectile Dysfunction Subgroups

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

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

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

7.1.1.2. Study TA-302

Study design, objectives, locations and dates

Study TA-302 was a randomised, double blind, placebo controlled study of the efficacy of avanafil 100 mg and 200 mg in subjects with diabetes mellitus. The study was conducted at 39 centres in the US from December 2008 to February 2010.

Inclusion and exclusion criteria

The inclusion criteria were the same as for Study TA-301 with the exception of:

- Documented diagnosis of diabetes (type 1 or type 2) prior to screening

The exclusion criteria were the same as for Study TA-301 with the exception of:

- History of 3 or more episodes of hypoglycemia requiring assistance within the last 2 years
- Uncontrolled diabetes (haemoglobin A1c [HbA1c] > 9%)
- Fasting blood glucose > 270 mg/dL (15 mmol/L)

The randomisation criteria were the same as for Study TA-301.

Study treatments

The study treatments were:

1. Avanafil 1 x 100 mg tablet
2. Avanafil 2 x 100 mg tablets
3. Placebo

Subjects were instructed to take one dose (two tablets: active and/or placebo) 30 minutes prior to intercourse.

Efficacy variables and outcomes

The outcome measures were the same as for Study TA-301 (see above). The schedule of study visits was the same as for Study TA-301.

Randomisation and blinding methods

Randomisation was in the ratio 1:1:1 and blinding was maintained by using identical placebo tablets.

Analysis populations

These were defined the same as for Study TA-301 (see above)

Sample size

The sample size calculation was based on all three primary efficacy outcome measures. A sample size of 125 subjects in each group would provide the following power:

- Successful penetration: using a SD of 32 for the change in percentage of subjects, there was > 90% power to detect a 13% difference
- Successful intercourse: using a SD of 33 for the change in percentage of subjects, there was > 90% power to detect a 29% difference
- IIEF erectile function domain score: using a SD of 7.0 for the change in IIEF erectile function domain score, there was 90% power to detect a mean difference of 5 points

Statistical methods

These were defined the same as for Study TA-301 (see above)

Participant flow

There were 1378 subjects enrolled in the study, and 390 were randomised: 129 to avanafil 100 mg, 131 to 200 mg and 130 to placebo (Table 30). A total of 330 (85.4%) subjects completed the study: 109 (84.5%) in the avanafil 100 mg group, 114 (87.0%) in the 200 mg and 110 (84.6%) in the placebo. Only 4 (1.0%) subjects discontinued because of an adverse event.

Table 30: Subject Disposition All Enrolled Subjects

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

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

Major protocol violations/deviations

There were no protocol deviations that resulted in exclusion of a subject from an analysis population.

Baseline data

The age range was 30 to 78 years, and there were 105 (26.9%) subjects aged ≥ 65 years. The treatment groups were disproportionate in race because there was a lower proportion of Black subjects in the avanafil 100 mg group (Table 31). However, the treatment groups were well matched in ED severity, other demographic characteristics and diabetes characteristics. There were 260 (67.0%) subjects with a history of hypertension and 54 (13.9%) with a history of coronary artery disease. The mean (SD) time from treatment administration to intercourse was 53.1 (31.61) minutes for avanafil 100 mg, 53.2 (43.63) minutes for 200 mg and 54.9 (42.81) minutes for placebo. Common concomitant medications were antihypertensives for 239 (61.6%) subjects, alpha blockers for 24 (6.2%) and antidepressants for 23 (5.9%).

Table 31: Demographic and Baseline Characteristics – Randomized Population

	Placebo (N=130)	Avanafil 100 mg (N=129)	Avanafil 200 mg (N=131)	Total (N=390)
Age (years) [1]				
n	130	129	131	390
Mean (SD)	58.2 (8.62)	58.2 (9.62)	57.5 (8.99)	58.0 (9.07)
Minimum, maximum	39, 78	30, 78	35, 77	30, 78
Age category n (%)				
<50 years	23 (17.7)	30 (23.3)	26 (19.8)	79 (20.3)
≥50 years and <65 years	72 (55.4)	61 (47.3)	73 (55.7)	206 (52.8)
≥65 years	35 (26.9)	38 (29.5)	32 (24.4)	105 (26.9)
Race n (%)				
White	103 (79.2)	111 (86.0)	100 (76.3)	314 (80.5)
Black	24 (18.5)	16 (12.4)	27 (20.6)	67 (17.2)
Asian	1 (0.8)	2 (1.6)	3 (2.3)	6 (1.5)
Multiple	1 (0.8)	0 (0.0)	1 (0.8)	2 (0.5)
Unknown	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Ethnicity n (%)				
Hispanic or Latino	20 (15.4)	33 (25.6)	26 (19.8)	79 (20.3)
Not Hispanic or Latino	110 (84.6)	96 (74.4)	105 (80.2)	311 (79.7)
Weight (kg)				
n	130	129	130	389
Mean (SD)	100.0 (19.87)	98.6 (18.16)	99.6 (18.68)	99.4 (18.88)
Height (cm)				
n	130	129	131	390
Mean (SD)	178.2 (7.01)	177.6 (7.54)	177.2 (7.69)	177.7 (7.41)
Body mass index (kg/m^2)				
n	130	129	130	389
Mean (SD)	31.5 (5.86)	31.3 (5.36)	31.8 (5.47)	31.5 (5.56)
Erectile dysfunction severity n (%)				
Mild	29 (22.3)	28 (21.7)	28 (21.4)	85 (21.8)
Moderate	40 (30.8)	40 (31.0)	42 (32.1)	122 (31.3)
Severe	61 (46.9)	61 (47.3)	61 (46.6)	183 (46.9)
Erectile dysfunction duration (months) [1]				
n	130	129	131	390
Mean (SD)	78.7 (66.59)	73.8 (53.08)	64.6 (44.69)	72.3 (55.67)
Erectile dysfunction duration category n (%)				
<24 months	19 (14.6)	17 (13.2)	19 (14.5)	55 (14.1)
≥24 months and <60 months	41 (31.5)	49 (38.0)	52 (39.7)	142 (36.4)
≥60 months	70 (53.8)	63 (48.8)	60 (45.8)	193 (49.5)

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

Results for the primary efficacy outcome

- Successful intercourse: Both avanafil treatment groups were superior to placebo, and there was no difference in effect between the 100 mg and 200 mg groups. The mean (SD) change from baseline in % successful intercourse was 10.5 (27.73) % for placebo, 26.2 (33.71) % for 100 mg and 32.1 (32.94) % for 200 mg.
- Successful penetration: Both avanafil treatment groups were superior to placebo, and there was no difference in effect between the 100 mg and 200 mg groups. The mean (SD) change from baseline in % successful penetration was 5.9 (31.16) % for placebo, 21.5 (37.19) % for 100 mg and 22.0 (35.00) % for 200 mg.
- The change in IIEF Erectile Function Domain Score was greater for both avanafil treatment groups compared to placebo, and there was no significant difference between the avanafil 100 mg and 200 mg groups. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 1.8 (6.24) for placebo, 4.6 (7.00) for avanafil 100 mg and 5.3 (7.50) % for 200 mg.

Results for other efficacy outcomes

- The change in IIEF Orgasmic Function Domain Score was greater for both avanafil treatment groups compared to placebo.
- There was no significant difference between either avanafil dose and placebo in the change in IIEF Sexual Desire Domain Score.
- The change in IIEF Intercourse Satisfaction Domain Score was greater for both avanafil treatment groups compared to placebo.
- The change in IIEF Overall Satisfaction Domain Score was greater for both avanafil treatment groups compared to placebo.
- There was a significant improvement in the ability to achieve an erection in the avanafil 200 mg group compared to placebo, but not in the 100 mg group.
- Satisfaction with erection increased compared to placebo in both treatment groups.
- The global response was improved compared to placebo both treatment groups.
- The percentage of subjects who would use the treatment again was 27% for placebo, 47% for 100 mg and 57% for 200 mg.
- There was a difference in time of onset of effect between the avanafil 100 mg and 200 mg treatments. The increase in the proportion of successful intercourse was from ≥ 15 minutes after ingestion for 100 mg but from > 15 minutes for 200 mg. There was a similar pattern for Satisfaction with Sexual Experience and proportion of successful penetration.

There was no difference in efficacy by type of diabetes or duration of diabetes. The subgroup analysis indicated decreased effect in the Black subgroup, but this was based on a small sample size. There was no difference in effect by Baseline Erectile Dysfunction severity or duration of ED.

7.1.1.3. Study TA-303

Study design, objectives, locations and dates

Study TA-303 was a randomised, double blind, placebo controlled study of the efficacy and safety of avanafil in subjects with ED following bilateral nerve-sparing radical prostatectomy. The study was conducted at 53 centres in the US from April 2009 to October 2011.

Inclusion and exclusion criteria

The inclusion criteria were the same as for Study TA-301 with the exception of:

- Males ≥ 18 years and ≤ 70 years of age at the time of screening
- History of ED of at least 6 months duration following bilateral nerve-sparing retropubic radical prostatectomy, as evidenced by an inability to penetrate their partner on at least 50% of attempts at sexual intercourse without the use of medical therapy
- History of bilateral nerve-sparing retropubic radical prostatectomy for localized carcinoma of the prostate at least 6 months prior to screening
- Prostate carcinoma stage ≤ pT2 and Gleason score ≤ 7 (4 + 3)
- Prostate specific antigen (PSA) level at screening consistent with the absence of residual prostate cancer
- History of sexual potency prior to radical prostatectomy that did not require routine medical therapy to achieve or maintain an erection

The exclusion criteria were similar to those for Study TA-301, the important differences being:

- History of dose-limiting adverse effects during prior treatment with a PDE5 inhibitor or discontinued use of more than one PDE5 inhibitor more than 6 months post-operatively due to lack of efficacy at the highest tolerated dose
- History of severe erectile dysfunction requiring routine medical therapy prior to bilateral nerve-sparing radical prostatectomy

The randomisation criteria were the same as for Study TA-301.

Study treatments

The study treatments were:

1. Avanafil 1 x 100 mg tablet
2. Avanafil 2 x 100 mg tablets
3. Placebo

Subjects were instructed to take one dose (two tablets: active and/or placebo) 30 minutes prior to intercourse.

Efficacy variables and outcomes

The outcome measures were the same as for Study TA-301 (see above). The schedule of study visits was the same as for Study TA-301.

Randomisation and blinding methods

Randomisation was stratified by IIEF Erectile Function Domain Score in a ratio 1:1:1 and conducted using IVRS.

Analysis populations

These were defined the same as for Study TA-301 (see above)

Sample size

The sample size calculation was based on all three primary efficacy outcome measures and used prior data from a study of vardenafil conducted in a similar population. A sample size of 100 subjects in each group would provide the following power:

- Successful penetration: using a SD of 57.4 for the change in percentage of subjects, there was 86% power to detect a 25.7% difference
- Successful intercourse: using a SD of 56 for the change in percentage of subjects, there was >86% power to detect a 24.3% difference
- IIEF erectile function domain score: using a SD of 11.8 for the change in IIEF erectile function domain score, there was 86% power to detect a mean difference of 6.1 points

Statistical methods

The statistical methods were the same as for Study TA-301 (see above).

Participant flow

There were 528 subjects enrolled in the study, and 298 were randomised to treatment: 99 to avanafil 100 mg, 99 to 200 mg and 100 to placebo (Table 32). A total of 252 (84.6%) subjects completed the study: 85 (85.9%) in the avanafil 100 mg group, 91 (91.9%) in the 200 mg and 76 (76.0%) in the placebo. Five (1.7%) subjects discontinued because of an adverse event.

Table 32: Subject Disposition – All Enrolled Subjects

	Placebo n (%)	Avanafil 100 mg n (%)	Avanafil 200 mg n (%)	Total n (%)
Enrolled [1]				528
Randomized	100 (100.0)	99 (100.0)	99 (100.0)	298 (100.0)
Completed study	76 (76.0)	85 (85.9)	91 (91.9)	252 (84.6)
Discontinued from study	24 (24.0)	14 (14.1)	8 (8.1)	46 (15.4)
Withdrew consent	14 (14.0)	7 (7.1)	2 (2.0)	23 (7.7)
Subject lost to follow-up	5 (5.0)	4 (4.0)	1 (1.0)	10 (3.4)
Protocol non-compliance	3 (3.0)	1 (1.0)	3 (3.0)	7 (2.3)
Adverse event	1 (1.0)	2 (2.0)	2 (2.0)	5 (1.7)
Other	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Safety Population [2]	100 (100.0)	99 (100.0)	99 (100.0)	298 (100.0)
Intent-to-Treat Population [3]	96 (96.0)	94 (94.9)	96 (97.0)	286 (96.0)
Evaluable Population [4]	87 (87.0)	90 (90.9)	94 (94.9)	271 (90.9)

1. Subjects who enrolled in the study include all subjects who signed the informed consent form.
2. The Safety Population includes all subjects who received at least one dose of study drug and had any safety data available. Subjects were assumed to have dosed if they returned fewer tablets of study drug than were dispensed. Subjects were included in the treatment group reflective of the treatment they actually received, if different from the randomized treatment. A subject was summarized by the first active treatment group received if that subject received study drug from more than one treatment group.
3. The Intent-to-Treat Population includes all subjects who were randomized, reported taking at least one dose of study drug, and had at least one post-dose efficacy assessment.
4. The Evaluable Population includes all Intent-to-Treat subjects who reported using at least 6 doses of study drug during the treatment period and had at least 4 attempts at intercourse during the non-treatment run-in period.

Major protocol violations/deviations

There were no protocol deviations that resulted in a subject being excluded from an analysis population.

Baseline data

The age range was 40 to 70 years and there were 48 (16.1%) subjects aged ≥ 65 years. The treatment groups were similar in demographic characteristics, baseline ED characteristics, prior treatment and rehabilitation (Table 33). There were 125 (41.9%) subjects with a history of hypertension, 38 (12.8%) with other cardiovascular disease and seven (2.3%) with coronary artery disease. There were 118 (39.6%) taking concomitant antihypertensives, 28 (9.4%) antidepressants and four (1.3%) alpha blockers.

