25 April 2013
EMA/321885/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

International non-proprietary name: avanafil

Procedure No. EMEA/H/C/002581/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Spedra
Applicant:	VIVUS BV Prins Bernhardplein 200, 1097 JB Amsterdam The Netherlands
Active substance:	Avanafil
International Nonproprietary Name/Common Name:	Avanafil
Pharmaco-therapeutic group (ATC Code):	Not yet assigned.
Therapeutic indication:	Treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required.
Pharmaceutical form:	Tablet
Strengths:	50 mg, 100 mg and 200 mg
Route of administration:	Oral use
Packaging:	blister (PP/alu)
Package sizes:	2 tablets, 4 tablets, 8 tablets and 12 tablets

Executive summary

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual performance. Normal erectile function requires the coordination of psychological, hormonal, neurological, vascular and anatomic factors. Alteration of any of these is sufficient to cause ED. The main causes of ED are chronic systemic illnesses (diabetes mellitus, heart disease, hypertension and peripheral vascular disease), neurological disorders (post-traumatic spinal-cord injuries, multiple sclerosis) or post-surgical lesions (after radical prostatectomy).

There are several approaches to the management of erectile dysfunction: psychosexual counselling, hormonal therapy, mechanical devices, vascular surgery and pharmacological treatment (including intracavernosal pharmacotherapy and intra-urethral prostaglandin as well as oral treatments). The currently available oral pharmacological treatments for ED are based on inhibitors of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE) that increase penile blood flow and erection in response to sexual stimulation.

PDE type 5 (PDE5) is the predominant form of the enzyme in the smooth muscle of the corpora cavernosa. In men, sexual stimulation causes nitric oxide to be released from nerves and endothelial cells, which diffuses into smooth muscle cells in the walls of penile arteries and spongy erectile tissue. Nitric oxide stimulates the enzyme guanylate cyclase to synthesise cyclic guanosine monophosphate (cGMP), leading in turn to decreased Ca2+ concentrations in smooth muscle cells. This causes smooth muscle relaxation and increased blood flow, thus producing penile erection. In erectile tissues, cGMP is degraded by PDE5. Administration of a PDE5 inhibitor leads to higher cGMP levels and thus enhanced smooth muscle relaxation and penile blood flow.

Avanafil (also referred to as TA-1790), is a new PDE5 inhibitor for oral administration that was developed for its high selectivity for the PDE5 isoenzyme relative to other PDE5 inhibitors. In April 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of Spedra (avanafil), for the treatment of erectile dysfunction in adult men. The recommended dose is 100 mg taken as needed approximately 30 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 a day. In order for avanafil to be effective, sexual stimulation is required. If avanafil is taken with food, the onset of activity may be delayed compared to the fasting state.

Clinical efficacy of avanafil in males with ED is supported by three phase III pivotal studies and an open-label extension study. The study design of the pivotal trials was performed in line with other available PDE5 inhibitors on the market. Unfortunately, no comparison was made with other PDE5 inhibitors to allow a better understanding of the efficacy results in the context of the current standard of care for treatment of ED.

In the general population of patients with ED, avanafil, at both the 100 mg and 200 mg doses, resulted in a roughly 30% gain over placebo in the percentage of successful intercourses and 20% increase in vaginal penetration; the change in the assessment score for erectile function (delta in International Index of Erectile Function (IIEF) questionnaire) was greater than 5 points ($p<0.001$ for all comparisons). A comparison between the 100-mg and 200-mg doses showed no statistically significant difference.

Reduced efficacy of avanafil was seen in ED subjects with diabetes mellitus. This was expected and is in line with the generally observed lower efficacy of PDE5 inhibitors in this patient population. In subjects with ED following a nerve-sparing prostatectomy, a statistically significant improvement over baseline for all three primary efficacy endpoints was observed for avanafil in subjects.

Although the avanafil clinical development program allowed inclusion of males with no upper age limit, due to the low number of elderly subjects enrolled, it is uncertain whether efficacy and safety have been well characterised in this subgroup of subjects, especially the elderly (⩾70 years old).

The most common side effects are headache, flushing, nasal and sinus congestion, dyspepsia and back pain.

To rule out any effect of avanafil on QTc, the Applicant has been requested to present data from a study evaluating QTc prolongation with avanafil. Furthermore the Applicant is conducting a study evaluating the effect on spermatogenesis in healthy adult male subjects, and the report will be submitted as defined in the risk management plan.

So far, available data do not allow a definite conclusion on the potential risk of avanafil to the environment. The Applicant will update the interim ERA report incorporating the additional test results required and submit it to the EMA in February 2014.

Overall, the efficacy of avanafil over placebo has been demonstrated. The adverse effect profile of avanafil is concordant with those known for other PDE5 inhibitors already authorised and no new safety signals have been observed with avanafil.

The benefit/risk balance of avanafil in the treatment of erectile dysfunction in adult males is positive, for the intended indication “treatment of ED in adult males”.

A pharmacovigilance plan for Spedra will be implemented as part of the marketing authorisation.

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LIST OF ABBREVIATIONS

°C	Degrees Celsius
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AF	assessment factor
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
AUC	area under curve
AUC0-inf	Area under the concentration-time curve from time zero to infinity
AUC0-t	Area under the drug concentration-time curve from time zero to the time of last measurable concentration
AUC0-tau	Area under the drug concentration-time curve over the dosing interval
AUEC0-t	Area under the effect-time curve from time 0 to time t
BCF	bioconcentration factor
BID	Twice-daily dosing
BMI	Body mass index
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CLint	Intrinsic metabolic clearance
C_{max}	maximum concentration
Cmax	Maximum observed plasma concentration
Cmax,ss	Maximum observed plasma drug concentration at steady-state
CV	Coefficient of variation
DBP	Diastolic blood pressure
EAS	Erection Assessment Scale
ECG	Electrocardiogram
ED	erectile dysfunction
ED	Erectile dysfunction
EMEA	European Medicines Agency
ERA	environmental risk assessment
EU	European Union
f2	Similarity factor
IC_{50}	half maximal inhibitory concentration
IC50	Half maximal inhibitory concentration
IIEF	International Index of Erectile Function
INR	International normalized ratio
IR	immediate release
IR	Immediate release
ITT	Intent-to-Treat
Kg	kilogram
L/kg	liter per kilogram
LC/MS-MS	liquid chromatography and mass spectrometry
LLOQ	Lower limit of quantification

log Kow	logarithm of the octanol-water partition coefficient
LS	Least squares
MAA	Marketing Authorisation Application
MDCK-WT	Madin-Darby canine kidney wild type
MDR1	Multi-drug resistance gene
MedDRA	Medical Dictionary for
mg	milligram
mg/L	milligrams per liter
MRHD	maximum recommended human dose
NDA	New Drug Application
NO	nitric oxide
NOEC	no observed effect concentration
NS	Not statistically significant
OECD	Organization for Economic Co-operation and Development
Papp	Apparent permeability
PD	Pharmacodynamic
PDE5	Phosphodiesterase 5
PDE5	phosphodiesterase type 5
PEC	predicted environmental concentration
Pgp	P-glycoprotein
PK	Pharmacokinetic
PNEC	predicted no effect concentration
PT	Prothrombin time
QD	Once daily
QSAR	quantitative structure-activity relationship
QTcB	Bazett-corrected QT
QTcF	Fridericia-corrected QT
QTcI	Individual-corrected QT
RE	Efflux ratio
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SEP	Sexual Encounter Profile
SMQ	Standardized MedDRA query
t½	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TGD	Technical Guidance Document on Risk Assessment for New
Tmax	Time to reach the maximum plasma concentration
TQT	Thorough QT
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
µg/L	micrograms per liter

1. Background information on the procedure

1.1. *Submission of the dossier*

The applicant VIVUS BV submitted on 2 March 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Spedra, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 May 2011.

The applicant applied for the following indication: Treatment of erectile dysfunction in adult males.

The legal basis for this application refers to:

Article 8(3) of Directive No 2001/83/EC

The application submitted is composed of composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance avanafil contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Spedra has been given a Marketing Authorisation in South Korea on 21 October 2011 and in the USA on 27 April 2012.

1.2. *Manufacturers*

Manufacturer responsible for batch release

T D Packaging Ltd
Groundwell Industrial Estate, Unit 6, Stephenson Road, Swindon, Wiltshire, SN25 5AX, United Kingdom

1.3. *Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Concepcion Prieto Yerro** Co-Rapporteur: **Daniela Melchiorri**

- The application was received by the EMA on 2 March 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 November 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 December 2012.
- During the CHMP meeting on 17 January 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 02 April 2013.
- During the meeting on 8-11 April 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 22-25 April 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Spedra.

2. Scientific discussion

2.1. *Introduction*

Problem statement

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual performance.

Normal erectile function requires the coordination of psychological, hormonal, neurological, vascular and anatomic factors. Alteration of any of these is sufficient to cause ED. Main causes of ED are chronic systemic illnesses (diabetes mellitus, heart disease, hypertension and peripheral vascular disease), neurological disorders (post-traumatic spinal-cord injuries, multiple sclerosis) or post-surgical lesions (after radical prostatectomy).

There are several approaches to the management of erectile dysfunction: psychosexual counselling, hormonal therapy, mechanical devices, vascular surgery and pharmacological treatment (intracavernosal pharmacotherapy and intraurethral prostaglandin).

The current available pharmacological treatment of ED are based on inhibitors of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE) that increase penile blood flow and erection in response to sexual stimulation.