Table 33: Demographic and Baseline Characteristics – Randomized Population

	Placebo (N=100)	Avanafil 100 mg (N=99)	Avanafil 200 mg (N=99)	Total (N=298)
Age (years) [1]				
n	100	99	99	298
Mean (SD)	58.6 (5.87)	58.9 (5.88)	57.7 (6.60)	58.4 (6.13)
Minimum, maximum	40, 70	46, 69	42, 69	40, 70
Age category n (%)				
<50 years	6 (6.0)	8 (8.1)	13 (13.1)	27 (9.1)
≥50 years and <65 years	79 (79.0)	73 (73.7)	71 (71.7)	223 (74.8)
≥65 years	15 (15.0)	18 (18.2)	15 (15.2)	48 (16.1)
Race n (%)				
White	84 (84.0)	83 (83.8)	76 (76.8)	243 (81.5)
Black	16 (16.0)	16 (16.2)	22 (22.2)	54 (18.1)
Unknown	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Ethnicity n (%)				
Hispanic or Latino	4 (4.0)	4 (4.0)	6 (6.1)	14 (4.7)
Not Hispanic or Latino	96 (96.0)	95 (96.0)	93 (93.9)	284 (95.3)
Weight (kg)				
n	100	99	99	298
Mean (SD)	88.4 (13.91)	89.7 (13.00)	91.1 (14.50)	89.7 (13.82)
Height (cm)				
n	100	99	99	298
Mean (SD)	178.6 (7.28)	178.7 (7.50)	179.0 (7.73)	178.7 (7.48)
Body mass index (kg/m^2)				
n	100	99	99	298
Mean (SD)	27.7 (3.42)	28.1 (3.93)	28.4 (3.94)	28.1 (3.77)
Erectile dysfunction severity n (%)				
Mild	8 (8.0)	7 (7.1)	12 (12.1)	27 (9.1)
Moderate	22 (22.0)	17 (17.2)	19 (19.2)	58 (19.5)
Severe	70 (70.0)	75 (75.8)	68 (68.7)	213 (71.5)
Erectile dysfunction duration (months) [1]				
n	100	99	99	298
Mean (SD)	18.0 (10.89)	19.8 (15.36)	18.4 (13.03)	18.7 (13.19)
Erectile dysfunction duration category n (%)				
<12 months	35 (35.0)	31 (31.3)	36 (36.4)	102 (34.2)
≥12 months and <24 months	42 (42.0)	40 (40.4)	39 (39.4)	121 (40.6)
≥24 months	23 (23.0)	28 (28.3)	24 (24.2)	75 (25.2)
Type of radical prostatectomy surgical technique n (%)				
Open	14 (14.0)	19 (19.2)	9 (9.1)	42 (14.1)
Robotic	83 (83.0)	76 (76.8)	81 (81.8)	240 (80.5)
Laparoscopic	3 (3.0)	4 (4.0)	9 (9.1)	16 (5.4)
First post-operative erectile dysfunction treatment n (%)				
Oral medications, therapeutic on demand	38 (38.0)	46 (46.5)	49 (49.5)	133 (44.6)
Oral medications, daily sub-therapeutic	15 (15.0)	16 (16.2)	16 (16.2)	47 (15.8)
Oral medications, other	14 (14.0)	13 (13.1)	9 (9.1)	36 (12.1)
Vacuum pump/band	5 (5.0)	5 (5.1)	3 (3.0)	13 (4.4)
Intracavernosal injections/intra-urethral therapies	2 (2.0)	1 (1.0)	1 (1.0)	4 (1.3)
Multiple erectile dysfunction treatments with the same start date	23 (23.0)	16 (16.2)	21 (21.2)	60 (20.1)
None	3 (3.0)	2 (2.0)	0 (0.0)	5 (1.7)
First post-operative erectile dysfunction treatment effectiveness n (%) [2]				
Yes	26 (26.0)	17 (17.2)	22 (22.2)	65 (21.8)
Sometimes	46 (46.0)	59 (59.6)	57 (57.6)	162 (54.4)
No	25 (25.0)	21 (21.2)	20 (20.2)	66 (22.1)
Previous penile rehabilitation treatment initiation [3]				
Within 3 months	77 (77.0)	74 (74.7)	82 (82.8)	233 (78.2)
Beyond 3 months	20 (20.0)	21 (21.2)	17 (17.2)	58 (19.5)
Not applicable	3 (3.0)	4 (4.0)	0 (0.0)	7 (2.3)

Baseline was defined as the last measurement prior to the first dose of study drug.
1. Age and duration of erectile dysfunction were calculated at informed consent.
2. If a subject had multiple erectile dysfunction treatments with the same start date, the maximum effectiveness level was summarized.
3. Penile rehabilitation treatment included oral medications, intracavernosal injections, and/or intra-urethral therapies.

SD = standard deviation.

Results for the primary efficacy outcome

- Successful intercourse: Both avanafil treatment groups were superior to placebo, and there was no significant difference in effect between the 100 mg and 200 mg groups.The mean (SD) change from baseline in % successful intercourse was 4.8 (19.89) % for placebo, 18.3 (30.18) % for 100 mg and 21.1 (31.83) % for 200 mg.
- Successful penetration: Both avanafil treatment groups were superior to placebo, and there was no significant difference in effect between the 100 mg and 200 mg groups. The mean (SD) change from baseline in % successful penetration was -0.4 (21.59) % for placebo, 15.3 (32.21) % for 100 mg and 20.8 (31.78) % for 200 mg.
- The change in IIEF Erectile Function Domain Score was greater for both avanafil treatment groups compared to placebo, and there was no significant difference between the avanafil 100 mg and 200 mg groups. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 0.1 (3.56) for placebo, 3.6 (7.04) for avanafil 100 mg and 5.2 (7.00) % for 200 mg.

Results for other efficacy outcomes

- The change in IIEF Orgasmic Function Domain Score was greater for the avanafil treatment group compared to placebo, but there was no significant difference for the 100 mg group.
- There was no significant difference between either avanafil dose and placebo in the change in IIEF Sexual Desire Domain Score.
- The change in IIEF Intercourse Satisfaction Domain Score was greater both avanafil treatment groups compared to placebo.
- The change in IIEF Overall Satisfaction Domain Score was greater both avanafil treatment groups compared to placebo.
- There was a significant improvement in the ability to achieve an erection both avanafil groups compared to placebo.
- Satisfaction with erection increased compared to placebo in both treatment groups.
- Satisfaction with sexual experience increased compared to placebo in both treatment groups.
- The global response was improved compared to placebo both treatment groups.
- The percentage of subjects who would use the treatment again was 27.7% for placebo, 39.8% for 100 mg and 57.6% for 200 mg.
- There was similar time of onset of effect for the avanafil 100 mg and 200 mg treatments. However, the effect for the 100 mg dose was greater ≤ 15 minutes post ingestion than the 200 mg dose, but effect decreased from that time point (Table 34). There was a similar pattern for proportion of successful penetration (Table 35).

Table 34: Summary of Attempts in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) by Time Interval – Intent-to-Treat Population

Time Interval From Dose to Attempt Statistic	Placebo (N=96)	Avanafil 100 mg (N=94)	Avanafil 200 mg (N=96)
≤15 minutes			
Number of attempts	44	22	55
Successful intercourse [1] n (%)	2 (4.5)	10 (45.5)	18 (32.7)
>15 minutes and ≤30 minutes			
Number of attempts	439	413	519
Successful intercourse [1] n (%)	34 (7.7)	123 (29.8)	158 (30.4)
>30 minutes and ≤45 minutes			
Number of attempts	465	430	542
Successful intercourse [1] n (%)	56 (12.0)	110 (25.6)	171 (31.5)
>45 minutes and ≤60 minutes			
Number of attempts	279	298	274
Successful intercourse [1] n (%)	28 (10.0)	76 (25.5)	99 (36.1)
>60 minutes and ≤120 minutes			
Number of attempts	173	190	237
Successful intercourse [1] n (%)	10 (5.8)	40 (21.1)	78 (32.9)
>120 minutes and ≤240 minutes			
Number of attempts	38	48	38
Successful intercourse [1] n (%)	2 (5.3)	10 (20.8)	13 (34.2)
>240 minutes and ≤360 minutes			
Number of attempts	12	11	13
Successful intercourse [1] n (%)	1 (8.3)	9 (81.8)	5 (38.5)
>360 minutes			
Number of attempts	13	13	20
Successful intercourse [1] n (%)	2 (15.4)	9 (69.2)	6 (30.0)

Number of attempts is the number of diary entries for the specified time interval and is used as the denominator in the corresponding calculation of the proportion of successes.

1. Successful intercourse defined as a YES response to the diary question "Did your erection last long enough for you to have successful intercourse?"

Table 35: Summary of Attempts in Which Subjects Were Able to Insert Their Penis Into Their Partner's Vagina (SEP2) by Time Interval – Intent-to-Treat Population

Time Interval From Dose to Attempt Statistic	Placebo (N=96)	Avanafil 100 mg (N=94)	Avanafil 200 mg (N=96)
≤15 minutes			
Number of attempts	44	22	55
Successful insertions [1] n (%)	7 (15.9)	10 (45.5)	19 (34.5)
>15 minutes and ≤30 minutes			
Number of attempts	439	413	519
Successful insertions [1] n (%)	80 (18.2)	159 (38.5)	263 (50.7)
>30 minutes and ≤45 minutes			
Number of attempts	465	430	542
Successful insertions [1] n (%)	102 (21.9)	150 (34.9)	226 (41.7)
>45 minutes and ≤60 minutes			
Number of attempts	279	298	274
Successful insertions [1] n (%)	61 (21.9)	111 (37.2)	123 (44.9)
>60 minutes and ≤120 minutes			
Number of attempts	173	190	237
Successful insertions [1] n (%)	35 (20.2)	58 (30.5)	104 (43.9)
>120 minutes and ≤240 minutes			
Number of attempts	38	48	38
Successful insertions [1] n (%)	4 (10.5)	12 (25.0)	19 (50.0)
>240 minutes and ≤360 minutes			
Number of attempts	12	11	13
Successful insertions [1] n (%)	1 (8.3)	9 (81.8)	11 (84.6)
>360 minutes			
Number of attempts	13	13	20
Successful insertions [1] n (%)	2 (15.4)	9 (69.2)	9 (45.0)

Number of attempts is the number of diary entries for the specified time interval and is used as the denominator in the corresponding calculation of the proportion of successes.

1. Successful insertion defined as a YES response to the diary question "Were you able to insert your penis into your partner's vagina?"

There was no apparent subgroup effect, but for many of the subgroups the numbers in each group were small.

7.1.1.4. Study TA-501

Study design, objectives, locations and dates

Study TA-501 was a randomised, double-blind, placebo-controlled, parallel group, three-arm efficacy and safety trial of avanafil for on-demand treatment of men with ED. The study was conducted at 30 centres in the US from September 2012 to April 2013.

Inclusion and exclusion criteria

The inclusion criteria were the same as for Study TA-301 (see above) except for:

- Had a history of mild to severe erectile dysfunction of at least 6 months duration, as evidenced by a greater than 50% failure rate in maintaining an erection of sufficient duration to allow successful intercourse, without the use of medical therapy

The exclusion criteria were similar to those for Study TA-301 (see above).

The randomisation criteria were the same as for Study TA-301 (see above).

Study treatments

The study treatments were:

1. Avanafil 1 x 100 mg tablet
2. Avanafil 2 x 100 mg tablets
3. Placebo

Subjects were instructed to take one dose (two tablets: active and/or placebo) 15 minutes prior to intercourse. No more than one dose was allowed per 24 hour period.

Efficacy variables and outcomes

The primary efficacy outcome measure was:

- The per-subject proportion of sexual attempts that had an erectogenic effect within approximately 15 minutes following dosing, where an erectogenic effect was defined as an erection sufficient for vaginal penetration and that enabled satisfactory completion of sexual intercourse. This was subsequently defined as being ≤ 17 minutes after dosing.

The secondary efficacy outcome measures were:

- Earliest time point after dosing where there was a statistically significant treatment difference in the average per-subject proportion of sexual attempts that had an erectogenic effect
- Successful intercourse: Proportion of positive ('YES') responses to diary question 5 regarding the subject's ability to maintain an erection sufficient for successful intercourse (SEP3)
- Successful penetration: Proportion of positive ('YES') responses to diary question 4 regarding the subject's ability to insert penis into the vagina (SEP2); IIEF-EF domain scores during the 8-week treatment period.

The safety outcome measures were: AEs, clinical laboratory evaluations, vital sign measurements, and physical examinations.

The schedule of study visits was summarised.

Randomisation and blinding methods

Randomisation was by IVRS, in the ratio of 1:1:1 and stratified by IIEF-EF domain score at baseline. Blinding was maintained by using identical placebo tablets.

Analysis populations

These were defined the same as for Study TA-301 (see above).

Sample size

The sample size calculation was determined for the primary efficacy outcome measure and was based on the prior data from the avanafil Phase III studies. The sample size was based on comparing each active treatment group with placebo, but not on a comparison between the active treatment groups. Assuming a treatment difference of 12.5%, and a SD of 30%, a sample size of 123 subjects per group would provide 90% power with an alpha of 0.05. Assuming a 12% drop-out rate, 140 subjects would be required in each treatment group.

Statistical methods

Hypothesis tests were performed using ANCOVA models with treatment, diabetes status, and baseline severity of erectile dysfunction included in the model as factors and with the baseline values of the dependent variable included as a covariate. Missing values were imputed using LOCF. Multiplicity was addressed using a step-down approach to hypothesis testing.

Participant flow

There were 832 subject enrolled and 440 were randomised to treatment: 147 to avanafil 100 mg, 148 to 200 mg and 145 to placebo. There were 124 (84.4%) subjects in the avanafil 100 mg group, 127 (85.8%) in the 200 mg and 116 (80.0%) in the placebo who completed (Table 36). There were seven (1.6%) subjects who withdrew because of an AE. The ITT population included 139 (94.6%) subjects in the avanafil 100 mg group, 139 (93.9%) in the 200 mg and 136 (93.8%) in the placebo.

Table 36: Subject Disposition by Treatment (All Enrolled Subjects)

		Avanafil		
Disposition	**Placebo n=145**	**100 mg n=147**	**200 mg n=148**	**Total N=440**
Enrolled[a]				832
Randomized, n (%)	145 (100.0)	147 (100.0)	148 (100.0)	440 (100.0)
Completed the study	116 (80.0)	124 (84.4)	127 (85.8)	367 (83.4)
Discontinued from the study	29 (20.0)	23 (15.6)	21 (14.2)	73 (16.6)
Withdrew consent	19 (13.1)	9 (6.1)	9 (6.1)	37 (8.4)
Lost to follow-up	6 (4.1)	8 (5.4)	8 (5.4)	22 (5.0)
Adverse event	0	3 (2.0)	4 (2.7)	7 (1.6)
Protocol violation	2 (1.4)	3 (2.0)	0	5 (1.1)
Discretion of the investigator	2 (1.4)	0	0	2 (0.5)
Termination of study	0	0	0	0
Missing	0	0	0	0

Note: Percentages were based on the number of randomly assigned subjects in a treatment arm.
[a] A subject was enrolled into the study upon signing the informed consent.

Major protocol violations/deviations

There were no protocol violations that resulted in a subject being excluded from the ITT or safety populations.

Baseline data

The age range was 24 to 86 years and 129 (29.3%) subjects were aged ≥ 65 years. There were 333 (75.7%) White subjects and 94 (21.4%) Black or African American. The treatment groups were similar in demographic characteristics (Table 37). There were 240 (54.5%) subjects with a history of hypertension, 68 (15.5%) with other cardiovascular disease and 37 (8.4%) with coronary artery disease. There were 226 (52.0%) subjects taking concomitant antihypertensive medication, 57 (13.1%) taking alpha blockers and 28 (6.4%) taking antidepressants. ED treatment history was similar for the three treatment groups.

Table 37: Demographics and Baseline Characteristics (Randomized Population)

Characteristic/Statistic	Placebo n=145	Avanafil 100 mg n=147	Avanafil 200 mg n=148	Total N=440
Age (years)[a]				
n	145	147	148	440
Mean (SD)	58.3 (9.92)	58.5 (10.19)	57.9 (10.61)	58.2 (10.23)
Median	59.0	60.0	59.0	59.0
Minimum, maximum	24, 79	29, 83	25, 86	24, 86
Age category, n (%)				
<50 years	29 (20.0)	25 (17.0)	29 (19.6)	83 (18.9)
≥50 to <65 years	74 (51.0)	78 (53.1)	76 (51.4)	228 (51.8)
≥65 years	42 (29.0)	44 (29.9)	43 (29.1)	129 (29.3)
Race, n (%)				
White	102 (70.3)	107 (72.8)	124 (83.8)	333 (75.7)
Black or African American	37 (25.5)	35 (23.8)	22 (14.9)	94 (21.4)
Asian	3 (2.1)	3 (2.0)	1 (0.7)	7 (1.6)
American Indian or Alaska Native	2 (1.4)	1 (0.7)	0	3 (0.7)
Multiple races	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.7)
Ethnicity, n (%)				
Hispanic or Latino	3 (2.1)	7 (4.8)	9 (6.1)	19 (4.3)
Not Hispanic or Latino	142 (97.9)	140 (95.2)	139 (93.9)	421 (95.7)
Baseline height (cm)				
n	145	146	148	439
Mean (SD)	179.31 (6.640)	177.35 (7.251)	177.12 (7.099)	177.92 (7.055)
Median	177.80	177.80	176.53	177.80
Minimum, maximum	161.5, 200.7	152.4, 195.6	160.0, 198.1	152.4, 200.7
Baseline weight (kg)				
n	145	146	148	439
Mean (SD)	96.73 (17.529)	96.16 (18.290)	95.69 (18.256)	96.19 (17.995)
Median	93.98	93.31	92.99	93.44
Minimum, maximum	64.9, 161.0	58.5, 160.6	63.1, 182.6	58.5, 182.6
Baseline BMI (kg/m^2)[b]				
n	145	146	148	439
Mean (SD)	30.09 (5.294)	30.53 (5.297)	30.44 (5.066)	30.35 (5.211)
Median	29.16	29.54	29.46	29.48
Minimum, maximum	20.3, 50.9	21.1, 49.4	21.1, 56.1	20.3, 56.1
Baseline diabetes status, n (%)				
Diabetic	23 (15.9)	24 (16.3)	25 (16.9)	72 (16.4)
Not Diabetic	122 (84.1)	123 (83.7)	123 (83.1)	368 (83.6)
Smoking history				
Current	13 (9.0)	19 (12.9)	15 (10.1)	47 (10.7)
Former	49 (33.8)	46 (31.3)	55 (37.2)	150 (34.1)
Never	83 (57.2)	82 (55.8)	78 (52.7)	243 (55.2)
Baseline erectile dysfunction severity, n (%)				
Mild	39 (26.9)	36 (24.5)	37 (25.0)	112 (25.5)
Moderate	46 (31.7)	49 (33.3)	51 (34.5)	146 (33.2)
Severe	60 (41.4)	62 (42.2)	60 (40.5)	182 (41.4)
Duration of erectile dysfunction (months)[c]				
n	145	147	148	440
Mean (SD)	88.8 (61.98)	81.0 (58.17)	95.6 (86.31)	88.5 (70.11)
Median	70.5	69.3	69.3	69.5
Minimum, maximum	7, 337	8, 347	8, 442	7, 442
Duration of erectile dysfunction duration category, n (%)				
<24 months	21 (14.5)	14 (9.5)	23 (15.5)	58 (13.2)
≥24 to <60 months	38 (26.2)	55 (37.4)	43 (29.1)	136 (30.9)
≥60 months	86 (59.3)	78 (53.1)	82 (55.4)	246 (55.9)

Abbreviations: BMI, body mass index; SD, standard deviation.

Note: Baseline is defined as the last nonmissing observation prior to the first dose of study drug.

[a] Age was calculated at date of informed consent.

[b] BMI = (body weight in kilograms)/(height in meters)^2.

[c] Erectile dysfunction duration in months is calculated as (date of informed consent – date of erectile dysfunction onset)/30.44.

Results for the primary efficacy outcome

Both active treatments has superior erectogenic effect ≤ 17 minutes after dosing compared to placebo, but there was no significant difference between the avanafil 100 mg and 200 mg dose

levels (Table 38). The LS mean (SE) erectogenic effect was 24.71 (2.911) % for avanafil 100 mg, 28.18 (2.876) % for 200 mg and 13.78 (2.905) % for placebo. The difference in LS mean (95% CI) compared to placebo was 10.93 (3.87 to 17.99) %, p = 0.002 for the avanafil 100 mg dose and 14.39 (7.35 to 21.44) %, p <0.001 for the avanafil 200 mg dose. The difference in LS mean (95% CI) compared to avanafil 100 mg was 3.46 (-3.56 to 10.49) %, p = 0.33 for avanafil 200 mg. There was no subgroup effect for severity of ED at baseline, diabetes status, age category, race or duration of ED.

Table 38: Analysis of the Percentage of Sexual Attempts During the 8-Week Treatment Period in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse by Time Since Dose Administration (Intent-to-Treat Population)

Visit/ Time Point Statistic	Placebo n=136	Avanafil 100 mg n=139	Avanafil 200 mg n=139
Baseline (n)	136	139	139
Mean (SD)	11.38 (17.434)	11.13 (17.094)	11.00 (16.805)
Median	0.00	0.00	0.00
Minimum, maximum	0.0, 50.0	0.0, 50.0	0.0, 50.0
8-Week Treatment Period			
17-Minute Time Point (n)	136	139	139
Subjects with at least 1 success within 17 min, n (%)	55 (40.4)	80 (57.6)	83 (59.7)
Total number of successes within 17 min	251	460	567
Total number of attempts in 8-week treatment period[a]	1497	1608	1679
8-week treatment period within 17 min	136	138	139
Mean (SD)	14.91 (25.051)	25.85 (32.032)	29.09 (33.983)
Median	0.00	11.11	13.33
Minimum, maximum	0.0, 100.0	0.0, 100.0	0.0, 100.0
Model-adjusted percentage[b]			
LS mean (SE)	13.78 (2.905)	24.71 (2.911)	28.18 (2.876)
95% CI	(8.07, 19.49)	(18.99, 30.44)	(22.52, 33.83)
Pairwise comparison – active vs placebo[b]			
Difference in LS Mean (SE)		10.93 (3.590)	14.39 (3.586)
95% CI		(3.87, 17.99)	(7.35, 21.44)
p-value/rank ANCOVA p-value		0.002/0.001	<0.001/<0.001
Pairwise comparison – 200 mg vs 100 mg[b]			
Difference in LS Mean (SE)			3.46 (3.572)
95% CI			(-3.56, 10.49)
p-value/rank ANCOVA p-value			0.333/0.453

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error; vs, versus.

Results for other efficacy outcomes

- There was a significant erectogenic effect from 10 minutes after dosing for both avanafil doses.
- There was significantly greater proportion of successful intercourse for both avanafil groups compared to placebo, but no significant difference between the avanafil dose levels (Table 39). The LS mean (SE) proportion of successful intercourse was 47.03 (3.340) % for avanafil 100 mg, 48.70 (3.299) % for 200 mg and 27.69 (3.333) % for placebo.
- There was a significantly greater proportion of successful penetration for both avanafil groups compared to placebo, but no significant difference between the avanafil dose levels (Table 40). The LS mean (SE) proportion of successful penetration was 64.98 (3.202) % for avanafil 100 mg, 65.39 (3.159) % for 200 mg and 43.51 (3.191) % for placebo.
- There was significantly improvement in IIEF for both avanafil groups compared to placebo, but no significant difference between the avanafil dose levels (Table 41). The LS mean (SE) domain score was 18.10 (0.802) for avanafil 100 mg, 19.12 (0.788) for 200 mg and 13.89 (0.805) for placebo.

Table 39: Analysis of the Percentage of Sexual Attempts During the 8-Week Treatment Period in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse (Intent-to-Treat Population)

Visit/ Time Point Statistic	Placebo n=136	Avanafil 100 mg n=139	Avanafil 200 mg n=139
Baseline (n)	136	139	139
Mean (SD)	11.38 (17.434)	11.13 (17.094)	11.00 (16.805)
Median	0.00	0.00	0.00
Minimum, maximum	0.0, 50.0	0.0, 50.0	0.0, 50.0
8-week treatment period (n)	136	138	139
Mean (SD)	27.98 (34.612)	47.23 (37.062)	48.38 (38.277)
Median	10.82	50.00	54.55
Minimum, maximum	0.0, 100.0	0.0, 100.0	0.0, 100.0
Model-adjusted percentage[a]			
LS mean (SE)	27.69 (3.333)	47.03 (3.340)	48.70 (3.299)
95% CI	(21.14, 34.24)	(40.46, 53.60)	(42.21, 55.18)
Pairwise comparison – active vs placebo[a]			
Difference in LS Mean (SE)		19.34 (4.119)	21.01 (4.113)
95% CI		(11.24, 27.44)	(12.92, 29.09)
p-value		<0.001	<0.001
Pairwise comparison – 200 mg vs 100 mg[a]			
Difference in LS Mean (SE)			1.67 (4.098)
95% CI			(-6.39, 9.72)
p-value			0.685

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error; vs, versus.

Note: Baseline is the run-in period consisting of all subject diary data reported during the nontreatment interval from Visit 1 to Visit 2 (approximately 4 weeks). The 8-week treatment period is the on-treatment interval from Visit 2 to Visit 4 (8 weeks) or the early termination visit.

[a] Least squares (LS) means, standard errors, 95% confidence intervals, and p-values are from an ANCOVA model: Positive response percentage = treatment + baseline erectile dysfunction severity + diabetes status + baseline response percentage. The pairwise comparison p-values are from a 2-tailed *t* test for the difference in LS means.

Table 40: Analysis of the Percentage of Sexual Attempts During the 8-week Treatment Period in Which Subjects Were Able to Insert the Penis into the Partner's Vagina (Intent-to-Treat Population)

Visit/ Time Point Statistic	Placebo n=136	Avanafil 100 mg n=139	Avanafil 200 mg n=139
Baseline (n)	136	139	139
Mean (SD)	44.72 (36.723)	45.11 (37.375)	43.20 (35.190)
Median	50.00	50.00	44.44
Minimum, maximum	0.0, 100.0	0.0, 100.0	0.0, 100.0
8-week treatment period (n)	136	138	139
Mean (SD)	44.07 (40.981)	65.89 (35.495)	65.16 (38.438)
Median	44.95	76.92	85.71
Minimum, maximum	0.0, 100.0	0.0, 100.0	0.0, 100.0
Model-adjusted percentage[a]			
LS mean (SE)	43.51 (3.191)	64.98 (3.202)	65.39 (3.159)
95% CI	(37.24, 49.78)	(58.69, 71.28)	(59.18, 71.60)
Pairwise comparison – active vs placebo[a]			
Difference in LS Mean (SE)		21.47 (3.937)	21.88 (3.931)
95% CI		(13.73, 29.21)	(14.15, 29.61)
p-value		<0.001	<0.001
Pairwise comparison – 200 mg vs 100 mg[a]			
Difference in LS Mean (SE)			0.41 (3.917)
95% CI			(-7.29, 8.11)
p-value			0.917

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error; vs, versus.

Note: Baseline is the run-in period consisting of all subject diary data reported during the nontreatment interval from Visit 1 to Visit 2 (approximately 4 weeks). The 8-week treatment period is the on-treatment interval from Visit 2 to Visit 4 (8 weeks) or the early termination visit.

[a] Least squares (LS) means, standard errors, 95% confidence intervals, and p-values are from an ANCOVA model: Positive response percentage = treatment + baseline erectile dysfunction severity + diabetes status + baseline response percentage. The pairwise comparison p-values are from a 2-tailed *t* test for the difference in LS means.

Table 41: Analysis of the Erectile Function Domain Score on the International Index of Erectile Function Questionnaire by Visit and End-of-Treatment (Intent-to-Treat Population)

Visit/ Time Point Statistic	Placebo n=136	Avanafil 100 mg n=139	Avanafil 200 mg n=139
Visit 1 (Screening) (n)	136	138	139
Mean (SD)	14.18 (7.161)	13.64 (7.311)	13.81 (7.597)
Median	15.00	14.00	13.00
Minimum, maximum	1.0, 30.0	1.0, 30.0	1.0, 30.0
Visit 2 (Baseline) (n)	136	139	139
Mean (SD)	12.72 (5.039)	12.55 (5.135)	12.26 (4.930)
Median	12.00	12.00	12.00
Minimum, maximum	5.0, 23.0	6.0, 24.0	5.0, 23.0
Visit 3 (Week 4) (n)	119	130	131
Mean (SD)	14.41 (7.742)	17.85 (8.606)	18.73 (8.574)
Median	13.00	18.50	20.00
Minimum, maximum	2.0, 30.0	1.0, 30.0	4.0, 30.0
Model-adjusted domain score[a]			
LS mean (SE)	13.86 (0.792)	17.41 (0.771)	18.63 (0.757)
95% CI	(12.30, 15.42)	(15.90, 18.93)	(17.14, 20.12)
Pairwise comparison – active vs placebo[a]			
Difference in LS Mean (SE)		3.55 (0.952)	4.77 (0.951)
95% CI		(1.68, 5.43)	(2.90, 6.64)
p-value		<0.001	<0.001
Pairwise comparison – 200 mg vs 100 mg[a]			
Difference in LS Mean (SE)			1.22 (0.930)
95% CI			(-0.61, 3.04)
p-value			0.192
Visit 4 (Week 8) (n)	132	133	136
Mean (SD)	14.39 (8.126)	18.47 (9.107)	19.38 (9.027)
Median	13.00	21.00	22.00
Minimum, maximum	1.0, 30.0	1.0, 30.0	1.0, 30.0
Model-adjusted domain score[a]			
LS mean (SE)	13.98 (0.820)	18.17 (0.813)	19.33 (0.803)
95% CI	(12.36, 15.59)	(16.57, 19.77)	(17.75, 20.91)
Pairwise comparison – active vs placebo[a]			
Difference in LS Mean (SE)		4.20 (0.979)	5.35 (0.974)
95% CI		(2.27, 6.12)	(3.44, 7.27)
p-value		<0.001	<0.001
Pairwise comparison – 200 mg vs 100 mg[a]			
Difference in LS Mean (SE)			1.16 (0.972)
95% CI			(-0.75, 3.07)
p-value			0.235
End of treatment (n)	135	138	139
Mean (SD)	14.34 (8.126)	18.49 (9.068)	19.29 (9.061)
Median	13.00	21.00	22.00
Minimum, maximum	1.0, 30.0	1.0, 30.0	1.0, 30.0
Model-adjusted domain score[a]			
LS mean (SE)	13.89 (0.805)	18.10 (0.802)	19.12 (0.788)
95% CI	(12.30, 15.47)	(16.53, 19.68)	(17.57, 20.67)
Pairwise comparison – active vs placebo[a]			
Difference in LS Mean (SE)		4.22 (0.962)	5.24 (0.961)
95% CI		(2.33, 6.11)	(3.35, 7.13)
p-value		<0.001	<0.001
Pairwise comparison – 200 mg vs 100 mg[a]			
Difference in LS Mean (SE)			1.02 (0.955)
95% CI			(-0.86, 2.90)
p-value			0.287

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error; vs, versus.

Note: Baseline was the Visit 2 result for the IIEF-EF domain score. End of treatment was the Visit 4 result or last observation carried forward if Visit 4 result was missing.

[a] Least squares (LS) means, standard errors, 95% confidence intervals, and p-values are from an ANCOVA model: IIEF-EF domain = treatment + baseline erectile dysfunction severity + diabetes status + baseline IIEF-EF domain score. The pairwise comparison p-values are from a 2-tailed *t*-test for the difference in LS means.

7.1.2. Other efficacy studies

7.1.2.1. Study TA-314

Study TA-314 was an open label extension of Study TA-301 and Study TA-302 to evaluate the long-term safety, tolerability and efficacy of avanafil in men with mild to severe ED. The study was conducted at 40 centres in the US from March 2009 to April 2010. The study included subjects who had completed Study TA-301 and Study TA-302. The study treatments were:

1. Avanafil 50 mg tablet
2. Avanafil 100 mg tablet
3. Avanafil 200 mg tablet

There was no comparator treatment. Subjects were instructed to take one tablet with water approximately 30 minutes prior to the initiation of sexual activity. All subjects were initially allocated to avanafil 100 mg and dose adjustments were permitted. Up to two doses of study drug were permitted in a 24 hour period provided the second dose was not taken until at least 12 hours after the first. The study used the same outcome measures as Study TA-301 and Study TA-302. The study included 712 subjects: 493 completed to Week 26 and 153 to Week 52. The age range was 23 to 88 years and 85% were White. The demographic characteristics were summarised. The efficacy analyses were performed using the data from the subjects last study visit, but are presented as a 52 week analysis. Hence these should be interpreted as the results for the last study visit. There were insufficient data in the 'other doses' group to provide meaningful conclusions. At last study visit:

- The proportion of subjects with successful intercourse was 67.7% for avanafil 100 mg and 66.3% for 100 mg and 200 mg combined. At Week 52, there were seven subjects in the avanafil 50 mg group, and the proportion of attempts with successful intercourse was 76.62%, seven in the 100 mg with 97.32% success and ten in the 200 mg with 96.25% success.
- The proportion of subjects with successful penetration was 83.3% for avanafil 100 mg and 79.4% for 100 mg and 200 mg combined. At Week 52, there were seven subjects in the avanafil 50 mg group, and the proportion of attempts with successful penetration was 51.98%, seven in the 100 mg with 35.48% success and ten in the 200 mg with 71.89% success.
- Mean (SD) IIEF Erectile Function Domain score was 22.2 (8.57) for avanafil 100 mg and 22.7 (8.12) for 100 mg and 200 mg combined.
- Global assessment (Has the treatment improved your erections?): 104 (77.0%) for avanafil 100 mg, 407 (80.3%) for 100 mg and 200 mg combined.
- Future use: 123 (67.6%) for avanafil 50 mg, 118 (66.7%) for 100 mg and 137 (75.3%) for 200 mg.

The secondary efficacy outcome measures were presented as summary statistics and were supportive of the primary efficacy outcome measures.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

In the Summary of Clinical Efficacy the sponsor provides data from a pooled analysis of Study TA-301, Study TA-302 and Study TA-05. These data indicate superior efficacy compared to placebo for avanafil 50 mg, 100 mg and 200 mg; that both the 100 mg and 200 mg doses are superior to the 50 mg; and that there was no significant difference between the 100 mg and 200 mg doses for successful intercourse (Table 42), successful penetration (Table 43), and IIEF Erectile Function Domain Score (Table 44). Successful intercourse within 15 minutes of

administration was reported in 53 (62.4%) attempts in the avanafil 50 mg group, 121 (60.5%) in the 100 mg, 63 (56.3%) in the 200 mg and 34 (27.6%) in the placebo.