About the product

Avanafil, the active substance of Spedra (also referred to as TA-1790), is a new PDE5 inhibitor for oral administration, which was developed for its high selectivity for the PDE5 isoenzyme relative to other PDE5 inhibitors. PDE type 5 (PDE5) is the predominant enzyme in the corpus cavernosum smooth muscle. In men, sexual stimulation causes nitric oxide to be released from nerves and endothelial cell, which diffuses into smooth muscle cells in the walls of penile arteries and spongy erectile tissue. Nitric oxide stimulates the guanylate cyclase enzyme to synthesise cyclic guanosine monophosphate (cGMP) leading to decreased Ca^{2+} concentrations in smooth muscle cells causing smooth muscle relaxation and increased blood flow, thus causing penile erection to occur. In erectile tissues, cGMP is degraded by PDE5. Administration of a PDE5 inhibitor leads to higher cGMP levels and thus enhanced smooth muscle relaxation and penile blood flow.

The product is formulated as immediate release (IR) tablet in strengths of 50, 100 and 200 mg for oral use.

The applicant initially applied for the following indication: “Treatment of erectile dysfunction in adult males".
The finally approved indication is as follows: “Treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required”.

2.2. *Quality aspects*

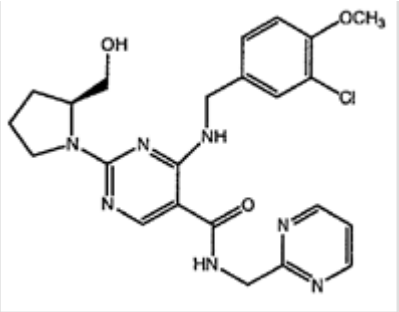
2.2.1. Introduction

The finished product is presented as tablets containing 50, 100 and 200 mg of avanafil as active substance.

Other ingredients are: mannitol, fumaric acid, hydroxypropylcellulose, low substituted hydroxypropylcellulose, precipitated calcium carbonate, magnesium stearate and yellow ferric oxide (E172). The product is available in PVC/PCTFE/Aluminium foil blisters.

2.2.2. Active Substance

The chemical name of avanafil is (*S*)-4-(3-Chloro-4-methoxybenzylamino)-2-(2-hydroxymethylpyrrolidin-1-yl)-*N*-pyrimidin-2-ylmethyl-5-pyrimidinecarboxamide and has the following structural formula:



Avanafil is a white crystal or white crystalline powder, slightly soluble in methanol and ethanol and practically insoluble in water. Avanafil has only one crystalline form, therefore no polymorphism was observed.

The structure of Avanafil was supported by elemental analysis, IR, UV, ^{1}H and ^{13}C NMR, MS and XRD.

Avanafil exhibits stereoisomerism due to the presence of 1 chiral center and exists as S conformer. The stereochemical configuration was determined by XRD.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure within the current Marketing Authorisation Application.

Manufacture

Avanafil is synthesized using commercially available starting materials.

The active substance is manufactured by one manufacturer. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential impurities were well discussed with regards to their origin and characterised.

The levels of the impurities were supported by the results of toxicological studies and appropriate specification limits have been set.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for description, identification (IR, HPLC), assay (HPLC), purity (HPLC), residual solvents (GC), heavy metals (Ph Eur), palladium (ICP-MS), optical isomer (HPLC),reagent (GC) and residual ignition.

The analytical methods used have been sufficiently described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data of 9 commercial scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch. However, a complete description and validation data of the analytical methods used to control each of a specified solvent, reagent and catalyst in the active substance specifications should be submitted. In addition, additional batch results, confirming that the level of a residual solvent is lower than specified, should be provided.

Stability

3 production scale batches of the active substance packed in the intended commercial package (double polyethylene bags which are individually sealed with plastic ties and placed into fibre drums closed with metal lids with security pegs) from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for 18 months, and accelerated (40°C/75%RH) for up 6 months for three batches. Photostability test following ICH guidelines Q1B was performed on one batch. Results on stress conditions 50+2ºC/75+5%RH during 3 months were also provided on one batch. Avanafil was investigated under conditions prepared with water, acidic and basis reagents, and hydrogen peroxide.

Other supportive stabilities studies were conducted on other batches with some differences on the manufacturing process, manufacturing site and container closure system.

The following parameters were tested: description, purity, optical isomer, loss of drying and assay.

The stability studies have proven that avanafil is mostly sensitive to oxidative conditions and to light exposure when it is in the liquid state.

Stability results showed that the active substance manufactured by the proposed supplier is very stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The finished product was developed as an immediate-release, oral tablet formulation because a rapid onset of efficacy was desired.

Although the solubility of avanafil is high under acidic conditions, it is very low in the neutral to alkali pH. Thus, a highly water soluble organic acid was desired as a solubilizing agent to improve the solubility of the active substance. Fumaric acid was specifically chosen because it exhibited the best compatibility with the active substance of the agents tested. The optimal ratio of fumaric acid to avanafil resulting in tablets with acceptable properties (weight, thickness, hardness) and dissolution characteristics was determined in a formulation study. Active granules (avanafil/mannitol/hydroxypropylcellulose) were prepared with different particle sizes of the active substance.

Using the aforementioned active granules, the method for addition of the fumaric acid was determined in a study as a part of manufacturing process development.

In order to accelerate the disintegration and dissolution of the tablets in an acidic environment (e.g., the stomach) the effect of adding precipitated calcium carbonate was studied. The formulation with precipitated calcium carbonate disintegrated faster than that without precipitated calcium carbonate in all test medium because of the bubbling effect between acid and base. From this study, the optimal

amount of calcium carbonate that resulted in rapid disintegration of Avanafil tablets without significantly raising the pH was determined. Therefore, precipitated calcium carbonate was included in the Avanafil tablet formulation.

Compatibility with conventional immediate release excipients were evaluated by preliminary stability studies. All of the chosen excipients were compatible with the active substance under the tested storage conditions. Compatibility has also been confirmed by the results of stability studies of the finished product.

The Critical Quality Attributes (CQAs) of the immediate-release Avanafil tablets are dissolution rate and dose uniformity. A set of experiments was conducted to elucidate the Critical Process Parameters (CPPs) for the Avanafil tablet manufacturing process. Control ranges have been established for these parameters to assure reproducibility of the CQAs of the product.

Two formulations (Formulation I and II) were used in clinical studies during the Avanafil Tablet development program. Both formulations have identical excipients (with the exception of the colorant added to Formulation II). The formulation used in Phase 3 clinical studies (Formulation II) is the proposed formulation for the commercial product. A clinical bioequivalence study was performed to compare Formulation I and Formulation II, and bioequivalence between the two formulations were demonstrated.

The primary packaging proposed is PVC/PCTFE/Aluminium foil blisters. The material complies with PhEur requirements and it is adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of 6 main steps: milling, preparation of binder solutions, formation of active granules, formation of fumaric acid granules, blending and tableting.

The process is considered to be a standard manufacturing process. Therefore, the absence of process validation data on commercial scale batches in the dossier is considered acceptable. The applicant submitted the validation scheme and the commitment to perform process validation at commercial scale (3 consecutive batches) prior to placing the medicinal product on the market for two strengths (100 mg and 200 mg). With regard to the 50 mg strength a concurrent validation was applied for. The Annex 15 to the EU Guide to Good Manufacturing Practice states that in particular circumstances it may be possible to validate a process during routine production (concurrent validation). In this case, considering that the granule is the same for the different strengths (50 mg, 100 mg and 200 mg), and that only one batch of the 50 mg strength will be manufactured per year, the proposal was considered acceptable.

Product specification

The finished product release specifications include appropriate tests for description, identification (HPLC), assay (HPLC), purity (HPLC), uniformity of dosage unit (Ph Eur), dissolution (Ph Eur), Total Aerobic Microbial Count (Ph Eur), Total Combined Yeast and Mold Count (Ph Eur), and *Escherichia coli* (Ph Eur).

Batch analysis results in 3 pilot scale batches per strength used in clinical trials confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of 9 pilot scale batches, three of each dose strength (50 mg, 100 mg and

200 mg), packaged in the proposed commercial packaging configuration stored under long term conditions for 18-24 months at 25ºC/60%RH and for up to 12 months under both intermediate conditions at 30°C/65% RH and accelerate conditions at 40ºC/75%RH according to ICH guidelines were provided. The pilot batches used are identical to those proposed for marketing and were packed in the same primary packaging proposed for marketing.

Samples were tested for description (appearance), identification (HPLC), assay (HPLC), purity (HPLC), dissolution (Ph Eur), total aerobic microbial count (Ph Eur), total combined yeast and mold count (Ph Eur). The analytical procedures used were stability indicating.

In addition, three batches (one of each dose strength) were exposed to stress conditions (50°C and 40°C/75% RH, open container) and were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.assess the stability of the product when exposed directly to conditions of high temperature.

Based on available stability data, the proposed shelf-life as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. A complete description and validation data of the analytical methods used to control each of a specified solvent, reagent and catalyst in the active substance specifications should be submitted. In addition, additional batch results, confirming that the level of a residual solvent is lower than specified, should be provided.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

A complete description and validation data of the analytical methods used to control each of a specified solvent, reagent and catalystin the active substance specifications should be submitted. In addition, additional batch results, confirming that the level of a residual solvent is lower than specified, should be provided.

2.3. *Non-clinical aspects*

2.3.1. Introduction

The design of the non-clinical testing program for avanafil was based on the guidance provided by ICH M3 (R2): Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals. The non-clinical testing strategy included pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies, an assessment of carcinogenic potential and *in vitro* biochemical evaluation.

The drug substance used in the toxicology studies was produced using the same process used to manufacture avanafil for the clinical trials.