Table 42: Change in the Percentage of Sexual Attempts between the Run-in Period and the Treatment Period in which Subjects were able to Maintain an Erection of Sufficient Duration to have Successful Intercourse (SEP3) – Integrated Analysis of Studies TA-301, TA-302, and TA-05 – Intent-to-Treat Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	337	12.3 (17.72)	24.9 (30.46)	12.6 (28.03)	12.2 (1.77)	<0.0001
Avanafil 50 mg	210	15.5 (19.12)	44.5 (35.73)	29.0 (33.83)	25.2 (2.31)	<0.0001
Avanafil 100 mg	343	12.7 (18.98)	49.0 (37.36)	36.3 (34.75)	36.1 (1.75)	<0.0001
Avanafil 200 mg	338	12.1 (17.79)	51.5 (37.49)	39.4 (34.70)	38.8 (1.76)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [4]		
	LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)	26.6 (2.42)	(21.9 , 31.4)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)	23.9 (2.41)	(19.1 , 28.6)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)	13.0 (2.87)	(7.4 , 18.6)	<0.0001
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	13.6 (2.87)	(8.0 , 19.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	10.9 (2.86)	(5.3 , 16.5)	0.0001
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)	2.8 (2.41)	(-2.0 , 7.5)	0.2549

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

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

Table 43: Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which Subjects Were Able to Achieve Successful Vaginal Penetration (SEP2) – Integrated Analysis of Studies TA-301, TA-302, and TA-05 – Intent-to-Treat Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	337	44.3 (37.02)	50.5 (38.75)	6.2 (32.38)	4.3 (1.65)	0.0092
Avanafil 50 mg	210	51.4 (36.30)	67.5 (35.74)	16.1 (34.67)	14.4 (2.16)	<0.0001
Avanafil 100 mg	343	44.0 (37.86)	67.5 (35.68)	23.5 (35.28)	21.4 (1.63)	<0.0001
Avanafil 200 mg	338	48.8 (37.80)	72.6 (34.44)	23.7 (35.64)	24.2 (1.65)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [4]		
	LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)	19.9 (2.27)	(15.4 , 24.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)	17.1 (2.26)	(12.7 , 21.6)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)	10.1 (2.69)	(4.8 , 15.3)	0.0002
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	9.8 (2.68)	(4.6 , 15.1)	0.0003
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	7.1 (2.67)	(1.8 , 12.3)	0.0083
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)	2.8 (2.26)	(-1.7 , 7.2)	0.2220

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

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

Table 44: Change in IIEF Erectile Function Domain Score from Baseline to End of Treatment – Integrated Analysis of Studies TA-301, TA-302, and TA-05 – Intent-to-Treat Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	331	12.6 (5.12)	14.8 (7.78)	2.2 (6.36)	1.9 (0.39)	<0.0001
Avanafil 50 mg	208	13.6 (5.03)	18.4 (7.84)	4.8 (7.59)	3.7 (0.51)	<0.0001
Avanafil 100 mg	341	12.7 (5.23)	19.3 (8.32)	6.6 (7.44)	6.3 (0.39)	<0.0001
Avanafil 200 mg	336	13.1 (5.09)	20.4 (8.36)	7.3 (7.46)	7.2 (0.39)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [4]		
	LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)	5.3 (0.54)	(4.2 , 6.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)	4.4 (0.54)	(3.3 , 5.4)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)	1.8 (0.64)	(0.6 , 3.1)	0.0042
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	3.4 (0.64)	(2.2 , 4.7)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	2.6 (0.63)	(1.3 , 3.8)	<0.0001
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)	0.9 (0.54)	(-0.2 , 1.9)	0.1023

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

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

7.1.4. Evaluator's conclusions on clinical efficacy for erectile dysfunction

Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED. The 100 mg and 200 mg dose levels were both superior to 50 mg. In Study TA-301, in subjects with mild to severe ED, the mean (SD) change from baseline in % successful penetration was 7.1 (32.07) % for placebo, 18.9 (35.51) % for avanafil 50 mg, 27.3 (35.17) % for 100 mg and 29.0 (35.90) % for 200 mg. The mean (SD) change from baseline in % successful intercourse was 14.4 (27.63) % for placebo, 27.8 (33.86) % for avanafil 50 mg, 43.2 (33.86) % for 100 mg and 44.6 (35.67) % for 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 2.9 (6.38) for placebo, 5.4 (7.54) for avanafil 50 mg, 8.3 (7.67) for 100 mg and 9.5 (7.03) % for 200 mg.

Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED. In Study TA-302, the mean (SD) change from baseline in % successful intercourse was 10.5 (27.73) % for placebo, 26.2 (33.71) % for 100 mg and 32.1 (32.94) % for 200 mg. The mean (SD) change from baseline in % successful penetration was 5.9 (31.16) % for placebo, 21.5 (37.19) % for 100 mg and 22.0 (35.00) % for 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 1.8 (6.24) for placebo, 4.6 (7.00) for avanafil 100 mg and 5.3 (7.50) % for 200 mg.

Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve-sparing radical prostatectomy. In Study TA-303, the mean (SD) change from baseline in % successful intercourse was 4.8 (19.89) % for placebo, 18.3 (30.18) % for 100 mg and 21.1 (31.83) % for 200 mg. The mean (SD) change from baseline in % successful penetration was -0.4 (21.59) % for placebo, 15.3 (32.21) % for 100 mg and 20.8 (31.78) % for 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 0.1 (3.56) for placebo, 3.6 (7.04) for avanafil 100 mg and 5.2 (7.00) % for 200 mg.

Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake. In Study TA-501 Both active treatments has superior erectogenic effect ≤ 17 minutes after dosing compared to placebo, and there was no significant difference between the avanafil 100 mg and 200 mg dose levels. The LS mean (SE) erectogenic effect was 24.71 (2.911) % for avanafil 100

mg, 28.18 (2.876) % for 200 mg and 13.78 (2.905) % for placebo. In Study TA-301 the increase in the proportion of successful intercourse was from ≥ 15 minutes after ingestion. However, in Study TA-302, time of onset of effect was shorter for avanafil 100 mg than avanafil 200 mg for successful intercourse, successful penetration and Satisfaction with Sexual Experience.

The effects of avanafil appear to be maintained over a 52 week period. In Study TA-314, in subjects followed up for up to 52 months, at last study visit the proportion of subjects with successful intercourse was 67.7% for avanafil 100 mg and 66.3% for 100 mg and 200 mg combined. At Week 52, there were seven subjects in the avanafil 50 mg group, and the proportion of attempts with successful intercourse was 76.62%, seven in the 100 mg with 97.32% success and ten in the 200 mg with 96.25% success. The proportion of subjects with successful penetration was 83.3% for avanafil 100 mg and 79.4% for 100 mg and 200 mg combined. At Week 52, there were seven subjects in the avanafil 50 mg group, and the proportion of attempts with successful penetration was 51.98%, seven in the 100 mg with 35.48% success and ten in the 200 mg with 71.89% success. Mean (SD) IIEF Erectile Function Domain score was 22.2 (8.57) for avanafil 100 mg and 22.7 (8.12) for 100 mg and 200 mg combined.

For Study TA-314, the efficacy analyses were performed using the data from the subjects last study visit, but are presented as a 52 week analysis. Hence these should be interpreted as the results for the last study visit. There were insufficient data in the other doses group to provide meaningful conclusions. The data also represent a responder analysis. A more useful analysis would be to present the results by study visit.

The outcome measures used in the clinical trials were clinically relevant. The statistical measures, including those addressing imputation and multiplicity, were appropriate. The population of patients studied in the clinical trials was similar to that intended for marketing in Australia. The PI reflects this study population.

The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by AEs, clinical laboratory tests, vital signs and ECGs.

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows: AEs, clinical laboratory tests and ECGs.

8.1.4. Clinical pharmacology studies

The clinical pharmacology studies provided safety data, as follows: AEs, clinical laboratory tests and ECGs.

8.2. Patient exposure

There were 2144 subjects exposed to avanafil in the development program, including 644 in Phase I, 360 in Phase II and 1140 in Phase III (Table 45).

In Study TA-01 there were 27 subjects exposed to a single dose of avanafil 50 mg, 28 to 100 mg, and 28 to 200 mg

In Study TA-03 there were 49 subjects exposed to up to 12 doses of avanafil 200 mg.

In Study TA-05 subjects received up to 18 doses and a median of 16 doses. There were 57 subjects exposed to avanafil 50 mg, 61 to 100 mg, 59 to 200 mg, and 59 to 300 mg.

In Study TA-301 there were 150 subjects exposed to avanafil 50 mg, 161 to avanafil 100 mg and 162 to avanafil 200 mg for up to 12 weeks. In the study there were 144 (22.3%) subjects aged ≥ 65 years, 233 (36.2%) subjects with a history of hypertension and 61 (9.5%) subjects with a history of coronary artery disease.

In Study TA-302, conducted in subjects with diabetes mellitus, there were 127 subjects exposed to avanafil 100 mg and 131 to 200 mg for up to 12 weeks. In the study there were 105 (26.9%) subjects aged ≥ 65 years, 260 (67.0%) subjects with a history of hypertension, and 54 (13.9%) with a history of coronary artery disease.

In Study TA-303, conducted in subjects with a history of bilateral nerve-sparing retropubic radical prostatectomy, there were 99 subjects exposed to avanafil 100 mg and 99 to 200 mg for up to 12 weeks. There were 48 (16.1%) subjects aged ≥ 65 years, 125 (41.9%) subjects with a history of hypertension, 38 (12.8%) with other cardiovascular disease and seven (2.3%) with coronary artery disease.

In Study TA-501 there were 146 subjects exposed to avanafil 100 mg and 146 to 200 mg, with a median number of doses of 11. There were 129 (29.3%) subjects were aged ≥ 65 years.

In Study TA-314 there were 153 subjects exposed to avanafil for ≥ 12 months and 493 for ≥ 6 months.

Table 45: Summary of Avanafil Exposure During the Clinical Development Program

		Total Exposure	Total Avanafil Exposure	Avanafil ≤50 mg [1]	Avanafil 100 mg	Avanafil 200 mg	Avanafil 300-800 mg [2]	Placebo
Phase 1 Studies								
TOTAL	18 completed Phase 1 Studies	**680**	**644**	**83**	**73**	**485**	**80**	**330**
Phase 2 Studies								
TA-01	Visual stimulation (crossover study)	83	82	27	27	28	NA	82
TA-03	Home administration (crossover study)	49	49	NA	NA	49	NA	NA
TA-05	Safety and efficacy	284	229	56	60	56	57	55
TOTAL		**416**	**360**	**83**	**87**	**133**	**57**	**137**
Phase 3 Studies								
TA-301	Generalized ED	644	483	160	161	162	NA	161
TA-302	Subjects with diabetes	388	258	NA	127	131	NA	130
TA-303	Subjects following radical prostatectomy	298	198	-	99	99	-	100
TA-314	Open-label, long-term roll over from TA-301 and TA-302		201 [3]	-	-	-	NA	NA
TOTAL		**1330**	**1140**	**160**	**387**	**392**	**0**	**391**
PROGRAM TOTAL		**2426**	**2144**	**326**	**547**	**1010**	**137**	**858**

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

ED = erectile dysfunction; NA = not applicable.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

In Study TA-301 TEAEs were reported in 52 (32.5%) subjects in the avanafil 50 mg group, 68 (42.2%) in the 100 mg, 63 (38.9%) in the 200 mg and 42 (26.1%) in the placebo. The commonest TEAE was headache, reported in seven (4.4%) subjects in the avanafil 50 mg group, twelve (7.5%) in the 100 mg, 15 (9.3%) in the 200 mg and two (1.2%) in the placebo.

In Study TA-302 TEAEs were reported in 45 (35.4%) subjects in the avanafil 100 mg group, 42 (32.1%) in the 200 mg and 31 (23.8%) in the placebo. Headache was reported in five (3.9%) subjects in the avanafil 100 mg group, 15 (11.5%) in the 200 mg and two (1.5%) in the placebo.

In Study TA-303 TEAEs were reported in 38 (38.4%) subjects in the avanafil 100 mg group, 45 (45.5%) in the 200 mg and 23 (23.0%) in the placebo. Headache was reported in eight (8.1%) subjects in the avanafil 100 mg group, 12 (12.1%) in the 200 mg and one (1.0%) in the placebo.

In Study TA-501 TEAEs were reported in 30 (20.5%) subjects in the avanafil 100 mg group, 40 (27.4%) in the 200 mg group and 30 (21.0%) in the placebo. Headache was reported in two (1.4%) subjects in the avanafil 100 mg group, 13 (8.9%) in the 200 mg and one (0.7%) in the placebo.

Overall, in the double blind cohort studies (which included Study TA-301, Study TA-302 and Study TA-05) the rates of TEAE did not appear to be influenced by age (Table 46). The risk of TEAE was not influenced by race, diabetes status or coronary artery disease subgroup.

Table 46: Overview of Adverse Events – Age Subgroups – Integrated Double-Blind Cohort

	Subjects <50 Years of Age				Subjects ≥50 Years and <65 Years of Age				Subjects ≥65 Years of Age			
	Placebo (N=88) n (%)	Avanafil 50 mg (N=66) n (%)	Avanafil 100 mg (N=94) n (%)	Avanafil 200 mg (N=83) n (%)	Placebo (N=178) n (%)	Avanafil 50 mg (N=116) n (%)	Avanafil 100 mg (N=169) n (%)	Avanafil 200 mg (N=186) n (%)	Placebo (N=83) n (%)	Avanafil 50 mg (N=35) n (%)	Avanafil 100 mg (N=86) n (%)	Avanafil 200 mg (N=83) n (%)
Subjects with TEAEs												
Any TEAE	24 (27.3)	25 (37.9)	36 (38.3)	24 (28.9)	47 (26.4)	33 (28.4)	66 (39.1)	71 (38.2)	18 (21.7)	10 (28.6)	38 (44.2)	33 (39.8)
Any drug-related TEAE	5 (5.7)	10 (15.2)	16 (17.0)	9 (10.8)	7 (3.9)	11 (9.5)	22 (13.0)	40 (21.5)	3 (3.6)	2 (5.7)	12 (14.0)	12 (14.5)
Maximum severity of TEAEs												
Mild	12 (13.6)	18 (27.3)	21 (22.3)	18 (21.7)	24 (13.5)	16 (13.8)	35 (20.7)	42 (22.6)	15 (18.1)	7 (20.0)	21 (24.4)	15 (18.1)
Moderate	11 (12.5)	7 (10.6)	13 (13.8)	6 (7.2)	20 (11.2)	16 (13.8)	26 (15.4)	27 (14.5)	3 (3.6)	2 (5.7)	15 (17.4)	16 (19.3)
Severe	1 (1.1)	0 (0.0)	2 (2.1)	0 (0.0)	3 (1.7)	1 (0.9)	5 (3.0)	2 (1.1)	0 (0.0)	1 (2.9)	2 (2.3)	2 (2.4)
Maximum severity of drug-related TEAEs												
Mild	2 (2.3)	9 (13.6)	11 (11.7)	8 (9.6)	7 (3.9)	7 (6.0)	15 (8.9)	31 (16.7)	3 (3.6)	1 (2.9)	11 (12.8)	6 (7.2)
Moderate	3 (3.4)	1 (1.5)	4 (4.3)	1 (1.2)	0 (0.0)	4 (3.4)	6 (3.6)	9 (4.8)	0 (0.0)	1 (2.9)	1 (1.2)	6 (7.2)
Severe	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with SAEs												
Any SAE	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	2 (1.1)	2 (1.7)	3 (1.8)	5 (2.7)	0 (0.0)	0 (0.0)	2 (2.3)	2 (2.4)
Any treatment-emergent SAE	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)	2 (1.7)	3 (1.8)	5 (2.7)	0 (0.0)	0 (0.0)	2 (2.3)	2 (2.4)
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study drug discontinuations due to adverse events												
Any adverse event	2 (2.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)	3 (2.6)	4 (2.4)	3 (1.6)	2 (2.4)	0 (0.0)	3 (3.5)	3 (3.6)
Any TEAE	2 (2.3)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)	3 (2.6)	3 (1.8)	3 (1.6)	2 (2.4)	0 (0.0)	3 (3.5)	3 (3.6)
Any drug-related TEAE	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Any SAE	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (1.2)	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)

Data from studies TA-05, TA-301 and TA-302 are included.
Treatment-emergent adverse events were defined as adverse events occurring after the first dose of study drug or after the first drug dispense date (if the first dose date was missing) and up to 28 days after the last dose of study drug.
SAE = serious adverse event; TEAE = treatment-emergent adverse event.

8.3.1.2. Other studies

In Study TA-01 TEAEs were reported in 4 (14.8%) subjects with avanafil 50 mg, 3 (11.1%) with 100 mg, 4 (14.3%) with 200 mg. TEAEs were reported in 7.1% to 14.8% subjects treated with sildenafil and 3.7% to 7.4% subjects treated with placebo. The only TEAE reported in ≥ 1

subject with any avanafil dose level was flushing: four (14.8%) subjects with 50 mg, two (7.4%) with 100 mg and two (7.1%) with 200 mg.

In Study TA-03 TEAEs were reported in eleven (22.4%) subjects with avanafil 200 mg 5 to 10 minutes prior to intercourse, 8 (17.0%) with avanafil 200 mg 2 hours prior and 15 (20.6%) with sildenafil 5 to 10 minutes prior. Headache was reported in 4 (8.2%) subjects with avanafil 200 mg 5 to 10 minutes prior to intercourse, 3 (6.4%) with avanafil 200 mg 2 hours prior and 5 (10.2%) with sildenafil 5 to 10 minutes prior. Nasal congestion was reported in 2 (4.1%) subjects with avanafil 200 mg 5 to 10 minutes prior to intercourse, 3 (6.4%) with avanafil 200 mg 2 hours prior and 5 (10.2%) with sildenafil 5 to 10 minutes prior.

In Study TA-05 TEAEs were reported by 18 (28.6%) subjects in the avanafil 50 mg group, 27 (45.0%) in the 100 mg, 22 (39.3%) in the 200 mg, 29 (50.9%) in the 300 mg and 16 (29.1%) in the placebo. Headache was dose related and was reported in four (7.1%) subjects in the avanafil 50 mg group, seven (11.7%) in the 100 mg, seven (12.5%) in the 200 mg, 15 (26.3%) in the 300 mg and two (3.6%) in the placebo.

In Study TA-314 TEAEs were reported in three (75.0%) subjects with avanafil 50 mg, 135 (19.0%) with 100 mg and 183 (35.6%) with 200 mg. Headache was reported by one (25.0%) subject with avanafil 50 mg, 19 (2.7%) with 100 mg and 36 (7.0%) with 200 mg.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

In Study TA-301 treatment related TEAEs were reported in 14 (8.8%) subjects in the avanafil 50 mg group, 25 (15.5%) in the 100 mg, 26 (16.0%) in the 200 mg and four (2.5%) in the placebo. Headache was attributed to treatment in six (3.8%) subjects in the avanafil 50 mg group, ten (6.2%) in the 100 mg, 16 (7.4%) in the 200 mg and none in the placebo; flushing in six (3.8%) subjects in the avanafil 50 mg group, ten (6.2%) in the 100 mg, six (3.7%) in the 200 mg and none in the placebo; and nasal congestion in one (0.6%) subjects in the avanafil 50 mg group, four (2.5%) in the 100 mg, three (1.9%) in the 200 mg and one (0.6%) in the placebo.

In Study TA-302 treatment related TEAEs were reported in nine (7.1%) subjects in the avanafil 100 mg group, 20 (15.3%) in the 200 mg and five (3.8%) in the placebo. Headache was attributed to treatment in three (2.4%) subjects in the 100 mg group, five (9.2%) in the 200 mg and two (1.5%) in the placebo; flushing in two (1.6%) in the 100 mg, five (3.8%) in the 200 mg and none in the placebo; and sinus congestion in one (0.6%) subjects in the avanafil 100 mg group, four (3.1%) in the 200 mg and none in the placebo.

In Study TA-303 treatment related TEAEs were reported in 13 (13.1%) subjects in the avanafil 100 mg group, 23 (23.2%) in the 200 mg and four (4.0%) in the placebo. Flushing was attributed to treatment in five (5.1%) subjects in the 100 mg group, ten (10.1%) in the 200 mg and none in the placebo; headache in five (5.1%) in the 100 mg, eight (8.1%) in the 200 mg and one (1.0%) in the placebo; and nasal congestion in three (3.0%) subjects in the avanafil 100 mg group, one (1.0%) in the 200 mg and none in the placebo.

In Study TA-501 treatment related TEAEs were reported in three (2.1%) subjects in the avanafil 100 mg group, 16 (11.0%) in the 200 mg group and one (0.7%) in the placebo. Headache was attributed to treatment in two (1.4%) subjects in the 100 mg group, nine (6.2%) in the 200 mg and one (0.7%) in the placebo; nasal congestion in one (0.7%) in the 100 mg, five (3.4%) in the 200 mg and none in the placebo; and flushing in one (0.7%) subject in the avanafil 100 mg group, two (1.4%) in the 200 mg and none in the placebo.

8.3.2.2. Other studies

In Study HP-01 there were 31 TEAEs were reported in 20 (30.8%) subjects. The highest incidence of TEAEs was in the 600 mg and 800 mg groups: 83.3% and 100% respectively. Headache and nausea appear to be dose related.

In Study TA-140 there were 33 TEAEs in 18 subjects following avanafil 100 mg, 215 in 44 following avanafil 800 mg, 28 in eight following moxifloxacin and 20 in 13 following placebo. Following avanafil 800 mg, 37 (66.1%) subjects reported headache, 23 (41.1%) nausea, 15 (26.8%) vomiting, 10 (17.9%) dizziness, and 7 (12.5%) nasal congestion.

In Study TA-05 treatment related TEAEs were reported by nine (16.1%) subjects in the avanafil 50 mg group, 16 (26.7%) in the 100 mg, 15 (26.8%) in the 200 mg, 22 (38.6%) in the 300 mg and six (10.9%) in the placebo. Treatment related headache was dose related and was reported in four (7.1%) subjects in the avanafil 50 mg group, seven (11.7%) in the 100 mg, seven (12.5%) in the 200 mg, 15 (26.3%) in the 300 mg and two (3.6%) in the placebo.

In Study TA-314 treatment related TEAEs were reported in three (75.0%) subjects with avanafil 50 mg, 42 (5.9%) with 100 mg and 50 (9.7%) with 200 mg. Headache was attributed to treatment in one (25.0%) subject in the avanafil 50 mg group, 15 (2.1%) in the 100 mg and 22 (4.3%) in the 200 mg; flushing was attributed to treatment in no subjects in the avanafil 50 mg group, nine (1.3%) in the 100 mg and 17 (3.3%) in the 200 mg; and nasal congestion was attributed to treatment in no subjects in the avanafil 50 mg group, seven (1.0%) in the 100 mg and seven (1.4%) in the 200 mg.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

In Study TA-301 there was one death, which occurred in the avanafil 100 mg group from self-inflicted gunshot wound. SAEs were reported in one (0.6%) subject in the avanafil 50 mg group (acute myocardial infarction), three (1.9%) in the 100 mg (prostate cancer, gunshot wound, bladder cancer), three (1.9%) in the 200 mg (hypoesthesia, coronary artery disease, infected bites) and two (1.2%) in the placebo (non-cardiac chest pain, depression suicidal).

In Study TA-302 there were no deaths. SAEs were reported in three (2.4%) subjects in the avanafil 100 mg group (deep vein thrombosis, urinary tract infection, localised infection), four (3.1%) in the 200 mg (pain in extremity/muscular weakness, angina unstable, pneumonia, bladder cancer) and one (0.8%) in the placebo (spinal compression fracture).

In Study TA-303 there were no deaths or SAEs.

In Study TA-501 there were no deaths. SAEs were reported in four (2.7%) subjects in the avanafil 100 mg group (atrial flutter, nephrolithiasis, cerebrovascular accident, acute myocardial infarction/unstable angina), three (2.1%) in the 200 mg group (tendon rupture, dyspnoea/coronary artery disease, atrial flutter/atrioventricular block) and two (1.4%) in the placebo (hypertension/bladder outlet obstruction).

8.3.3.2. Other studies

In Study TA-02 there was one SAE: pharyngolaryngeal pain due to tonsillar abscess, leading to DAE. There were no deaths.

In Study TA-05 there were no deaths. There were three SAEs: two in the 300 mg group: abdominal and head injury due to a motor vehicle accident (MVA), and partner of the same subject also injured in the MVA; and one subject in the 50 mg group had dizziness recorded as a SAE.

In Study TA-01 and Study TA-03 there were no deaths and no SAEs.

In Study TA-314 there were no deaths. SAEs were reported in no subjects with avanafil 50 mg, six (0.8%) with 100 mg and five (1.0%) with 200 mg. There was no apparent pattern to the SAEs.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

In Study TA-301 DAE was reported for three (1.9%) subjects in the avanafil 50 mg group, six (3.7%) in the 100 mg, four (2.5%) in the 200 mg and five (3.1%) in the placebo. Two subjects in the avanafil 100 mg group and one in the 200 mg discontinued because of headache.

In Study TA-302 DAE was reported for two (1.6%) subjects in the avanafil 100 mg group (Peyronie's disease, urinary tract infection), two (1.5%) in the 200 mg (angina unstable, headache) and none in the placebo.

In Study TA-303 DAE was reported for three (3.0%) subjects in the avanafil 100 mg group (abdominal pain upper, vision blurred/headache/nausea, vomiting/dyspepsia), two (2.0%) in the 200 mg (hypertension, psychomotor hyperactivity/inappropriate affect/headache) and one (1.0%) in the placebo (lumbar spinal stenosis).

In Study TA-501 DAE were reported for four (2.7%) subjects in the avanafil 100 mg group (inguinal hernia, nephrolithiasis, headache/flushing, acute myocardial infarction/unstable angina/hyperlipidaemia), three (2.1%) in the 200 mg group (dyspnoea/congestive cardiac failure/coronary artery disease, headache, muscle spasms) and none in the placebo.

8.3.4.2. Other studies

In Study TA-02 there was one DAE: pharyngolaryngeal pain due to tonsillar abscess.

In Study TA-07 there were two subjects with DAE: the first reported bilateral eye redness/ blurred vision/ bilateral hamstring cramping/low back pain/testicular pain/and difficulty sleeping; the second reported bilateral hamstring aches/bilateral quadriceps aches/difficulty sleeping/and an acidic stomach.

In Study TA-03 there was one DAE: partner became pregnant. However, in the context of the treatment indication this might not be considered an AE.

In Study TA-05 there were five DAEs: three in the 300 mg group: headache, scoliosis, abdominal injury/head injury; one in the 200 mg group: insomnia; and one in the placebo: genital herpes.

In Study TA-314 DAE was reported for one (25.0%) subject with avanafil 50 mg, 13 (1.8%) with 100 mg and six (1.2%) with 200 mg. There was no apparent pattern to the DAEs.

In Study TA-01 there were no DAEs.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

In Study TA-301 the sponsor reported no subjects with clinically significant abnormalities in hepatic function. A shift to above ULN from within range for ALT occurred for 16 (3.7%) subjects in the avanafil groups and five (3.4%) in the placebo; and for AST occurred for nine (2.1%) subjects in the avanafil groups and six (4.1%) in the placebo.

In Study TA-302 one subject in the placebo group had an elevation of ALT recorded as a TEAE.

In Study TA-303 two subjects in the avanafil 200 mg group had elevations in ALT reported as TEAEs.

In Study TA-501 shifts from normal to above ULN in ALT occurred for three (2.5%) subjects in the avanafil 100 mg group, nine (6.9%) in the 200 mg and six (5.0%) in the placebo. Shifts from normal to above ULN in AST occurred for one (0.8%) subjects in the avanafil 100 mg group, two (1.2%) in the 200 mg and six (5.0%) in the placebo.

Overall, in the double blind cohort studies (which included Study TA-301, Study TA-302 and Study TA-05) elevation of ALT > 3xULN was reported in only one subject in the avanafil 200 mg group. Elevation of AST >3xULN was reported in one (0.3%) subject in the avanafil 100 mg group, two (0.6%) in the 200 mg and none in either the 50 mg or placebo.

8.4.1.2. Other studies

In Study TA-05 one subject in the placebo group had elevated ALT and AST. One subject in the avanafil 300 mg group had elevated serum bilirubin following a MVA.

In Study TA-01, Study TA-03 and Study TA-314 there were no clinically significant abnormalities in hepatic function.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

In Study TA-301 the sponsor reported no subjects with clinically significant abnormalities in renal function. A shift to below LLN from within range for creatinine clearance occurred for four (0.9%) subjects in the avanafil groups and none in the placebo.

In Study TA-302 there were no clinically significant treatment emergent abnormalities in renal function.

In Study TA-303 two subjects in the avanafil 200 mg group had elevations in serum creatinine reported as TEAEs.

In Study TA-501 shifts from normal to above ULN in serum creatinine occurred for four (3.3%) subjects in the avanafil 100 mg group, two (1.5%) in the 200 mg and none in the placebo.

Overall, in the double blind cohort studies (which included Study TA-301, Study TA-302 and Study TA-05) elevation of serum creatinine was reported in 13 (6.6%) subjects treated with avanafil 50 mg, 28 (8.8%) with 100 mg, 31 (9.7%) with 200 mg and 26 (8.3%) with placebo.

8.4.2.2. Other studies

In Study TA-05 one subject in the avanafil 200 mg group had microscopic haematuria at study exit.

In Study TA-01, Study TA-03 and Study TA-314 there were no clinically significant abnormalities in renal function.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

In the pivotal studies there were no clinically significant abnormalities in other clinical chemistry.

8.4.3.2. Other studies

In Study TA-05 one subject in the avanafil 300 mg group had elevated serum potassium following a MVA. One subject in the placebo group had elevated blood glucose at exit.

In Study TA-314 one subject discontinued because of hyperkalaemia.

In Study TA-01 and Study TA-03 there were no clinically significant abnormalities in other clinical chemistry.

8.4.4. Haematology

8.4.4.1. Pivotal studies

In Study TA-301, Study TA-302, Study TA-303 and Study TA-501 the sponsor reported no clinically significant abnormalities in haematology.

8.4.4.2. Other studies

In Study TA-05 one subject in the avanafil 200 mg group had elevated haematocrit at study exit.

In Study TA-01, Study TA-03 and Study TA-314 there were no clinically significant abnormalities in haematology.

8.4.5. Electrocardiograph

8.4.5.1. Pivotal studies

In Study TA-303 treatment emergent abnormalities in ECG were reported in three (3.0%) subjects in the avanafil 200 mg group: early repolarisation with non-specific ST segment changes; sinus bradycardia (rate 57) with high lateral ST abnormalities and possible ischaemia; borderline rhythm.

In Study TA-301 and Study TA-302 no treatment emergent abnormalities in ECG were reported.

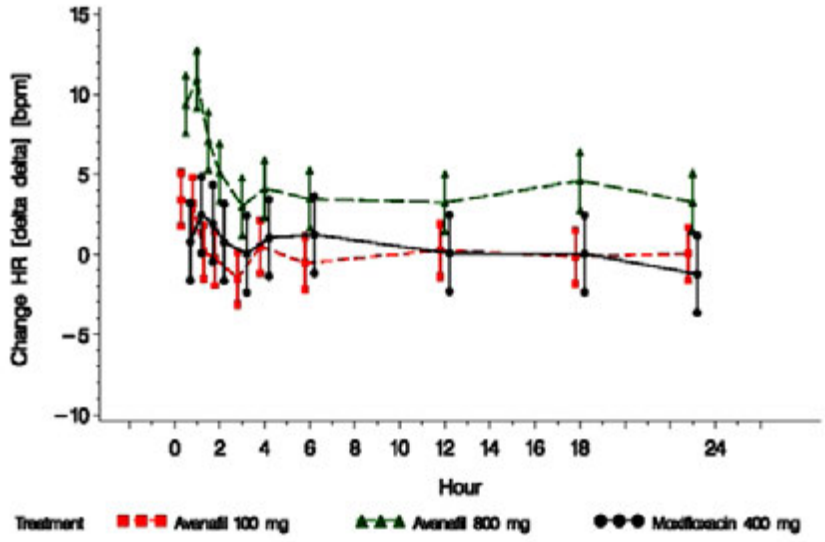
8.4.5.2. Other studies

In Study TA-02 conducted in healthy volunteers, one subject in the 200 mg group had a treatment emergent QTcF > 430 ms (438.8 ms). One subject in the 50 mg group had a prolonged PR interval: 217 ms (192 pre-study and 229 post-study).