GLP

The primary pharmacology studies were non-Good Laboratory Practices (GLP). The Applicant refers that many of the safety pharmacology studies (cardiovascular, respiratory, central nervous and gastrointestinal systems, as well as studies of ocular and retinal function) were conducted under non-GLP conditions, however, the core cardiovascular, respiratory, CNS and ocular Safety Pharmacology studies were conducted under GLP conditions.

All the toxicology studies were performed in accordance with GLP with the exception of a single oral dose (capsule) study in dogs (10 AVANAFIL-TOX 14), an one week repeat dose oral toxicity study in rats (10 AVANAFIL TOX-07), and a one week repeat dose oral toxicity study in dogs (10 AVANAFIL TOX-15). Nevertheless, the applicant confirms that the toxicology studies were conducted in accordance with the study protocols and laboratory standard operating procedures, and met the requirements of the International Conference on Harmonization (ICH) guidelines for the conduct of these studies. Any deviations that occurred during the performance of the non-clinical studies were minor and did not affect the integrity of the study or the interpretation of the data.

In addition, two toxicokinetic studies in male rats and pregnant rats (Study 1060 048) and pregnant rabbits (1060 049), performed to provide supportive exposure information, were not conducted in compliance with GLPs. However, the Applicant provided acceptable justification of the quality of these studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Results of *in vitro* and *in vivo* studies indicated that avanafil is an inhibitor of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase5 (PDE5) enzyme, and is highly selective for the PDE5 isoenzyme relative to other phosphodiesterases (>100-fold for PDE6; >1,000-fold for PDE4, PDE8 and PDE10; >5,000-fold for PDE2 and PDE7; and >10,000-fold for PDE1, PDE3, PDE9, and PDE11) and a wide variety of cellular targets. Avanafil showed a more favourable profile against other enzymes known to be affected by this class of drugs, especially PDE6, where avanafil was more than 100-fold less potent than at the PDE5. Therefore, avanafil had a low propensity for visual disturbances. Avanafil displayed higher selectivity for PDE5 versus PDE6 (121-fold) as compared with sildenafil (16-fold) and

vardenafil (21- fold) but much lower selective compared to tadalafil (550-fold). Its selectivity for PDE5 with respect to PDE1, PDE3 was similar to that showed by tadalafil, and much lower respect to PDE4 compared with tadalafil.

In canine lung tissue, avanafil exhibited a potent PDE5 inhibition (IC_{50} = 4.2-5.2 nM) with high selectivity versus other PDE isoforms as expressed in native animal tissues or recombinant human enzyme expressed in cell lines. Avanafil inhibited PDE5 isolated from human platelets with an IC_{50} of 8.9 nM. For PDE5, the isozyme of primary interest, avanafil showed an *in vitro* potency (IC_{50}=5.2nM) on PDE5 particularly much lower than vardenafil (IC_{50}=0.084 nM) and sildenafil (IC_{50}=1.6nM), and lower to a lesser extent to tadalafil (IC_{50}=4.0 nM). Thus, the high potency of avanafil claimed by the Applicant seems not supported.

Three avanafil metabolites (M4, M16 and M27) observed in both rats and humans were selected for *in vitro* profiling against PDE isoforms. The plasma concentrations of the major circulating metabolites, M4 and M16, were approximately 23% and 29% that of the parent compound, respectively. A third circulating metabolite, M27, accounted for about 3.8% of total radioactivity in humans. Since avanafil undergoes significant and rapid metabolism, M27 is not considered a major circulating human metabolite (<10% radioactive dose). The M4 metabolite showed an *in vitro* inhibitory potency for PDE5 that is 18% of that of avanafil, and a phosphodiesterase selectivity profile similar to that of avanafil. Therefore, M4 may produce at most a minor contribution to the therapeutic activity of avanafil (4% of total pharmacologic activity). The Applicant states that remaining findings with avanafil metabolites are unlikely to be of physiological significance due to their higher IC_{50} values (4,100 and 4,500nM for M16 and M27, respectively) and lower exposures relative to parent drug. Testing of the metabolites for activity against PDE isoforms other than PDE5 yielded no findings of clinical significance.

The dose-dependent potentiating of penile tumescence in rabbits administered single dose IV of both avanafil and sildenafil was no indicative of any treatment effect; statistical significance was only registered for doses ranging 100-1000 ug/kg of both treatments vs. vehicle. At plasma levels comparable to human free C_{max} (18.3 ng/ml) reached with doses ranging from approx. 10 and 30 ug/kg for avanafil and 30 ug/kg for sildenafil, no statistical difference was observed between placebo and treatments.

The potentiating of penile tumescence induced by avanafil 1000 µg/kg in dogs administered ID, was statistically significant only 10 minutes after administration versus vehicle; its effect rapidly decreased. The efficacy peak reached by sildenafil after 10 minutes from administration, although lower than the effect reached after the same time point with avanafil, was maintained almost constantly in 90 minutes except for 300 ug/kg for which the response less clear. The same trend applies when considering the plasma concentrations. This datum has not as much relevance as the Applicant stressed for supporting the clinical rapid onset for avanafil; considering the plasma concentration of 18.3 ng/ml as the one reached in the human plasma following administration of the maximum tolerated dose of avanafil 200 mg, the lowest dose of avanafil 100 ug/kg and sildenafil 100 ug/kg exerted the same effect in terms of extent.

The potentiating of the stimulation induced tumescence induced by avanafil and sildenafil in monkey administered IV, was similar and both compounds at 1000 ug/kg were statistically significant only vs. vehicle. This dose correspond to 3.2–6.2 µM that is higher than the free human C_{max} (0.038 uM).

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed. This was considered not necessary due to the high selectivity of avanafil for PDE5. Avanafil shows selectivity for the PDE5 isozyme as compared to other PDEs (from 121-fold to >19000-fold) and displays low activity against a variety of cellular

targets. The off-target activity of avanafil compares favourably with sildenafil, particularly at the PDE6 isozyme and at adenosine and α1 adrenergic receptors (Please refer to Receptor Binding in Safety Pharmacology Section).

Safety pharmacology programme

As it is required in the guidelines currently in force, the core safety pharmacology studies included an assessment of potential effects of avanafil on cardiac function, respiratory system, and central nervous system and were conducted under GLP conditions. Besides the core safety pharmacology evaluation, supportive studies on specific drug class effects like ocular and retinal function, the receptor binding and selectivity of avanafil versus a number of target tissues other than corpus cavernosum, like smooth muscle (vas deferens tissue), platelet, and urine volume and electrolyte excretion, were performed. Many of these studies were supportive and were conducted under non-GLP conditions.

Cardiovascular effect

A battery of *in vitro* assays for cardiovascular safety tests was performed. In the hERG assay, a test to predict the potential for lengthening of the QT Interval, avanafil was positive in blocking hERG at concentrations tested (1, 10, 30 and 100 µM). Avanafil had an IC_{50} of 15.8 µM which represents a concentration approximately 416-fold above the unbound C_{max} in human at the MRHD. The IC_{50} could not be calculated in the studies examining the function of L-type calcium channels and sodium channels. Thus, avanafil appeared not to cause conduction delays associated with re-entrant arrhythmias nor action potential shortening in atrial fibrillation.

Further tests of avanafil at concentrations up to a 100 µM in isolated Beagle dog (male and female) Purkinje fibres showed a slight decrease in the duration of cardiac action potentials. This is consistent with effects of Ca^{2+} channel block but at concentrations unlikely to be clinically relevant (>2600-fold the free concentration at MRHD). Avanafil showed no decreased effect in the duration of cardiac action potentials at concentrations up to up to 10 µM in isolated guinea pig cardiac papillary muscle.

The calcium antagonist-like effect was studied on isolated, K^+ depolarized denuded rat aorta models. Avanafil showed to be less potent than sildenafil in inducing vasorelaxation (higher EC_{50} values for $CaCl_2$). The vasorelaxation effect of sildenafil was shown to be concentration dependent, while for avanafil it is not dose-dependently antagonized. This difference might be explained by the hypothesis that the vasorelaxant effect of higher levels of sildenafil is mediated by mechanisms other than the PDE5 inhibition effect (i.e. a direct blocking action on the L-type Ca^{2+} channel), in contrast with a specific PDE5 inhibitor effect of avanafil.

The haemodynamic effects of avanafil at concentrations of 10 and 100 ug/kg/min were similar to those of sildenafil and reduced the mean arterial pressure in anesthetized dog. In open chest dogs, both avanafil and sildenafil significantly decreased mean arterial pressure while at 300 ug/kg/min avanafil significantly reduced the pulmonary arterial pressure vs. sildenafil. Sildenafil, but not avanafil, significantly increased HR at 1 ug/kg/min vs. vehicle and at 300 ug/kg/min also vs. avanafil. When orally administered to Beagle dogs avanafil decreased the blood pressure and increased the heart rate at the 30 mg/kg (corresponding to a C_{max} of 3.67 ug/mL or 7.58 µM that is higher than the free human C_{max} = 0.038 uM); there were no other consistent effects on haemodynamic or electrocardiographic parameters (no potential for delaying ventricular repolarisation (QT interval prolongation). The lack of QT prolongation in dog is in line with the high IC_{50} value (15.8 uM) of avanafil in the hERG channel assay. Collectively, these results suggest a low risk of electrocardiographic abnormalities in human. A clinical QT study (TA-140) was conducted and no evident effect on electrocardiography at the recommended therapeutic dose of 100 mg nor at higher dose of 800 mg was observed.