Study TA-140 was a Thorough QT study that explored the effects on QTc of avanafil 100 mg and 800 mg. There were no concerns with regard the 100 mg dose level. For the 800 mg dose level, at 3 hours post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) ms. The upper 90% CI was > 10, which is the level of regulatory concern. It is the opinion of the sponsor that this result is spurious because the 800 mg dose resulted in an increase in heart rate compared to the other three treatments (Figure 2). The data for QTcF and QTcB were not presented in the report. QTcF would be of particular interest because it provides a better correction in relation to higher heart rates.

In Study TA-314 one subject developed a clinically significant ECG abnormality on active treatment.

Figure 2: Change in Heart Rate (delta delta; bpm) Versus Time Avanafil and Moxifloxacin



8.4.6. Vital signs

8.4.6.1. Pivotal studies

In Study TA-301 no clinically significant abnormalities in vital signs were reported. Elevated SBP was reported in three (1.9%) subjects in the avanafil 50 mg group, one (0.6%) in the 100

mg, one (0.6%) in the 200 mg and one (0.6%) in the placebo. Elevated DBP was reported in four (2.5%) subjects in the avanafil 50 mg group, two (1.2%) in the 100 mg, none in the 200 mg and three (1.9%) in the placebo.

In Study TA-302 no clinically significant abnormalities in vital signs were reported. Elevated SBP was reported in three (2.4%) subjects in the avanafil 100 mg group, three (2.3%) in the 200 mg and four (3.1%) in the placebo. Elevated DBP was reported in three (2.4%) subjects in the avanafil 100 mg group, none in the 200 mg and one (0.8%) in the placebo.

In Study TA-303 one subject in the avanafil 200 mg group had hypertension reported as a TEAE. Elevated SBP was reported in one (1.0%) subject in the avanafil 100 mg group, one (1.0%) in the 200 mg and one (1.0%) in the placebo. Elevated DBP was reported in one (1.0%) subject in the avanafil 100 mg group, five (5.1%) in the 200 mg and two (2.0%) in the placebo.

In Study TA-501 no clinically significant abnormalities in vital signs were reported.

8.4.6.2. Other studies

In Study TA-05 there were six subjects with significant abnormalities in vital signs. One subject in the placebo group and two in the avanafil 100 mg had hypertension at study exit. One subject in the 200 mg group had exertional dyspnoea. One subject in the 300 mg group had palpitations. One subject in the 300 mg group had AV block and bradycardia the day after a MVA.

Study TA-314 31 (4.4%) subjects had abnormal SBP during treatment (defined as an increase of > 20 mmHg from baseline and > 140 mmHg on two or more occasions or any value > 180 mmHg); and 26 (3.7%) had abnormal DBP during treatment (defined as an increase of > 15 mmHg from baseline on two or more occasions or any value > 110 mmHg).

In Study TA-01 and Study TA-03 there were no clinically significant abnormalities in vital signs with avanafil.

8.5. Post-marketing experience

8.5.1. Risk Minimisation Plan

The sponsor, A Menarini Australia Pty Ltd, will be marketing Spedra in Australia under a contractual agreement with the global license partner, Vivus. Vivus holds the global safety database for avanafil and will be responsible for the preparation of PSURs. No additional risk management activities are planned for Australia. The pharmacovigilance processes in Australia will be carried out by Commercial Eyes Pty Ltd under a third party service agreement with A Menarini Australia Pty Ltd.

The important identified risks are:

- Pre-existing cardiovascular disease
- Prolonged erection (priapism)

The important potential risks are:

- Hypotension/increased hypotensive effect
- Non-arteritic anterior ischaemic optic neuropathy
- Sudden hearing loss

Important missing information is:

- Very elderly males > 70 years of age
- Adult males with significant pre-existing cardiovascular disease
- Use in subjects with severe renal or hepatic failure

- Adult males with ED due to spinal cord injury
- Patients with retinitis pigmentosa
- Patients with bleeding disorders or active peptic ulceration
- Effect of avanafil on spermatogenesis in healthy adult males and adult males with mild ED
- Effects of avanafil on multiple parameters of vision

8.5.2. Post-marketing data

A single PSUR was included in the submission covering the time period up to 20 December 2013. The international birthdate for avanafil is 17 August 2011 which is the date of first market authorisation, which was in South Korea. During the time period covered by the PSUR no regulatory actions had been taken. During the time period covered by the PSUR total sales of avanafil were: 41,623 avanafil 100 mg tablets and 288,334 avanafil 200 mg tablets. Spontaneous reports consisted of a total of 40 ADRs in 32 patients. There were no spontaneous reports of serious ADRs.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

The data did not identify any safety issues with regard to liver toxicity. However, the sponsor did not provide a listing of subjects who fulfilled the criteria of Hy's law.

8.6.2. Haematological toxicity

The data did not identify any safety issues with regard to haematological toxicity.

8.6.3. Serious skin reactions

The data did not identify any safety issues with regard to serious skin reactions.

8.6.4. Cardiovascular safety

The data identified a potential safety issue with regard to prolongation of QTc. For the 800 mg dose level, at 3 hours post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) ms, the upper 90% CI being > 10, which is the level of regulatory concern. The data were incomplete because the results for QTcB and QTcF were not provided in the submission.

8.6.5. Unwanted immunological events

The data did not identify any safety issues with regard to serious skin reactions.

8.7. Other safety issues

8.7.1. Safety in special populations

Safety in special populations was not addressed in the development program. However, avanafil is intended for a specific population (males with ED) and this population has been studied in the development program. There were 426 subjects aged ≥ 65 years in the development program.

8.7.2. Safety related to drug-drug interactions and other interactions

In combination with GTN there was an increased risk of headache, dizziness and nausea with avanafil, which was similar to the risk with sildenafil. In Study TA-02 there were 43 TEAEs reported by 25 (23.6%) subjects prior to GTN, and 248 TEAEs reported by 67 (63.2%) after GTN. Headache was reported in 24 (24%) subjects after avanafil, 25 (26%) after sildenafil and 16 (16%) after placebo; dizziness in 18 (18%) after avanafil, 22 (23%) after sildenafil and 10

(10%) after placebo; and nausea in ten (10%) after avanafil, nine (9%) after sildenafil and one (1%) after placebo.

8.8. Evaluator's overall conclusions on clinical safety

The rates of TEAEs were higher in the avanafil treatment groups compared to placebo. Headache was more common in the avanafil groups and appeared to be dose related. Up to 13% of subjects in the avanafil 200 mg groups reported headache. The risk of TEAE was not influenced by age, race, diabetes status or coronary artery disease.

Treatment related TEAEs were more common with avanafil than placebo, and the rate increased with dose. Up to 23% of subjects in the avanafil 200 mg group had TEAEs attributed to treatment. TEAEs attributed to treatment included headache, flushing and nasal congestion. All of these AEs appeared to be dose related. At doses of avanafil 800 mg all subjects reported TEAEs.

There was one death reported in the development program for avanafil: self-inflicted gunshot injury. This was not attributed to treatment. SAEs were uncommon and did not have any apparent pattern

DAE was uncommon and did not have any apparent pattern.

Elevations in ALT were uncommon in the avanafil treatment groups and none were considered to be clinically significant by the sponsor. However, the sponsor has not stated whether any subjects fulfilled the criteria of Hy's law for drug induced liver injury. There were no clinically significant abnormalities in renal function or haematology reported during the development program for avanafil. Shifts from normal to abnormal occurred at similar rates for avanafil and placebo.

In the Thorough QT study, although there were no concerns with regard the 100 mg dose level, for the 800 mg dose level, at 3 hours post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) ms. The upper 90% CI was > 10, which is the level of regulatory concern. It is the opinion of the sponsor that this result is spurious because the 800 mg dose resulted in an increase in heart rate compared to the other three treatments. However, the results for QTcB and QTcF were not provided in the report.

Abnormalities in vital signs were uncommon with avanafil and did not appear to be clinically significant.

In combination with GTN there was an increased risk of headache, dizziness and nausea with avanfil, which was similar to the risk with sildenafil.

There were an adequate number of subjects exposed to avanafil for long-term use: > 100 subjects have been exposed for > 12 months and > 300 subjects have been exposed for > 6 months. In Study TA-314 there were 153 subjects exposed to avanafil for ≥ 12 months and 493 for ≥ 6 months.

There were adequate subjects aged ≥ 65 years in the development program: 426 in the pivotal studies. There were also adequate subjects with comorbidities such as hypertension or coronary artery disease.

There were no data submitted regarding potential interactions with treatments for premature ejaculation, such as dapoxetine, or with illicit drugs.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of avanafil in the proposed usage are:

- Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve-sparing radical prostatectomy.
- Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake.
- The effects of avanafil appear to be maintained over a 52 week period.

The benefits of avanafil were clinically significant.

Food does not appear to have a clinically significant effect on rapidity of onset of effect. Although, compared to the fasted state, food delayed absorption and decreased C_{max} for avanafil overall exposure was unchanged. In the pivotal studies, avanafil had rapid onset of effect regardless of food intake. Hence, in the opinion of the evaluator, there is no need for dosing instructions with regard to food.

The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet. There were differences in the rate of absorption between the 50 mg and 200 mg tablet sizes that may affect the speed of onset of effect.

9.2. First round assessment of risks

The risks of avanafil in the proposed usage are:

- Avanafil has a dose related risk for headaches, flushing and nasal congestion. Headache was more common in the avanafil groups and appeared to be dose related. Up to 13% of subjects in the avanafil 200 mg groups reported headache.
- Overall, the rates of TEAEs were higher in the avanafil treatment groups compared to placebo. The risk of TEAE was not influenced by age, race, diabetes status or coronary artery disease.
- Treatment related TEAEs were more common, and the rate increased with dose. Up to 23% of subjects in the avanafil 200 mg group had TEAEs attributed to treatment. TEAEs attributed to treatment included headache, flushing and nasal congestion. All of these AEs appeared to be dose related. At doses of avanafil 800 mg all subjects reported TEAEs.
- There were no deaths in the development program that were attributed to avanafil. There was one death reported in the development program for avanafil: self-inflicted gunshot injury.
- In combination with GTN there were increased risks of headache, dizziness and nausea with avanfil, which were similar to the risks with sildenafil.
- SAEs were uncommon and did not have any apparent pattern
- DAE was uncommon and did not have any apparent pattern.

There are a number of potential risks that require clarification:

- Elevation in liver enzymes was reported in the avanafil treatment groups and the sponsor has not stated whether any subjects fulfilled the criteria of Hy's law.
- In the Thorough QT study, although there were no concerns with regard the 100 mg dose level, for the 800 mg dose level, at 3 hours post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) ms. The upper 90% CI was > 10, which is the level of regulatory concern. It is the opinion of the sponsor that this result is spurious because the 800 mg dose resulted in an increase in heart rate compared to the other three treatments. However, the results for QTcB and QTcF were not provided in the report.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of avanafil, given the proposed usage, is unfavourable. This is because there are safety issues that require clarification. If the sponsor can satisfactorily clarify that there were no cases of drug induced liver injury and no QTc prolongation of regulatory concern in the development program then the benefit-risk balance of avanafil would become favourable.

10. First round recommendation regarding authorisation

The application to register Spedra (avanafil) should be rejected.

The reason for rejection is that there are unresolved safety issues regarding whether any cases of drug induced liver injury and/or QTc prolongation of regulatory concern exist in the data from the development program of avanafil.

11. Clinical questions

11.1. Pharmacokinetics

1. In the PK data, the 50 mg tablet formulation was absorbed more rapidly than the 200 mg. Did the subsequent clinical trial data indicate any differences in the rate of onset of effect?
2. In the PK data, food increased T_{max} from 0.75 hours to 2.0 hours. Did the subsequent clinical trial data indicate any effect of food on the rate of onset of effect?

11.2. Pharmacodynamics

3. From Study TA-140, please provide the tabulations of the placebo corrected change from baseline for QTcF and QTcB, with 90% CI, for the time points 0.5, 1, 1.5, 2, 3, 4, 6, 12, 18 and 23 hours after dosing for avanafil 100 mg, avanafil 800 mg and moxifloxacin 400 mg.

11.3. Efficacy

4. The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet. There were differences in the rate of absorption between the 50 mg and 200 mg tablet sizes that may affect the speed of onset of effect. Does the sponsor have data that demonstrate the 200 mg tablet size has similar time to onset of effect as either the 50 mg or 100 mg tablet sizes?
5. For Study TA-314, please provide summary tabulations of efficacy measures by study visit.

11.4. Safety

6. As per above, please provide summary tabulations for QTcF and QTcB from Study TA-140.
7. In Study TA-314 one subject developed a clinically significant ECG abnormality on active treatment. Please provide a description of the ECG abnormalities.
8. Does the sponsor have data regarding potential interactions between avanafil and treatments for premature ejaculation, such as dapoxetine, or with illicit drugs?
9. Please provide a tabulation, and case descriptions, for all subjects with ALT or AST > 3xULN and bilirubin > 2xULN.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Comments in relation to the PI

In precautions the following statement appears:

'Arrhythmia

A QT prolonging effect has been observed with drugs belonging to the same pharmacological class but not with Spedra. Nevertheless, caution is required when prescribing Spedra to patients with a history of arrhythmia or heart disease or long QT syndrome or taking QT-prolonging anti-arrhythmic drugs such as quinidine, procainamide, amiodarone or sotalol'. In the opinion of the Evaluator, the question as to whether avanafil can prolong the QT interval is unresolved and the statement is unsupported.

12.1.1. Sponsor response

The sponsor has explained that this warning was inserted early in the process of registration for avanafil as the statement was present in the contraindications and warning section of the PI of other products in this class. It states that there is no evidence from the Thorough QT study to support this statement. The EMA has endorsed a text where the aforementioned warning was deleted. The sponsor proposes to delete the precaution pertaining to arrhythmias in the precautions section of the PI.

12.1.2. Clinical evaluator response (See also Question 3 Pharmacodynamics)

The clinical evaluator agrees that the QT study did not demonstrate any evidence of QT prolongation of the 100 mg dose in healthy volunteers. The results of the QT study for the 800 mg dose were not entirely negative, and discussed in Question 3- Pharmacodynamics.

There have been no documented cases of VT, VF, syncope or prolongation of the QT over 500ms in any clinical trials or post market setting.

The safety of the 200 mg dose on the QT interval, particularly if used with medications that inhibit CYP3A4 and increase avanafil exposure or in men with other cardiac risk factors, or using drugs that also increase the QT interval is unknown and of concern.

Discussion about the potential for prolongation of the QT interval is important to include in the PI, however it is reasonable to remove this from the precautions section as there have been no substantiated risks on the QT or QTc at a therapeutic dose of avanafil, nor any increased risk of VT, VF or Torsades de Pointe. The clinical evaluator's recommendations in relation to dose are discussed in other sections.

12.2. Question 1 pharmacokinetics

In the PK data, the 50 mg tablet formulation was absorbed more rapidly than the 200 mg. Did the subsequent clinical trial data indicate any differences in the rate of onset of effect?

12.2.1. Sponsor response

The sponsor considers the rate of absorption of the 50 mg and 200 mg tablet to be not clinically relevant in view of the efficacy results in the pivotal studies TA-301, TA-302 and TA-314. The results are summarised in Tables 47 and 48.