Central Nervous system effect

In studies examining effects on the CNS, avanafil produced effects only at relatively high doses. Avanafil decreased spontaneous locomotor activity in the mouse and rat a 1000mg/kg p.o. and increased pentobarbital-induced sleeping time in the mouse (300mg/kg p.o). Otherwise, avanafil had no effect on spontaneous locomotor activity, no anti-convulsant effects after the maximal electroshock, no effects on pentylenetetrazol (PTZ)-induced convulsions and deaths, no proconvulsant activity in following both the subliminal electroshock and subliminal PTZ procedures, and no analgesic activities in the acetic acid-induced writhing test in mice at doses up to 300 mg/kg p.o.

Gastrointestinal System effect

Overall, no relevant effects on gastrointestinal system were highlighted for avanafil following *in vitro* and *in vivo* studies performed. No effect on the spontaneous contraction of isolated rabbit jejunum or of guinea pig ileum. Avanafil decreased gastric excretion in rat, after single intraduodenal administration of 300 mg/kg, the free C_{max} associated with this doe is 10-fold above the human free C_{max}.

Ocular effect

A series of studies were undertaken to evaluate the effects of avanafil on retinal function in isolated rabbit retinas and on in vivo retinal/ocular function in dogs. The weak effects of avanafil on *in vitro* electroretinogram are likely due to the less potent inhibitory activity of avanafil on PDE6 (higher IC_{50} than that of sildenafil, but lower than that of tadalafil). In the only *in vivo* GLP study carried out on dogs, avanafil did not exert any ocular event up to 100 mg/kg which corresponded to a mean C_{max} of 11 ug/ml much higher than the human effective free C_{max} (18.3 ng/ml).

Platelet Aggregation Effect

Avanafil (10 µM) was found to potentiate the anti-aggregation of sodium nitroprussiate (nitric oxide donor) on human collagen-induced platelet aggregation; this effect was similar to the one when sildenafil was used. Avanafil has no effect on blood coagulation and fibrinolysis parameters in rats.

Receptor selectivity

Besides the selectivity of avanafil in inhibiting PDE5 relative to other PDE isozymes, the specificity of avanafil to PDE5 over other enzymes, receptors, and ion channels has been elucidated in radio-ligand binding studies.

Concentrations tested (1 and 10 uM) were much higher than the IC_{50} vs. PDE5 for avanafil calculated in canine lung (5.2 or 4.2 nM) or in human platelets (8.9 nM). They were even higher than IC_{50} values for sildenafil (1.6 nM calculated both in canine lung and human platelets); thus the ability of sildenafil to compete on adenosine A_1, A_{2A}, A_{2B} and α1 adrenergic receptors is of limited interests. Avanafil had no clinical significant affinity for adrenergic, dopaminergic, histaminergic, muscarinic, serotonergic and calcium channel binding sites, and does not inhibit constitutive or inducible nitric oxide synthase.

Pharmacodynamic drug interactions

PDE5 inhibitors have been shown to interact with nitrates, and are therefore contraindicated in patients receiving organic nitrates due to the risk of a potentiation of their hypotensive effect.

The effect of co-administration of avanafil with nitroglycerin on mean arterial blood pressure was evaluated. Avanafil potentiated the effects of nitroglycerin in dogs (0.1 and 1.0 mg/kg, intraduodenally). In addition, steps have been taken to address the risk for to augment the hypotensive effects of nitrates in the section 4.3 and 4.4 of the SmPC.

2.3.3. Pharmacokinetics

Evaluation of absorption, distribution, metabolism and excretion (ADME) of avanafil was performed in pharmacokinetic studies both *in vitro* and *in vivo* in mice, rats, rabbits, dogs and monkeys after single and repeat oral administrations. The species used for analyses of pharmacokinetics were also used in the safety pharmacology and toxicology studies.

Methods of analysis

PK evaluation for avanafil and metabolites M4 and M16 was carried out according to the general principles of ICH topic M3 (R2) "*Non-clinical guidance including test species and in vitro biochemical evaluation*". Since M4 and M16 are those metabolites whose exposure in humans is greater than 10% respect to the parent compound exposure, they were also characterised from the PK point of view.

Absorption

To characterize the absorption profile of avanafil the applicant has conducted studies in several animal models (mice, rats, dogs, rabbit and monkeys). Plasma pharmacokinetic properties of avanafil were shown to be consistent across these non-clinical species. Following oral administration of avanafil, the intended clinical route of administration, avanafil was rapidly and relatively well absorbed from the gastrointestinal tract in the toxicology species and humans, with low to moderate oral bioavailability (1.5% in rats, 30-40% in dogs, and 15% in monkeys), short t_{max} (0.5-2h), short $t_{1/2}$ (0.82-2.5h) and high systemic clearance. Low to moderate oral bioavailability suggests that avanafil appears to undergo a first-pass effect in the absorption process from the digestive tract and/ or liver. Avanafil was rapidly absorbed and rapidly metabolized to M4 and M16; the pharmacokinetics of the 2 major human metabolites was evaluated in rats and rabbits.

In toxicology studies with mice, rats and dogs, mean C_{max} and AUC values for avanafil, M4 and M16 generally increased in a dose-related manner up to 2000 mg/kg (mouse, rat) and 100 mg/kg (dog). In repeat dose studies using oral administration, avanafil showed a short half-life of 0.7–2.5 h in all animal models, thus no accumulation phenomena were observed, except for dogs. The exposure to avanafil was higher in female rats than for male rats, while no marked gender-related differences were observed in the mouse and dog. Avanafil exposure was slightly lower in pregnant female rats than non-pregnant females; a 23% reduction in C_{max} and 36–18% reduction in AUC.

Distribution

Distribution was assessed in rat following oral or IV administration of the single dose of 3 mg/kg; since avanafil has a short half-life in all animal species, an almost complete elimination (rat 99.8%, dog 97.5%, monkey 93.5%, human 84.5%) and no unanticipated organ toxicity, no repeated dose tissue distribution assays were considered necessary. Moreover, in repeated dose PK or TK studies the steady-state levels of Avanafil or metabolites was not higher than levels predicted from single dose PK studies *(ICH Topic S3B PK: repeated dose tissue distribution studies*).

Following oral administration, the highest concentrations of avanafil seen at 0.5 h post-dose were in the gastrointestinal contents and excretory organs (liver and kidney); the passage through blood-brain barrier and blood-testis barrier was minimal (< 20% as seen in blood). Most of the compound was excreted after 24 h.

The pattern of distribution following IV administration was similar to those observed following oral administration also in pigmented rats; in this latter animal model, the amount of avanafil in melanin-containing tissues (uveal tract of the eyes and hair follicles) was higher and lasting up to 18 h. No determination of melanin affinity for metabolites M4 and M16 was assessed.

Avanafil (0.3–3.0 µg/mL), M4 and M16 exhibited high (concentration-independent) protein binding in the plasma of rat, dog and rabbit. In humans the avanafil was bound for 99% independently from age of the subjects. In humans, M4 was bound for 97% and M16 for 84%. Metabolites M4 and M16 were approximately less bound to plasma protein in animal models than in human; M16 was less bound than M4 and avanafil in both animal and clinical species; they were less potent (higher IC_{50} values) in inhibiting the PDE5 than the parent compound, thus resulting practically inactive.

Metabolism

Avanafil is mainly metabolised by liver enzymes via CYP3A4 with a minor contribution from CYP32C: *in vitro* metabolism of avanafil (TA-1790) is consistent across animal species and humans, and *in vivo*, the metabolic profile was qualitatively similar among rat, dog, and human. There was no human unique metabolite identified. The conversion of avanafil to M4 and M16, were rapid in the toxicology species and humans. In male rats, exposure to M4 was 2-3 fold greater than that of avanafil, while high exposure to M16 was seen in the pregnant female rabbits. In humans, avanafil still represented the major component in plasma and accounted for 37% of total radioactive dose within 12 hours post-dosing. The plasma concentrations of the major circulating metabolites, M4 and M16, were approximately 23% and 29% that of the parent compound, respectively. The third circulating metabolite, M27, accounted for about 10% of unchanged avanafil in humans, not being considered a major circulating human metabolite. Hence, the PK profile of avanafil and M4 and M16 metabolites were similar, characterized by early t_{max} and short t½. Although the amount of each metabolite varied among animal species (rat and dog), the metabolite profiles were similar, and that there was no human unique metabolite identified. Since M4 and M16 are those metabolites whose exposure in humans is greater than 10% respect to the parent compound exposure, they were the only one characterised from the PK point of view.

Excretion

After oral administration in male rats, dogs, monkeys and human, avanafil was mainly eliminated via faecal/biliary route as the primary elimination pathway.

Pharmacokinetic drug interactions

According to CYP450 induction/inhibition data, it is likely that avanafil cause drug-drug interaction with moderate to strong CYP3A4 inhibitors, resulting in an increase in avanafil C_{max} and AUC. Therefore, contraindications for patients taking CYP3A4 inhibitors have been included.

In vitro studies on human liver microsomes demonstrated low potential of avanafil to inhibit activities of CYP1A1/2, CYP2A6, CYP2B6, and CYP2E1, likely potential to inhibit CYP2C19 activity; and possible potential to inhibit CYP3A4, CYP2C8, CYP2C9 and 2D6 activities. The metabolites, M4 and M16 also demonstrated a low potential to inhibit the activities of CYPs 1A, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. At clinically relevant concentrations, avanafil is not expected to induce CYP1A2, CYP2B6, and CYP3A4 activities *in vivo*.

In vitro results showed high membrane permeability for avanafil, a modest potential for acting as P-glycoprotein substrate and a relatively modest effect regarding the potential to act as a P-gp inhibitor with Digoxin as a substrate. The *in vitro* study suggests an inhibitory effect on avanafil on P-gp and based on intestinal concentrations (maximum dose/250 ml), a clinically relevant inhibitory effect on P-gp may not be excluded. Therefore, in the absence of data on humans, the potential of avanafil to interfere with the transport of other medicinal products mediated by P-glycoprotein is reported in SmPC section 4.5 and reflected in the RMP section 1.8.

The CHMP agreed that avanafil should be evaluated *in vitro* to determine whether it is a potential substrate of Breast Cancer Resistance Protein (BCRP), which is expressed in the gastrointestinal tract,

liver, and kidney, and have a role in limiting oral bioavailability. In addition, given that hepatic pathway is significant, *in vitro* study to determine whether it is a substrate of hepatic uptake transporters OATP1B1/OATP1B3 should be provided as well as renal uptake transporters OAT1, OAT3 and OCT2. Additionally, evaluation of avanafil as inhibitors of BCRP, OATP1B1/OATP1B3, OAT1/OAT3 and OCT2 should be considered according to the draft Guideline on the Investigation of Drug Interactions [CPMP/EWP/560/95/Rev. 1 – Corr.*].

However, at 10 µM, avanafil was shown to be a highly permeable compound; a mean absorptive, apical to basolateral, Papp value of 44.6•10-6 cm/s and a mean, secretory, basolateral to apical, Papp value of 73.4•10-6 cm/s were determined from 3 studies with a total of nine replicates (10-AVANAFIL-BCS-01). The mean efflux ratio was 1.8, which is less than the efflux transporter cut-off value of 2, suggesting that avanafil is unlikely a substrate of efflux transporters (i.e., P-gp and BCRP). In addition, high permeability drugs in this class do not give transporters sufficient access to the drug and the extensive metabolism of avanafil facilitates the creation of a concentration gradient that favours drug entry from basolateral side of hepatocytes with the likelihood of being minimally impacted by hepatic uptake transporters such as OATP1B1 and OATP1B3, which are located on the basolateral side of the hepatocytes. Therefore, the issue regarding the evaluation of avanafil as a substrate for drug transporters is considered solved.

2.3.4. Toxicology

The nonclinical toxicology programme has been conducted in mouse, rat, rabbit and dog species. The rationale for the selection of these species for toxicity studies is considered adequately justified. Characterization of avanafil toxic effects with respect to target organs, dose-dependence, relation to exposure and potential reversibility, were assessed with a battery of toxicity studies. No new toxicity sign for this new PDE inhibitor emerged.

Single dose toxicity

The acute toxicity information has been obtained from three mammalian species (mouse, rat and dog) using both the clinical and intravenous route of administration in the mouse and rat and oral route of administration in dogs, which is considered adequate. The proposed maximum tolerated single oral dose of 2000 mg/kg and single intravenous dose of 40 mg/kg are considered adequate taking into account the results from the single toxicity study in mice, rats and dogs did not produce toxicologically significant effects.

Repeat dose toxicity

The Applicant has performed 10 repeat-dose studies in animal models to characterize the toxicology profile of avanafil: 1 in mice, 5 in rats and 4 in dogs. The studies included adequate number of animals. The dosing regimen employed in these studies provided constant tissue exposures and administered doses were more than 9-fold the intended dose in humans and provide an acceptable safety margin to the proposed maximum recommended human dose of avanafil (200mg). In addition the duration of the toxicology studies are in accordance with the current requirements and the route of administration covers the oral administration intended for clinical use. During the development of avanafil, cardiovascular (blood pressure and QT prolongation) and ocular issues already identified with approved PDE5 inhibitors were addressed in safety pharmacology studies and in repeat-dose toxicity studies.

Following repeated administration, avanafil at high doses primarily produced a decrease in body weight or body weight gain, increased liver weight, and histopathological changes in the liver consistent with induction of increased drug metabolizing enzyme activities. Significant adverse toxicity (measured by

clinical signs as convulsions, hunched posture, thin appearance, audible, irregular, and laboured respiration, rough hair coat, tremors, hypoactivity, yellow hair coat (perineal area), cold to touch, and/or blue skin in mice; and inanimation, shivering, decreased activity, deep sedation, hypothermia, ptosis, and miosis in dogs) was only observed following the administration of high doses (2000 mg/kg/day in mice and 100 mg/Kg/day in dogs). Therefore, the NOAEL doses were 200,300, and 30 mg/kg/day in the 13-week mouse study, the 26-week rat study, and the 9-month dog study, respectively. The avanafil margin at NOAEL was 9x in rats and 36x in dogs.

In rats, as for mice, the liver was the primary target organ. In this organ as well as the thyroid (which exhibited microscopic changes following chronic dosing), the Applicant declares that the effects are considered to be adaptive or compensatory and not adverse. It is accepted that centrilobular hepatocellular hypertrophy (related to liver enzyme induction) is not an adverse change and that extramedullary haematopoiesis is a compensatory response to decreases in red blood cell parameters. The thyroid changes are likely a compensatory response to increased metabolism of thyroid hormones by the liver.

The findings in the heart were unique to mice, but the other changes were consistent with the toxicity profile in the other nonclinical species following repeated dosing. The changes in electroretinograms were isolated (one-week rat study and one-week dog study) and not replicated in the chronic toxicity study. Further support for the low propensity of avanafil to produce visual disturbances comes from the excellent selectivity versus PDE6, where avanafil is more than 100-fold less potent than at PDE5, and the relatively superior results compared with sildenafil observed in safety pharmacology studies examining retinal and ocular function.

Dogs exhibited cardiovascular effects (increased heart rate and decreased blood pressure) following administration of high doses of avanafil (100mg/kg/day) as well as effects on body weight, as were noted in the rodent species. Microscopic changes were only noted in the one-week and 28-day studies, and the organs and findings noted were not consistent and were not observed at the same doses administered for longer durations (9-month study). The heart rate and blood pressure effects in animals likely represent an exaggerated pharmacological response to avanafil, since the drug acts via a mechanism of vasodilatation, and that similar changes were also noted with other PDE5 inhibitors (tadalafil, vardenafil, sildenafil).

As regards testicular toxicity, potential target organ for PDE-inhibitors, there was no indication that avanafil adversely affects the testes in rats and dogs. Only in dog, coronary artery and arterioles of the epididymis at 100 mg/kg/day, was observed.

Exposure information for avanafil was obtained from single-dose and shorter-term repeat dose studies for rodent species, from pregnant rats and rabbits, and following chronic exposure in dogs. With repeated dosing, prolonged absorption was noted at high doses in most species. C_{max} and AUC values increased with increasing dose; AUC tended to increase in a greater than dose proportional manner. Overall, repeated dosing did not affect the kinetic parameters in mice, rats, pregnant rabbits, and dogs for short-term treatment, but chronic dosing in dogs resulted in a slight decrease in exposure. The only indications of parent drug accumulation occurred in male rats and pregnant female rats at high doses in a toxicokinetic study.

Genotoxicity

Avanafil has been evaluated in a range of *in vitro* and *in vivo* tests to detect genotoxic activity, which is considered appropriate. Avanafil was not mutagenic in Ames assay; it was not clastogenic in chromosome aberration assays using Chinese hamster ovary and lung cells. Although avanafil was positive with metabolic activation *in vitro* Mouse Lymphoma Cell Gene Mutation Assay, avanafil was

negative in the micronucleus test using male and female ICR mice and did not affect DNA repair when tested in the rat unscheduled DNA synthesis assay. Thus, no indication for a genotoxic hazard was observed.

Carcinogenicity

Two long-term carcinogenicity studies were conducted in mice and rats. Neither a 2-year study in rats nor a 2-year study in mice revealed a carcinogenic potential of avanafil up to and including the highest dose tested. Although there are no TK data in the 2-year carcinogenicity studies and the exposures estimations calculated by the Applicant are not considered appropriate, considering the lack of carcinogenicity in the two studies and that there are no concerns regarding this issue in other similar pharmaceuticals, this issue is considered solved.

Reproduction Toxicity

Oral reproductive studies were performed in rat and rabbits including a fertility and general reproductive performance study in rats, embryofoetal development in rats and rabbits and prenatal and postnatal development, including maternal toxicity in rats.

In a male and female rat fertility study, effects on sperm (decreased motility, increased abnormal sperm), a non-statistically significant decrease in fertility, and changes in oestrous cycling (increased length of cycle, decreased number of cycles), were observed at the highest dose tested, 1000 mg/kg/day. Based on the effects at 1000 mg/kg/day in both males and females, the NOAEL for both parenteral toxicity as well as fertility and reproductive affects was determined to be 300 mg/kg/day. The margin for avanafil was 9x and 190x over the human exposure in male and female rats, respectively, at the NOAEL dose.

In a second fertility study in which only males were treated, there was no decrease in fertility, and after 9-week of treatment a decrease in sperm motility and an increase in the percentage of abnormal sperm were observed at 1000 mg/kg/day. However, following the recovery period, there were no effects on sperm parameters demonstrating a complete reversibility of the sign. The section 4.6 of the SmPC was updated to include the lack of data on the effect on spermatogenesis in humans, the non-clinical data is referenced in section 5.3. Furthermore a study evaluating the effect on spermatogenesis in Humans will be performed as described in the risk management plan.

An embryofoetal development study in rats produced maternal toxicity at 1000 mg/kg/day with no increase in foetal malformations or variations, and a decrease in foetal body weight at 1000 mg/kg/day. One high-dose female that was found dead had total litter resorption and one surviving high-dose female was pregnant by stain (total litter resorption). Therefore, the NOEL for maternal and developmental toxicity was 300 mg/kg/day. In pregnant rabbits, maternal toxicity was evident at 240 mg/kg/day due to mean body weight gains and food consumption were lower. There was no developmental toxicity and no increase in the incidence of foetal malformations or variations as compared to both the current controls and the historical controls. The maternal toxicity NOEL was 120 mg/kg/day and the developmental toxicity NOEL was 240 mg/kg/day in pregnant female rabbits. Thus, for embryo-foetal development including teratogenicity, the avanafil margin at the NOAEL was 121x in rats and 39x in rabbits.