Table 47: Percentage of sexual attempts in which subjects were able to maintain an erection to have sexual intercourse, derived from studies TA-301, TA-302 and TA-314, by time interval and tablet formulation

Time Interval from Dose to Attempt (min)	TA-301 200mg (4x50mg) n=156	TA-302 200mg (2x100mg) n=126	TA-314 100mg (1x100mg) n=147	TA-314 100mg to 200mg (1x100mg to 1x200mg) n=535*
≤15	70.9	35.6	94.20	87.90
(15,30]	57.5	44.9	94.70	89.10
(30,45]	61.5	41.9	92.80	88.80
(45,60]	61.5	35.4	94.90	89.30
(60,120]	66.8	48.3	97.30	87.70
(120,240]	65	58.8	93.30	86.10
(240,360]	69.6	40.9	94.70	88.00
>360	82.6	67.7	92.90	80.80

Source data: Table 14.2.8.8 of Clinical Study Report TA-314, Table 14.2.7.8 of Clinical Study Report TA-301 and Table 14.2.8.3 of Clinical Study Report TA-302 (Modified).
**Included all subjects who were able to tolerate treatment with avanafil 100 mg and that requested their Dose to be increased to 200 mg*

Table 48: Percentage of sexual attempts in which subjects were able to achieve vaginal penetration, derived from studies TA-301, TA-302 and TA-314, by time interval and tablet formulation

Time Interval from Dose to Attempt (min)	TA-301 200mg (4x50mg) n=156	TA-302 200mg (2x100mg) n=126	TA-314 100mg (1x100mg) n=147	TA-314 100mg to 200mg (1x100mg to 1x200mg) n=535*
≤15	87.3	62.2	84.50	78.70
(15,30]	81.8	68	87.30	77.80
(30,45]	82.1	66.4	84.00	77.70
(45,60]	78.7	61.5	88.30	80.20
(60,120]	79.5	69.3	92.50	78.40
(120,240]	79	72.5	87.40	74.60
(240,360]	73.9	77.3	89.50	75.30
>360	100	83.9	92.90	68.30

Source data: Table 14.2.8.7 of Clinical Study Report TA-314, Table 14.2.7.7 of Clinical Study Report TA-301 and Table 14.2.8.2 of Clinical Study Report TA-302 (Modified).
**Included all subjects who were able to tolerate treatment with avanafil 100 mg and that requested their Dose to be increased to 200 mg*

12.2.2. Second round clinical evaluator's response

The sponsor's response does not answer the question asked. None of the clinical studies submitted for evaluation have been designed to answer the question.

There are three PK studies that have examined the different formulations of avanafil. Study TA-022 compared 4 x 50 mg tablets to 2 x 100 mg tablets and 1 x 200 mg tablet. Bioequivalence of the three doses based on C_{max} and AUC was demonstrated, however the median T_{max} using the 50 mg formulations (0.5 hours, range 0.33-0.76), was similar to the 2 x 100 mg formulation (0.51hours, range 0.5-1.5) and lower than the 200 mg formulation (0.75 hours, range 0.25-2.00). Study HP-01, table 1.1.3 of this CER, was a dose escalation study of 12.5 mg to 800 mg of avanafil using 12.5 mg, 50 mg and 100 mg tablets. In this study the median T_{max} for a 200 mg dose using 2 x100 mg tablets was 0.88 hours, range 0.5-1.0. In Study TA-02, the mean T_{max} after a 200 mg tablet was 0.589 hours. Thus, there is a considerable variability in the T_{max} at given dose with different formulations.

Study TA-301 used a 50 mg formulation, study TA-302 a 100 mg formulation, and Study TA-314 50, 100 and 200 mg formulations. The studies are not directly comparable as there are a number of other factors that differed between the studies. The efficacy endpoints of TA-301 were at 12 weeks, and the efficacy endpoints from study TA-314 were at 52 weeks. TA-302 used subjects with diabetes, whereas these were excluded from study TA-301.

The clinical significance of the variability in T_{max} is unknown from the data, but unlikely to be significant. The sponsor may consider adding information about the changes in T_{max} with increasing doses and the higher formulations in the PK section of the PI. The recommended administration of avanafil 30 minutes prior to sexual stimulation is based on the protocol from clinical trials, and is acceptable.

12.3. Question 2 pharmacokinetics

In the PK data, food increased T_{max} from 0.75 hours to 2.0 hours. Did the subsequent clinical trial data indicate any effect of food on the rate of onset of effect?

12.3.1. Sponsor response

The slower absorption of avanafil under fed conditions (with high fat meal) versus fasting conditions is known and reflected in the 'pharmacokinetic section' of the product information. In all phase II clinical trials, there was no restriction on food or the timing of avanafil in relation to food.

12.3.2. Second round clinical evaluator response

The sponsor's response is satisfactory.

12.4. Question 3 pharmacodynamics

From Study TA-140, please provide the tabulations of the placebo corrected change from baseline for QTcF and QTcB, with 90% CI, for the time points 0.5, 1, 1.5, 2, 3, 4, 6, 12, 18 and 23 hours after dosing for avanafil 100 mg, avanafil 800 mg and moxifloxacin 400 mg.

12.4.1. Sponsor response

The sponsor has provided the placebo correct change from baseline for QTcF and QTcB from study TA-140, see Tables 49 and 50.

Table 49: Placebo corrected change from baseline- Estimates from mixed model ANOVA (1) QTcB (ms) from Study TA-140

	Avanafil 100 mg (n=54)			Avanafil 800 mg (n=56)			Moxifloxacin 400 mg (n=53)		
Time (hr)	Estimate [1]	Lower Bound[2]	Upper Bound[2]	Estimate [1]	Lower Bound[2]	Upper Bound[2]	Estimate [1]	Lower Bound[2]	Upper Bound[2]
0.5 hr	7.3	4.3	10.3	16.1	13.0	19.3	4.0	-0.2	8.3
1 hr	6.2	3.2	9.2	18.2	15.1	21.3	8.3	4.1	12.5
1.5 hr	1.0	-2.0	4.0	14.7	11.6	17.8	9.4	5.2	13.6
2 hr	0.8	-2.2	3.8	12.1	9.0	15.2	8.9	4.7	13.1
3 hr	0.3	-2.7	3.3	12.6	9.5	15.7	10.6	6.4	14.8
4 hr	-0.4	-3.4	2.5	10.3	7.2	13.4	9.2	5.0	13.4
6 hr	0.2	-2.8	3.1	8.8	5.7	11.9	7.0	2.8	11.2
12 hr	-1.6	-4.6	1.3	3.3	0.2	6.5	5.0	0.8	9.2
18 hr	1.4	-1.5	4.4	3.8	0.7	7.0	6.1	1.9	10.3
23 hr	-0.4	-3.3	2.6	0.9	-2.2	4.0	1.5	-2.7	5.7

[1] Mixed Effects General Linear Model (placebo-adjusted baseline-corrected) is fit for QTcB and includes terms for treatment, time, a time by treatment interaction and baseline value.
[2] Lower\upper Bound = lower\upper 2-sided 90% (1-sided 95%) ANOVA model based confidence limit.
Data source: ecg_all2.sas7bdat Program source: CalCI-ECG-corrected.sas

Table 50: Placebo corrected change from baseline –Estimates from mixed model ANOVA QTcF from Study TA-140

	Avanafil 100 mg (n=54)			Avanafil 800 mg (n=56)			Moxifloxacin 400 mg (n=53)		
Time (hr)	Estimate [1]	Lower Bound[2]	Upper Bound[2]	Estimate [1]	Lower Bound[2]	Upper Bound[2]	Estimate [1]	Lower Bound[2]	Upper Bound[2]
0.5 hr	3.6	1.4	5.8	6.1	3.8	8.4	3.3	0.0	6.6
1 hr	2.8	0.6	5.0	6.8	4.5	9.1	5.7	2.4	8.9
1.5 hr	0.8	-1.4	3.1	7.0	4.8	9.3	7.3	4.0	10.5
2 hr	1.2	-1.0	3.4	6.9	4.6	9.1	8.3	5.0	11.6
3 hr	1.9	-0.3	4.2	9.4	7.1	11.7	10.5	7.3	13.8
4 hr	-1.1	-3.3	1.1	5.8	3.5	8.1	8.1	4.8	11.3
6 hr	0.7	-1.5	2.9	5.4	3.1	7.7	5.9	2.6	9.1
12 hr	-1.6	-3.8	0.6	0.5	-1.8	2.8	5.0	1.7	8.3
18 hr	1.7	-0.5	3.9	-1.0	-3.3	1.3	6.4	3.1	9.6
23 hr	-0.2	-2.5	2.0	-2.3	-4.7	-0.0	3.0	-0.3	6.3

[1] Mixed Effects General Linear Model (placebo-adjusted baseline-corrected) is fit for QTcF and includes terms for treatment, time, a time by treatment interaction and baseline value
[2] Lower\upper Bound = lower\upper 2-sided 90% (1-sided 95%) ANOVA model based confidence limit
Data source: ecg_all2.sas7bdat Program source: CalCI-ECG-corrected.sas

The sponsor has explained that in Study TA-140 the main outcome factor was the corrected QT interval as heart rate inversely affects QT duration and high doses of avanafil increase heart rate. In cases such as this, Fridericia's correction is reliable whereas the Bazett correction was not.

The sponsor stated that there were no new morphologic changes and that the results of the PK-PD model for parent and metabolites showed that the supratherapeutic doses predicted QTcI change and upper CIs less than 5ms.

12.4.2. Second round clinical evaluator's response

The sponsor's explanation for placing more weight on the corrected QT interval and Fridericia's correction and being concerned about the accuracy of the Bazett correction is consistent with advice from the CHMP *Note for Guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs*. These state that the Bazett correction can underestimate at low heart rates and overestimate at high heart rates and may not be suitable in drugs which cause variable heart rates. However, these guidelines also acknowledge that it is unknown if QT or corrected QT is a better predictor of the risk of arrhythmia's. The sponsor has submitted a table of raw changes in QT as an average over time (see Table 51) but has not provided an analysis of the change raw QT intervals by time.

Table 51: Time averaged analysis of QT data for all subjects in study TA-140

	Treatment Group			
	Avanafil 100 mg	Avanafil 800 mg	Moxifloxacin 400 mg	Placebo
Total N [some parameters with less sample size by 1-2 subjects]	54	56	53	54
Heart Rate in bpm [a]	3.6	8.4	3.7	3.1
Heart Rate tachycardic outliers N (%)	0	3 (5%)	0	0
Heart Rate bradycardic outliers N (%)	1 (2%)	0	0	0
PR in ms [a]	-3.3	-4.8	-3.5	-2.9
PR outliers N (%)	0	0	1 (2%)	0
QRS in ms [a]	-0.3	-0.2	-0.4	-0.4
QRS outliers N (%)	0	0	0	0
QT in ms [a]	-10.2	-16.4	-5.2	-10.3
QT new >500 ms N (%)	0	0	0	0
QTcI in ms [a]	**-2.9**	**-0.9**	**2.2**	**-3.7**
QTcI new >500 ms N (%)	**0**	**0**	**0**	**0**
QTcI new >480 ms N (%)	**0**	**0**	**0**	**0**
QTcI 30-60 ms inc N (%)	**0**	**0**	**2 (4%)**	**0**
QTcI >60 ms inc N (%)	**0**	**0**	**0**	**0**
QTcF in ms [a]	-2.0	1.6	3.1	-3.1
QTcF new >500 ms N(%)	0	0	0	0
QTcF new >480 ms N (%)	0	0	0	0
QTcF 30-60 ms inc N (%)	0	0	2 (4%)	0
QTcF >60 ms inc N (%)	0	0	0	0
QTcB in ms [a]	2.0	10.7	7.2	0.5
QTcB new >500 ms N(%)	0	0	0	0
QTcB new >480 ms N (%)	0	0	0	0
QTcB 30-60 ms inc N (%)	5 (9%)	17 (30%)	3 (6%)	1 (2%)
QTcB >60 ms inc N (%)	0	1 (2%)	0	0
New abnormal U waves N (%)	0	0	0	0
New ST segment depression changes N (%)	1 (1.9%)	1 (1.8%)	0	1 (1.9%)
New T wave inverted N (%)	1 (1.9%)	2 (3.6%)	2 (3.8%)	2 (3.7%)
New 2nd and 3rd Degree Heart Block, Complete RBBB & LBBB, MI N (%)	0	0	0	0

The Thorough QT study submitted (TA-140) was a Phase I, double blind, randomized, four arm cross over study in healthy male subjects. The central ECG lab was blinded to treatment. The four treatments were placebo, 400 mg moxifloxacin (positive control), 100 mg avanafil, 800 mg avanafil. 52 subjects completed the study. This number of subjects gave the study a power of 80% to show that the upper limit of the 90% two sided CI for the comparison of QTcI of avanafil to placebo fell below 10ms. The study design was a non-inferiority test. The calculations were based on a difference in corrected QT of 3ms and SD of 8ms. The conduct of the study was appropriate. The method of statistical analysis for the ECG data is described in detail. It was rationale and consistent with the CHMP QT /QTc guidelines. The primary endpoint used for statistical analysis was QTcI, an individually determined QT correction based on comparing the QT and RR interval of study drug to the QT and RR intervals on the pre drug ECG and placebos.

There was a baseline adjusted change in HR of 0.6 bpm for moxifloxacin, 0.5 bpm for 100 mg avanafil and 5.3 bpm for 800 mg avanafil. The QTcI mean change from baseline placebo corrected for the therapeutic and supratherapeutic doses of avanafil were 0.8 ms and 2.8 ms respectively. The time matched analysis for the QTcI data revealed that all time points had a placebo and baseline corrected result of less than 10 ms for the upper CI except for the 3 hour time point for the supratherapeutic dose which reached 10.2 ms. This was considered to be a spurious result. However, at this time point the mean estimate was 7.9 ms, and at 1.5 to 6 hours the mean estimate was greater than 4 ms. The peak effect of the 100 mg avanafil tablet was also reached at 3 hours. There were no subjects with new U waves, a new 500 ms absolute QTc or a > 60 ms change from baseline. More adverse events were noted in the 800 mg group however there were no concerning changes in vital signs or safety ECGs.

Table 50 shows the QT intervals corrected using Bazett's correction. In this analysis, the QT changes for the 100 mg dose of avanafil are acceptable. The QT changes for the 800 mg dose are concerning. The mean estimates from 0.5 - 4 hours after administration of avanafil are all greater than 10ms, and the 90% CI from 0.5 - 6 hours are greater than 10ms. The mean estimate for 1 hour after avanafil was administered was greater than 20 ms.

Table 51 shows the QT intervals corrected using Fridericia's correction. In this analysis, the results are similar to those of the QTcI.

Figure 2 of this CER demonstrates a graphical display of the change in QTc with avanafil 100 and 800 mg and moxifloxacin.

Thus, the results of the QT study are negative at a therapeutic dose of 100 mg but not for a supratherapeutic dose of 800 mg. Although a dose of 800 mg is unlikely to be given therapeutically, an increased exposure to avanafil may occur in subjects with genetically slow P450 metabolism or who are treated with drugs that inhibit CYP3A4. There is no information about the effect of other doses such as 150 – 750 mg on QT interval.

Pre-clinical studies in dogs demonstrated a dose dependent decrease in BP and increase in heart rate, but there was no effect on the ECG.

12.5. Question 4 efficacy

The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet. There were differences in the rate of absorption between the 50 mg and 200 mg tablet sizes that may affect the speed of onset of effect. Does the sponsor have data that demonstrate the 200 mg tablet size has similar time to onset of effect as either the 50 mg or 100 mg tablet sizes?

12.5.1. Sponsor response

The sponsor indicated this question was addressed in its response to Question 1.

12.5.2. Second round clinical evaluator's response

There is a paucity of clinical efficacy data for the 200 mg formulation proposed by the sponsor. This formulation was only used in the open label follow up Study TA-314.

12.6. Question 5 efficacy

For Study TA-314, please provide summary tabulations of efficacy measures by study visit.

12.6.1. Sponsor response

The sponsor has provided summary tabulations of the primary efficacy endpoints by study visit, and referred to their study report for the analysis of secondary efficacy endpoints by study visit.