Finally, in a pre-/post-natal development study in rats, maternal toxicity was observed at 600mg/kg/day and decreases in offspring body weight and weight gain were reported at 300 and 600mg/kg/day with corresponding slight delays in markers of sexual maturation at 600mg/kg/day. The NOEL for growth of the F1 generation was 100mg/kg/day, while the NOAEL for behaviour and

reproduction in the F1 generation was 600mg/kg/day. Thus, for offspring growth and maturation following maternal exposure to avanafil, the margin was 27x at the NOAEL dose.

As a conclusion, administration of avanafil in pregnant rats decreased foetal and pup body weight occurred (with a concurrent delay in sexual maturation) at maternally toxic doses. But avanafil was not shown to be teratogenic in either rats or rabbits. As the therapeutic indication is directed to adult males only, the observed high dose effects on female reproduction and embryo-foetal development are not considered applicable in this case.

Toxicokinetic data

Toxicokinetic data indicate that the safety margins in terms of unbound avanafil plasma exposure (AUC) in male rats were 9x for avanafil, 56x for M4, and 1x for M16. For dogs, the margin at the NOAEL was 36x for avanafil. Because the parent drug is not significantly metabolized in dogs, margins were not calculated for M4 and M16.

In the first in man study (Study HP-01) oral doses of 12.5, 25, 50, 100, 200, 400, 600, or 800 mg avanafil or placebo tablets under the fasted condition were tested. To determine the exposure margins between animal models and humans, a comparison was made between the AUC values at the NOAEL doses in non-clinical chronic toxicity studies, and the AUC value in humans at the maximum recommended human dose (MRHD) of 200 mg. It should be noted that as reported in the SmPC, MRHD can be 400 mg (200 mg twice a day).

Local Tolerance

A local tolerance study was not conducted which was accepted by the CHMP.

Other toxicity studies

Juvenile animal toxicity studies are not deemed necessary given the intended therapeutic indication is for adult males only.

Signs of **immunotoxicity** were observed in the repeat-dose toxicity studies. In these studies, immune-related organs (i.e., thymus, spleen, lymph nodes, bone marrow) were weighed and evaluated microscopically and relevant haematology and clinical chemistry parameters (e.g., total and absolute differential white blood cell counts, serum globulins) were assessed. No avanafil-induced effects suggestive of immunotoxic potential were observed in mice, rats or dogs given avanafil.

The **impurity I-C** is specified at 0.30%, above the ICH threshold. *In vitro* genetic toxicity studies were conducted on Impurity I-C. This impurity was not genotoxic in the Ames and *in vitro* cytogenetic assay and this impurity is considered qualified in the general toxicology studies in rats and dogs.

In the **phototoxicity** study, avanafil did not caused any change in the skin or eyes following the oral administration of single doses up to and including 1000 mg/kg as compared to positive control.

2.3.5. Ecotoxicity / environmental risk assessment

An interim environmental risk assessment (ERA) has been submitted by the Applicant. This interim ERA evaluates environmental fate and exposure concentrations that are a direct result of post-use consumer avanafil (TA-1790) releases to wastewater treatment plants and subsequent release to the aquatic environment.

Due to the Phase I $PEC_{surfacewater}$ estimate for avanafil was greater than 0.01 µg/L, a Phase II Tier A evaluation was performed. Assessment of the environmental impact showed that preliminary PEC/PNEC

ratios for avanafil were much less than 1. Thus, the Applicant states that based on this interim ERA, the drug product is unlikely to cause adverse environmental effects. During the procedure the Applicant has changed the maximum recommended dose to 200 mg once per day instead of twice a day; therefore the $PEC_{surfacewater}$ estimate is 1 µg/L.

The available data is summarised in Table 1. Adsorption-Desorption Test (OECD Method 121) has been performed by the Applicant. According to the guideline *(EMEA/CHMP/SWP/4447/00),* it is acknowledged that OECD 121 Method is not a batch equilibrium method and hence it cannot replace batch equilibrium experiments (OECD 106 or OPPTS 835.1110) and is only suitable for indicative purposes. The Applicant will need to provide an OECD 106 study, an OECD 305 study as well as the complete analytical report for the Daphnia sp. reproduction study.

So far, available data do not allow concluding definitively on the potential risk of avanafil to the environment. According to the Applicant, all required laboratory testing and reporting will be completed by the end of 2013. The interim ERA report will be updated to incorporate all additional test results, and the final ERA report is expected to be submitted to EMA in February 2014.

Table 1. Summary of main study results

Substance (INN/Invented Name): Spedra					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}		3.16 L/kg			No screening for PBT
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.16 L/kg			
	BCF				**Pending**
Persistence	Ready biodegradability	Not reach 60% biodegradation within the 28 day study period			Persistence
Toxicity	NOEC				**Pending**
PBT-statement :	**Pending**				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	≥0.01	µg/L			Phase II environmental fate and effect analysis should be performed.
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	*log* K_{oc} = 3.41			**A batch equilibrium method necessary**
Ready Biodegradability Test	OECD 301				No readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			**Pending**
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	11	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	1	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	**Pending**
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>1000	mg/L	

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

All required laboratory testing and reporting will be completed by the end of 2013. The interim ERA report will be updated to incorporate all additional test results, and the final ERA report will be submitted to EMA in February 2014. The compliance to GLP will also be incorporated for each studies conducted in support of the ERA.

An adsorption-desorption test OECD 106 study (as required in 'Guideline on the environmental risk assessment of medicinal products for human use' EMA/CHMP/SWP/44609/2010) will be performed by the Applicant and submitted in February 2014.

A bioconcentration study OECD 305 (as required in 'Guideline on the environmental risk assessment of medicinal products for human use' EMA/CHMP/SWP/44609/2010 in phase II Tier B) will be performed by the Applicant and submitted in February 2014

Furthermore, the Applicant will submit the completed *Daphnia sp.* definitive test in February 2014.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The pharmacology development carried out with avanafil by the Applicant is considered appropriate since thorough information about pharmacology activity of phosphodiesterase 5 (PDE5) inhibitor as well as its effects on cardiovascular, respiratory, central nervous, ocular, gastrointestinal and genitourinary systems have been provided. The doses studied resulted in free plasma concentrations generally exceeding by the 10-fold or more those associated with the MRHD.

Results of *in vitro* and *in vivo* studies indicated that avanafil is an inhibitor of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase5 (PDE5) enzyme, and is highly selective for the PDE5 isoenzyme relative to other phosphodiesterases. Avanafil showed a more favourable profile against other enzymes known to be affected by this class of medicinal products, especially PDE6, where avanafil was more than 100-fold less potent than at the PDE5. Therefore, avanafil had a low propensity for visual disturbances. Avanafil displayed higher selectivity for PDE5 versus PDE6 (121-fold) as compared with sildenafil (16-fold) and vardenafil (21- fold) but much lower selective compared to tadalafil (550-fold). Its selectivity for PDE5 with respect to PDE1, PDE3 was similar to that showed by tadalafil, and much lower respect to PDE4 compared with tadalafil.

For PDE5, the isozyme of primary interest, avanafil showed an *in vitro* potency (IC_{50}=5.2nM) on PDE5 particularly much lower than vardenafil (IC_{50}=0.084 nM) and then sildenafil (IC_{50}=1.6nM), and lower to a lesser extent to tadalafil (IC_{50}=4.0 nM). Thus, the high potency of avanafil claimed by the Applicant seems not supported.

Avanafil showed to be less potent than sildenafil in inducing vasorelaxation (higher EC_{50} values for $CaCl_2$). The vasorelaxation effect of sildenafil was shown to be concentration dependent, while for avanafil it is not dose-dependently antagonized. This difference might be explained by the hypothesis that the vasorelaxant effect of higher levels of sildenafil is mediated by mechanisms other than the PDE5 inhibition effect (i.e. a direct blocking action on the L-type Ca^{2+} channel), in contrast with a specific PDE5 inhibitor effect of avanafil. The Applicant carried out three *in vivo* studies examining the effects of avanafil and a positive control sildenafil for their efficacy in increasing penile tumescence in rabbit, dog and monkey. Both avanafil and sildenafil produced a dose-dependent potentiation of penile tumescence.

Pharmacokinetics

The ADME properties of avanafil have been evaluated in both *in vitro* and *in vivo* studies and are consistent across multiple species including the mouse, rat rabbit, dog and monkey. The observed non-clinical pharmacokinetic properties of avanafil support the proposed dosing regimen for therapeutic use. Avanafil was rapidly and relatively well absorbed from the gastrointestinal tract after oral administration in toxicology species and humans. Avanafil distributed rapidly to systemic tissues, with high concentrations mainly in liver. The conversion of avanafil to the two major circulating human metabolites, M4 and M16 was rapid and extensive in nonclinical species and humans (early t_{max} and short t½); although in humans, avanafil still represented the major component in plasma. Although the amount of each metabolite varied among animal species (rat and dog), the metabolite profiles were similar and

there was no human unique metabolite identified. Since M4 and M16 are those metabolites whose exposure in humans is greater than 10% respect to the parent compound exposure, they were the only one characterised from the PK point of view.

CYP3A4 showed to catalyse the metabolism of avanafil, with a minor contribution by 2C. Avanafil was excreted primary into faeces mostly likely via bile. Avanafil and major metabolites had a low potential for causing pharmacokinetic drug interaction via CYP inhibition.

In vitro results showed for avanafil high membrane permeability, a modest potential for acting as P-glycoprotein substrate and a relatively modest effect regarding the potential to act as a P-gp inhibitor with Digoxin as a substrate. The *in vitro* study suggests an inhibitory effect on avanafil on P-gp and based on intestinal concentrations (maximum dose/250 ml), a clinically relevant inhibitory effect on P-gp may not be excluded. Therefore, in the absence of data on humans, the potential of avanafil to interfere with the transport of other medicinal products mediated by P-glycoprotein is reported in SmPC section 4.5 and reflected in the RMP section 1.8.

Toxicology

The non-clinical toxicology development conducted with avanafil provides a thorough profile of the product in compliance with GLPs The dosing regimen employed in these studies provided constant tissue exposures and administered doses were more than 9-fold the intended dose in humans and provide an acceptable safety margin to the proposed maximum recommended human dose of avanafil (200mg). In addition, the duration of the toxicology studies are in accordance with the current requirements and the route of administration covers the oral administration intended for clinical use.

Toxicity studies identify the liver as the primary target organ of avanafil. In this organ as well as the thyroid (which exhibited microscopic changes following chronic dosing), the main effects included body weight decreases, increased liver weight, and histopathological changes in the liver consistent with increased drug metabolizing enzyme activities are considered to be adaptive or compensatory and not adverse. It is accepted that centrilobular hepatocellular hypertrophy (related to liver enzyme induction) is not an adverse change and that extramedullary haematopoiesis is a compensatory response to decreases in red blood cell parameters. The thyroid changes are likely a compensatory response to increased metabolism of thyroid hormones by the liver. Significant adverse toxicity was only observed following the administration of high doses (2000 mg/kg/day in mice and 100 mg/Kg/day in dogs). Therefore, the NOAEL doses were 200,300, and 30 mg/kg/day in the 13-week mouse study, the 26-week rat study, and the 9-month dog study, respectively. The safety margins in terms of unbound avanafil plasma exposure (AUC) in male rats were 9x for avanafil, 56x for M4, and 1x for M16; and in dogs were 36x for avanafil.

During the development of avanafil, cardiovascular (blood pressure and QT prolongation) and ocular issues already identified with approved PDE5 inhibitors were addressed in safety pharmacology studies and in repeat-dose toxicity studies. Regarding ocular issues identified with the currently approved PDE5 inhibitors, avanafil showed low propensity to produce visual disturbances due to the selectivity versus PDE6 (100-fold less potent than at PDE5). Furthermore, no changes in electroretinograms were observed in the chronic toxicity studies at doses up to 1000mg/kg/day (26-week study in rats and 9-month study in dogs). With regards to cardiovascular issues, dogs exhibited cardiovascular effects (increased heart rate and decreased blood pressure) following administration of high doses of avanafil (100mg/kg/day). Microscopic changes were only noted in the one-week and 28-day studies, and the organs and findings noted were not consistent and were not observed at the same doses administered for longer durations (9-month study). The heart rate and blood pressure effects in animals likely represent an exaggerated pharmacological response to avanafil since the drug acts via a mechanism of vasodilatation, and that similar changes were also noted with other PDE5 inhibitors (tadalafil, vardenafil, sildenafil).

Neither a 2-year study in rats nor a 2-year study in mice revealed a carcinogenic potential of avanafil up to and including the highest dose tested.

A decrease in fertility, decreased sperm motility and an increased percentage of abnormal sperm (primarily detached sperm tails) occurred at the highest dose tested in male rats (1000 mg/kg/day). The effects on sperm parameters, including sperm motility and morphology were completely reversible after the recovery period. Effects of avanafil on female reproduction included increased oestrous cycle length and reduced fertility in female rats at 1000 mg/kg/day. The margin for avanafil was 9x and 190x over the human exposure in male and female rats, respectively. In pregnant animals, decreased foetal and pup body weight occurred in rats (with a concurrent delay in sexual maturation) at maternally toxic doses, but avanafil was not teratogenic in either rats or rabbits. Given the indication for avanafil in males only, the high dose effects on female reproduction and embryofoetal development are not relevant to intended human use. The section 4.6 of the SmPC was updated to include the lack of data on the effect on spermatogenesis in humans, the non-clinical data is referenced in section 5.3. Furthermore a study evaluating the effect on spermatogenesis in Humans will be performed as defined in the risk management plan.

The impurity I-C is specified at 0.30%, above the ICH threshold. *In vitro* genetic toxicity studies were conducted on Impurity I-C. This impurity was not genotoxic in the Ames and *in vitro* cytogenetic assay and is considered qualified in the general toxicology studies in rats and dogs.

An interim ERA presents a Phase II environmental fate and effects analysis, because the default predicted environmental concentration (PEC) of avanafil in surface water is greater than the Phase I screening level. According to the Guideline, the Phase II assessment should be conducted by evaluating the ratio of the predicted no-effect concentration (PNEC) to the PEC. For this interim ERA, measured fate and effects data for avanafil are available from several screening studies recommended by EMA (2006). So far, available data do not allow concluding definitively on the potential risk of avanafil to the environment. Certain aquatic fate and effects studies are in progress; the results from these studies will be assessed in the final ERA that will be submitted by the Applicant, although a schedule has not been provided yet. The ERA schedule will be updated upon resolution of the testing requirements. The Applicant will update the interim ERA report incorporating the additional test results required and submit it to the EMA in February 2014.

2.3.7. Conclusion on the non-clinical aspects

A nonclinical testing programme was performed, generating data on non-clinical pharmacology, pharmacokinetics and toxicology of avanafil and was considered appropriate to support the granting of a marketing authorisation.

Overall, the primary pharmacodynamics studies provided adequate evidence that avanafil is a selective PDE-inhibitor, less potent in terms of IC_{50} to the ones already approved and with higher selectivity for PDE5 versus PDE6 as compared with sildenafil, but lower as compared to tadalafil. Its selectivity for PDE5 respect to PDE1, PDE3 was similar to that showed by tadalafil, and much lower respect to PDE4 compared with tadalafil.

The general pharmacology studies showed that at concentrations comparable to the free plasma concentrations associated with the maximum tolerated dose of 200 mg, the ability to potentiate penile tumescence was demonstrated on different animal models (rabbit, dog, and monkey) but no conclusion on the faster onset respect to sildenafil can be drawn.

From the pharmacokinetic point of view, the avanafil was characterized by rapid and high oral absorption (53-69%), low to moderate oral bioavailability (1.5-30%), a t_{max} 0.5–2hr, a t½ 0.82–2.5 h, and high systemic clearance in the rat, dog, and monkey. No accumulation effect was noted.

Overall, the toxicology program revealed no new toxicity sign for this new PDE inhibitor. The slight decreased motility and increased abnormal sperm observed in rat after 9 week administration of 1000 mg/kg/day was completely resolved during the recovery period. Exposures to avanafil in pivotal toxicology studies were ≥9-fold over the human exposure. However, since the duration of the spermatogenesis cycle in humans is about 90 days, chronic dosing is more appropriate to investigate the effects of avanafil on spermatogenesis. The Applicant is conducting a study in healthy adult male subjects as detailed in the RMP.

So far, available data do not allow concluding definitively on the potential risk of avanafil to the environment. According to the Applicant, the ERA schedule will be updated upon resolution of the testing requirements, and potential risk to the environment of avanafil will be assessed with the full knowledge of the ERA. The final environmental risk assessment will be submitted to EMA in February 2014.

2.4. *Clinical aspects*

2.4.1. Introduction

The clinical development program to assess the efficacy and safety of avanafil in men with ED included 18 Phase 1 studies, 3 Phase 2 studies, and 4 Phase 3 studies. These studies evaluated the pharmacokinetics, efficacy, and safety of avanafil at doses ranging from 12.5 mg to 800 mg. The doses for which the applicant is seeking approval are 50 mg, 100 mg, and 200 mg. All of the studies of the clinical development program were conducted in various centres in the United States, with exception of one phase 1 PK study (HP-01), which included 65 young (ages 18-35 years) healthy volunteers and it was conducted in France.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- ***Tabular overview of clinical studies***