Table 52: Study TA-314: Change in percentage of sexual attempts in which patients were able to maintain an erection of sufficient duration to have sexual intercourse- by visit

			TA-314 100 mg (N=147)	TA-314 100 and 200 mg (N=535)	TA-314 Other (N=4)	Total (N=686)
Visit						
	VISIT 3	N	93	520	4	617
		Mean (SD)	86.9 (28.59)	54.2 (40.02)	59.4 (47.19)	59.2 (40.23)
		Median	100	62.5	62.5	71.4
	VISIT 4	N	80	442	3	525
		Mean (SD)	88.7 (27.26)	73.3 (35.80)	66.7 (57.74)	75.6 (35.14)
		Median	100	100	100	100
	VISIT 5	N	69	392	3	464
		Mean (SD)	90.4 (24.07)	78.3 (31.64)	66.7 (47.32)	80.0 (30.98)
		Median	100	100	87.5	100
	VISIT 6	N	37	221	3	261
		Mean (SD)	86.6 (27.24)	82.1 (25.85)	74.1 (42.56)	82.7 (26.18)
		Median	100	95.2	97.4	96.4
	VISIT 7	N	8	27		35
		Mean (SD)	93.9 (11.93)	86.6 (15.96)	-	88.2 (15.30)
		Median	100	93.3		95.8
	VISIT 8	N	8	26		34
		Mean (SD)	97.9 (5.89)	88.4 (22.36)	-	90.6 (20.08)
		Median	100	100		100
Change from baseline						
	VISIT 3	N	93	520	4	617
		Mean (SD)	71.8 (30.07)	42.6 (37.88)	53.1 (56.25)	47.0 (38.33)
		Median	75	42.9	62.5	50
	VISIT 4	N	80	442	3	525
		Mean (SD)	74.1 (28.12)	61.2 (36.36)	58.3 (72.17)	63.2 (35.68)
		Median	75	67.3	100	75
	VISIT 5	N	69	392	3	464
		Mean (SD)	74.8 (27.12)	66.2 (33.52)	58.3 (61.66)	67.4 (32.91)
		Median	75	75	87.5	75
	VISIT 6	N	37	221	3	261
		Mean (SD)	71.2 (27.73)	68.7 (28.61)	65.8 (56.99)	69.0 (28.73)
		Median	75	73.5	97.4	75
	VISIT 7	N	8	27		35
		Mean (SD)	82.1 (17.90)	67.7 (21.69)	-	71.0 (21.52)
		Median	81.7	62.5		75
	VISIT 8	N	8	26		34
		Mean (SD)	86.0 (17.90)	70.7 (22.58)	-	74.3 (22.32)
		Median	91.7	73.2		75

Table 53: Study TA-314: Change in percentage of sexual attempts in which patients were able to insert their penis into the partners vagina by visit

			TA-314 100 mg (N=147)	TA-314 100 and 200 mg (N=535)	TA-314 Other (N=4)	Total (N=686)
Visit						
	VISIT 3	N	93	520	4	617
		Mean (SD)	92.7 (22.15)	74.4 (36.95)	68.8 (37.50)	77.2 (35.69)
		Median	100	100	75	100
	VISIT 4	N	80	442	3	525
		Mean (SD)	95.8 (15.93)	85.4 (30.05)	81.0 (32.99)	87.0 (28.57)
		Median	100	100	100	100
	VISIT 5	N	69	392	3	464
		Mean (SD)	97.1 (13.23)	89.2 (25.98)	75.0 (43.30)	90.3 (24.77)
		Median	100	100	100	100
	VISIT 6	N	37	221	3	261
		Mean (SD)	93.4 (18.55)	91.5 (19.14)	81.7 (31.75)	91.7 (19.15)
		Median	100	100	100	100
	VISIT 7	N	8	27		35
		Mean (SD)	97.9 (5.89)	93.5 (11.02)	-	94.5 (10.17)
		Median	100	100		100
	VISIT 8	N	8	26		34
		Mean (SD)	97.9 (5.89)	93.0 (20.68)	-	94.2 (18.32)
		Median	100	100		100
Change from baseline						
	VISIT 3	N	93	520	4	617
		Mean (SD)	41.1 (36.95)	30.8 (36.17)	18.8 (37.50)	32.3 (36.43)
		Median	33.3	25	25	25
	VISIT 4	N	80	442	3	525
		Mean (SD)	42.5 (35.21)	39.8 (37.78)	14.3 (31.13)	40.1 (37.37)
		Median	40	33.3	0	33.3
	VISIT 5	N	69	392	3	464
		Mean (SD)	43.2 (36.35)	41.2 (37.05)	8.3 (38.19)	41.3 (36.97)
		Median	40	40	0	40
	VISIT 6	N	37	221	3	261
		Mean (SD)	50.5 (34.73)	38.8 (36.97)	15.0 (30.41)	40.2 (36.81)
		Median	50	33.3	0	35
	VISIT 7	N	8	27		35
		Mean (SD)	46.3 (29.77)	34.5 (32.41)	-	37.2 (31.79)
		Median	33.3	25		29.2
	VISIT 8	N	8	26		34
		Mean (SD)	46.3 (29.77)	37.5 (32.88)	-	39.6 (31.96)
		Median	33.3	29.2		33.3

Table 54: Change in score of the erectile function domain of the IEF questionnaire by visit

			TA-314 100 mg (N=147)	TA-314 100 and 200 mg (N=535)	TA-314 Other (N=4)	Total (N=686)
Visit						
	VISIT 5	N	67	393	3	463
		Mean (SD)	27.2 (4.41)	24.8 (6.07)	25.0 (7.00)	25.2 (5.92)
		Median	29	27	28	27
	VISIT 6	N	38	223	3	264
		Mean (SD)	26.0 (5.87)	25.4 (6.03)	24.7 (5.13)	25.5 (5.99)
		Median	28.5	28	26	28
	VISIT 8	N	92	394	3	489
		Mean (SD)	23.8 (7.36)	24.6 (6.59)	22.7 (4.16)	24.5 (6.72)
		Median	27	27	24	27
Change from baseline						
	VISIT 5	N	67	393	3	463
		Mean (SD)	11.7 (5.65)	12.6 (6.57)	15.7 (7.02)	12.4 (6.45)
		Median	12	13	15	12
	VISIT 6	N	38	223	3	264
		Mean (SD)	11.0 (7.17)	12.8 (7.07)	15.3 (5.86)	12.6 (7.08)
		Median	12	13	13	13
	VISIT 8	N	92	394	3	489
		Mean (SD)	9.6 (6.74)	12.3 (7.16)	13.3 (4.93)	11.8 (7.14)
		Median	10	12	11	12

12.6.1. Second round clinical evaluator's response

The sponsor's response is acceptable.

In Study TA-314, the intention to treat population consisted of all patients who had at least one dose of study drug. The end of treatment values were calculated from all entries beginning with the first dose of study drug in the present study and ending with the last visit. The by visit analysis was calculated from all entries corresponding to the time period beginning with the previous visit and ending with the visit of interest. For primary endpoints from the subjects diaries, only observed data were used. For primary data based on IIEF data, the last observation carried forward was used.

A major problem with the interpretation of the results from this study is the bias towards efficacy due to the study population. The study population is a fraction of those eligible to participate based on their involvement in previous clinical trials. Subjects who had a positive response to treatment with the study drug would have been more likely to be involved in study TA-314, and also more likely to remain in the study for longer.

The results of the percentage of subjects able to maintain an erection of sufficient duration to have sexual intercourse was greater when analysed by visit (Table 52) than when analysed from baseline to end of visit . This may be because patients who did not respond to treatment being more likely to drop out of the study. The results of the percentage of subjects being able to insert their penis into their partner's vagina and in the IEF domain were similar when assessed by end of visit than by visit (Tables 53 and 54).

12.7. Question 6 safety

Please provide summary tabulations for QTcF and QTcB from Study TA-140.

12.7.1. Sponsor response

The sponsor provided the tables as requested.

12.7.2. Second round clinical evaluator's response

There was no value for QTcF or QTcB greater than 500 ms.

The response is satisfactory.

12.8. Question 7 safety

In Study TA-314 one subject developed a clinically significant ECG abnormality on active treatment. Please provide a description of the ECG abnormalities.

12.8.1. Sponsor response

The subject was 58 years old and on treatment with 50 mg of avanafil. The event occurred at visit 8 [information redacted]. The ECG had a heart rate of 58 bpm, mean P axis of 66 degrees, PR duration of 148 ms, QT duration of 402 ms. There were extensive ST-T segment changes. The ECG changes were considered to be unrelated to the study drug.

12.8.2. Second round clinical evaluator response

The sponsor's response does not provide any information about whether this patient had risk factors for cardiac disease, symptoms, or the appearance of previous or subsequent ECGs. The ECG changes described are not suggestive of a conduction defect. It would be reasonable to consider them moderate (or mild) in severity and unrelated to the study medication.

12.9. Question 8 safety

Does the sponsor have data regarding potential interactions between avanafil and treatments for premature ejaculation, such as dapoxetine, or with illicit drugs?

12.9.1. Sponsor response

The sponsor searched for possible interactions between avanafil and treatments for premature ejaculation by searching it's database of Studies TA-301, TA-302, TA-303, TA-314 and TA-501. There were no patients taking dapoxetine (this is not registered for use in the USA). There was one patient in Study TA-301 taking tramadol for premature ejaculation. This patient was randomised to the 200 mg avanafil arm. He did not report any adverse effects and had no ECG abnormalities identified. This patient experienced an improvement of 54.5% in his ability to maintain an erection of sufficient duration for successful intercourse, but no improvement in his ability to insert his penis into his partner's vagina or in the IIEF domain.

The sponsor performed a literature review. It identified a Phase III study which examined the efficacy of dapoxetine (30-60 mg) compared to placebo in men with premature ejaculation and erectile dysfunction treated with other PDE-5i (sildenafil, vardenafil, or tadalafil). Higher rates of adverse events (suggestive of prodromal events for syncope) were more common in the dapoxetine plus PDE-5i group than the placebo plus PDE-5i group [1]. Pharmacokinetic interactions between dapoxetine and the PDE-5i inhibitors sildenafil and tadalafil were examined in an open labelled randomised cross over trial. Tadalafil did not alter the pharmacokinetics of dapoxetine; however sildenafil increased the dapoxetine AUC by 22%. These effects were no considered to be clinically important. Dapoxetine did not later the pharmacokinetics of tadalafil or sildenafil[2] .

There was no information from the company database about avanafil and illicit drugs.

12.9.2. Second round clinical evaluator's response

The sponsor's response is satisfactory.

12.10. Question 9 safety

Please provide a tabulation, and case descriptions, for all subjects with ALT or AST > 3xULN and bilirubin > 2xULN.

12.10.1. Sponsor 4 response

The sponsor has provided a table summarising marked abnormalities in laboratory tests during the Studies TA-05, TA-301, and TA-302. There were no subjects who reached the Hy law criteria. The rates of abnormal LFTs were low.

[1] McMahon CG et al. Efficacy and safety of dapoxetine in men with premature ejaculation and concomitant erectile dysfunction treated with a phosphodiesterase type 5 inhibitor: randomised, placebo-controlled, phase III study. J Sex Med. 2013 Sep;10(9):2312-25)

[2] Dresser MJ et al. Dapoxetine, a novel treatment for premature ejaculation, does not have pharmacokinetic interactions with phosphodiesterase-5 inhibitors (Int J Impot Res. 2006 Jan-Feb;18(1):104-10).

Table 55: Summary of the percentage of subjects from studies TA-05, TA-301 and TA-302 who had marked abnormalities of laboratory tests

Laboratory Parameter Category	Placebo n/N' (%)	Avanafil 50 mg n/N' (%)	Avanafil 100 mg n/N' (%)	Avanafil 200 mg n/N' (%)	Total n/N' (%)
ALT					
>2 × ULN	3/313 (1.0)	2/196 (1.0)	1/320 (0.3)	2/321 (0.6)	8/1150 (0.7)
>3 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	1/321 (0.3)	1/1150 (0.1)
AST					
>2 × ULN	3/313 (1.0)	0/196 (0.0)	2/320 (0.6)	2/321 (0.6)	7/1150 (0.6)
>3 × ULN	0/313 (0.0)	0/196 (0.0)	1/320 (0.3)	2/321 (0.6)	3/1150 (0.3)
Total bilirubin					
>1.5 × ULN	3/313 (1.0)	1/196 (0.5)	2/320 (0.6)	5/321 (1.6)	11/1150 (1.0)
>2 × ULN	1/313 (0.3)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	1/1150 (0.1)
Alkaline phosphatase					
>1.5 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	1/321 (0.3)	1/1150 (0.1)
ALT or AST with total bilirubin					
ALT or AST >3 × ULN and total bilirubin >1.5 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	0/1150 (0.0)
ALT or AST >3 × ULN and total bilirubin >2 × ULN	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	0/1150 (0.0)
White blood cell count					
Low	26/312 (8.3)	11/197 (5.6)	21/319 (6.6)	24/317 (7.6)	82/1145 (7.2)
High	5/312 (1.6)	2/197 (1.0)	2/319 (0.6)	5/317 (1.6)	14/1145 (1.2)
Serum creatinine					
Low	0/313 (0.0)	0/196 (0.0)	0/320 (0.0)	0/321 (0.0)	0/1150 (0.0)
High	26/313 (8.3)	13/196 (6.6)	28/320 (8.8)	31/321 (9.7)	98/1150 (8.5)
Hematocrit					
Low	31/310 (10.0)	10/197 (5.1)	30/318 (9.4)	30/315 (9.5)	101/1140 (8.9)
High	3/310 (1.0)	1/197 (0.5)	4/318 (1.3)	5/315 (1.6)	13/1140 (1.1)
Hemoglobin					
Low	19/311 (6.1)	10/197 (5.1)	21/319 (6.6)	21/317 (6.6)	71/1144 (6.2)
High	5/311 (1.6)	0/197 (0.0)	3/319 (0.9)	2/317 (0.6)	10/1144 (0.9)

Data from studies TA-05, TA-301 and TA-302 are included.
N' is the number of subjects with a baseline and post-baseline value for a given parameter.
ALT = alanine transaminase; AST= aspartate transaminase; ULN = upper limit of normal.

12.10.2. Second round evaluator comment

The response is satisfactory. More patients in the avanafil 200 mg group had levels of ALT or AST ≥ 3 x ULN, Bilirubin ≥ 2XULN or alkaline phosphatase ≥ 1.5 x ULN, however the numbers were very small.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of avanafil in the treatment of erectile dysfunction in adult men are unchanged.

- Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve-sparing radical prostatectomy.
- Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake.

- The effects of avanafil appear to be maintained over a 52 week period.

No benefit clinical benefit of 200 mg over 100 mg has been demonstrated.

13.2. Second round assessment of risks

After consideration of the responses to the clinical questions, the following concerns remain:

1. The 200 mg dose formulation was not used in the key pivotal studies; therefore the clinical efficacy of this formulation is unknown. Bioequivalence has been satisfactorily demonstrated based on the EU guidelines for C_{max} and AUC, but there is variability in T_{max} between different formulations. It is possible that this variability in T_{max} may have an impact on the onset and duration of action. A delayed onset of action may have a clinically significant impact on its effect on erectile function.
2. A QT study at a dose of 200 mg has not been performed, and the results of the QT study for the 800 mg dose are equivocal. Thus, the safety of the 200 mg dose in relation to QT prolongation is unknown.
3. The most common adverse effects of avanafil, such as headache, flushing and nausea, are dose proportional and more common at a higher dose.

13.3. Second round assessment of benefit-risk balance

There are clinical and statistically significant benefits of avanafil at a dose of 100 mg for the treatment of erectile dysfunction in males. The risks of avanafil at this dose are acceptable.

The clinical data submitted does not demonstrate superiority of a 200 mg dose over a 100 mg dose. There are more adverse effects observed with larger doses. The impact of the 200 mg dose on the QT interval is unknown. Although a repeat QT/QTc study using a dose of 200 mg of avanafil would help resolve the later issue, the benefit-risk balance of the large body of clinical evidence collected about the safety and efficacy of avanafil at a dose of 200 mg will remain unchanged.

Although disabling, erectile dysfunction is not associated with significant morbidity or limited life expectancy. The risks to the health and wellbeing of the population as a consequence of not approving the 200 mg dose are smaller than the risks associated approving this larger dose and formulation.

14. Second round recommendation regarding authorisation

The clinical evaluator recommends approval of avanafil for the *'Treatment of erectile dysfunction in adult men'* subject to the following:

1. A limitation of the dose to 100 mg daily
2. That the PI be amended to include
    a. A warning about the potential for QT prolongation with overdose
3. The addition of risks to the RMP including:
    a. Potential risk- prolongation of the QT interval with high exposure
    b. Missing Information – the use of avanafil with illicit drugs

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au