TA-01	Phase 2 Study Complete Final Clinical Study Report December 2010	To evaluate the safety and efficacy of 3 dose levels of TA-1790 given in conjunction with visual sexual stimulation in patients with ED	Randomized, single-blind, randomized, placebo- and active-controlled, crossover	Placebo SIL 50 mg tablet TA-1790 50 mg tablet TA-1790 100 mg tablet TA-1790 2 × 100 mg tablets Oral Single dose	89 males between 35 and 70 years of age with a history of mild to moderate ED for ≥6 months
TA-03	Phase 2 Study Complete Final Clinical Study Report November 2010	Primary: To evaluate the safety, efficacy, and onset of effect of TA-1790 200 mg administered at home in subjects with ED Secondary: To determine the effective duration of action of TA-1790 in the at-home setting	Randomized, active-controlled, double-blind, 3-way crossover	SIL 2 × 50 mg capsules TA-1790 2 × 100 mg capsules Oral 9–12 weeks	51 males between 35 and 70 years of age with a ≥3-month history of mild to moderate ED
TA-05	Phase 2 Study Complete Final Clinical Study Report September 2010	To evaluate the safety and efficacy of various dose levels of TA-1790 in subjects with mild to moderate ED	Randomized, placebo-controlled, double-blind, parallel	Placebo TA-1790 2 × 25 mg capsules TA-1790 2 × 50 mg capsules TA-1790 2 × 100 mg capsules TA-1790 2 × 150 mg capsules Oral 12 weeks	295 males between 35 and 70 years of age with a history of ED for ≥6 months
TA-301	Phase 3 Study Complete Final Clinical Study Report November 2010	To evaluate the safety and efficacy of TA-1790 in subjects with mild to severe ED	Randomized, double-blind, placebo-controlled, parallel	Placebo TA-1790 1 × 50 mg tablet TA-1790 2 × 50 mg tablets TA-1790 4 × 50 mg tablets Oral 4-week run-in period and a 12-week treatment period	646 males ≥18 years of age with a history of mild to severe ED for ≥6 months
TA-302	Phase 3 Study Complete Final Clinical Study Report December 2010	To evaluate the safety and efficacy of two doses of TA-1790 in the treatment of ED in adult males with type 1 or type 2 diabetes	Randomized, double-blind, placebo-controlled, parallel	Placebo TA-1790 1 × 100 mg tablet TA-1790 2 × 100 mg tablets Oral 4-week run-in period and a 12-week treatment period	390 males ≥18 years of age with a documented history of type 1 or type 2 diabetes and a history of mild to severe ED for ≥6 months
TA-303	Phase 3 Study Complete Final Clinical Study Report October 2011	To evaluate the safety and efficacy of two doses of TA-1790 in the treatment of ED in adult males following bilateral nerve-sparing radical prostatectomy	Randomized, double-blind, placebo-controlled, parallel	Placebo TA-1790 1 × 100 mg tablet TA-1790 2 × 100 mg tablets Oral 4-week run-in period and a 12-week treatment period	298 males ≥18 and ≤70 years of age with a history of ED for at least 6 months duration following bilateral nerve-sparing radical prostatectomy
TA-314	Phase 3 Study Complete Final Clinical Study Report March 2011	To evaluate the long-term safety, tolerability, and efficacy of TA-1790 in men with mild to severe ED	Open-label extension	TA-1790 50 mg tablet TA-1790 100 mg tablet TA-1790 200 mg tablet Oral 52 weeks	712 male subjects who successfully completed the treatment periods of studies TA-301 or TA-302

lodipine; BA = bioavailability; BID = twice daily; BMI = body mass index; DESI = desipramine; DOX = doxazosin; ECG = electrocardiogram; ED = erectile i; EFS = Erectile Function Domain score; ENAL = enalapril; ERY = erythromycin; h = hours; INR = international normalized ratio; KET = ketoconazole; xifloxacin; OME = omeprazole; PD = pharmacodynamics; PK = pharmacokinetic; QD = once daily; RIT = ritonavir; ROSI = rosiglitazone; SIL = sildenafil; avanafil; TAM = tamsulosin.

2.4.2. Pharmacokinetics

Eighteen clinical pharmacology studies have been completed for the avanafil development program. These studies investigated the safety, tolerability, pharmacokinetics, pharmacodynamics, bioequivalence, dose equivalence, effect of food and drug-drug interactions of avanafil in healthy subjects, as well as pharmacokinetics and pharmacodynamics of avanafil in special populations.

A total of 680 subjects participated in the clinical pharmacology program with a total of 644 being exposed to at least one dose of avanafil. Doses of avanafil used ranged from 12.5 to 800 mg for single oral dose studies, 50 to 200 mg for once daily dosing studies, and 200 mg for twice daily dosing studies. For drug-drug interactions studies, 50 mg or 200 mg doses were used alongside usual therapeutic doses of the co-administered drug of interest.

Absorption

- **Bioavailability**

After oral administration of 14 C avanafil, the radioactivity was excreted faster in urine than in faeces. The highest mean concentration of total radioactivity was observed in urine within 4 hours after dosing and in faeces, for each 24-hour interval, between 48 and 120 hours after dosing. Mean recovery of administered radioactivity was approximately 62% in faeces and 21% in urine. Faecal excretion was the major route of elimination of radioactivity. Mean recovery of the radioactive dose through 216 hours after dosing was approximately 62% in faeces and 21% in urine. The recovery of total radioactivity in urine and faeces ranged from 85% to 94%, with the exception of one subject. The data indicated that avanafil is almost completely absorbed and eliminated.

- **Bioequivalence**

The study of bioequivalence was the study **TA-020**. It was an open-label, randomized, four-period crossover study were designed to assess to determine the bioequivalence of two avanafil tablet formulations (2x100 mg Formulation I versus 2x100 mg Formulation II tablets) in the fasted state; and investigate the dose-proportionality of Formulation II avanafil tablets (1x50 mg versus 2x100 mg) in the fasted state.
Bioequivalence was concluded if the corresponding 90% CIs for the ratios of geometric LS Means of Treatment A to Treatment C were contained within the range of 80% to 125% for each of the parameters.

Statistical Comparisons of Plasma Avanafil Pharmacokinetic Parameters Following Treatment A (Formulation II) Versus Treatment C (Formulation I)

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

Treatment A = a single oral dose of two 100 mg avanafil tablets (Formulation II), fasted (Test)
Treatment C = a single oral dose of two 100 mg avanafil tablets (Formulation I), fasted (Reference)
The data for the following subjects were not included in the statistical analysis of AUC_{0-inf}, as the k_{el} values were not calculable due to one or more of the following: coefficient of determination (R^2 value) for k_{el} calculation was less than 0.8, slope was undefined, or $t_{1/2}$ was greater than half of the sampling interval: Subjects 5, 9, 12, 13, 17, and 20 (Treatment A), and Subjects 2, 4, 7, 9, 18, and 20 (Treatment C).
[a] C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented as geometric least-squares means (LS Means) with three significant figures, calculated by exponentiating the LS Means from the ANOVA. Parameters were log-transformed prior to analysis.
% Mean Ratio = 100*(test/reference).
CI = confidence interval
Source: Table 14.2.1.11 and Appendix 16.1.9

The statistical comparisons of avanafil Cmax and AUC0-inf between Treatment A (Formulation II) versus Treatment C (Formulation I) showed the 90% CIs of the geometric mean ratios of both Cmax and AUC_{0-inf} were completely within the 90% CIs of 80% to 125%. Comparable systemic exposure to M4 and M16 were also obtained between Formulations I and II under the fasted conditions. These results indicate that Formulation I is bioequivalent to Formulation II.

Distribution

The apparent volume of distribution was 47 to 83 l. **(HP-01)**. The *in vitro* protein binding of avanafil to plasma proteins was determined by ultrafiltration method in human plasma over a concentration range of 0.3 – 3.0 µg/mL. The plasma protein binding was consistent over the avanafil concentration ranges investigated. Using equilibrium dialysis, avanafil, its two major circulating metabolites M4 and M16 were shown to have plasma protein binding of ~99%, ~97% and ~81%, respectively.
The plasma protein binding was high for avanafil (≥99%) and M4 (>96%) and moderate for M16 (>80%) in these subjects, and the plasma protein binding for avanafil and its major circulating metabolites was independent of their total concentrations in plasma, age, renal and hepatic impairment.
The amount of avanafil and its metabolites in seminal fluid of healthy subjects were determined in two clinical pharmacology studies following a 200 mg avanafil dose **(TA-014 and TA-021)**. The mean amount of M16 found seminal fluid was comparable to that of M4, which was more than three times that of avanafil. The mean avanafil, M4 and M16 semen/plasma concentration ratios were fairly consistent between the two studies (approximately 0.07, 0.83, and 0.74, respectively for Study **TA-014** and 0.06, 0.70, and 0.37, respectively for Study **TA-021**). A very small fraction of the administered avanafil dose (≤0.0002%) was detected as unchanged avanafil in seminal fluid 45-90 minutes after dosing.

Table 11. Plasma Protein Binding of Avanafil, M4, and M16 in Human Subjects

Population	% Bound			Study
	Avanafil	M4	M16	
Male subjects	98.7	ND	ND	10-AVANAFIL-PK-12
Young male subjects	99.1	ND	ND	TA-014
Elderly male subjects	99.0	ND	ND	
Male subjects with normal hepatic function	99.1	97.2	84.4	TA-012
Male subjects with mild hepatic impairment	99.0	96.7	81.2	
Male subjects with moderate hepatic impairment	98.6	96.3	81.2	
Male subjects with normal renal function	99.1	97.0	80.3	TA-013
Male subjects with mild renal impairment	99.1	97.2	80.8	
Male subjects with moderate renal impairment	99.0	97.1	80.6	

ND = not determined.
Sources: 09-AVANAFIL-PK-02, 10-AVANAFIL-PK-01, 10-AVANAFIL-PK-02, and 10-AVANAFIL-PK-12

Elimination

Excretion

The excretion of avanafil were investigated in a 14C-labelled mass balance study (**TA-010**), in which a single dose of 600 mg 14C-avanafil was given to 6 healthy subjects. Mean recovery of administered radioactivity was approximately 62% in faeces and 21% in urine. Faecal excretion was the major route of elimination of radioactivity, with renal elimination playing a minimal role. Little or no total radioactivity was detected in blood and plasma after 10 hours. Maximal mean concentrations of radioactivity were observed at 1.2 hours after dosing, suggesting rapid absorption of [14C] - avanafil-related radioactivity. The mean terminal elimination t½ of unchanged avanafil in plasma was 12.7 hours, which contributed little to the total systemic exposure of avanafil.
The shorter mean t½ of total radioactivity observed in blood and plasma (between 1 and 2 hours) likely represented a distribution phase rather than a true elimination phase.

As shown in Studies **HP-01** and **TA-010**, the mean terminal elimination t½ estimates were reported from 6 to 17 hours. The large variation in t1/2 across studies was mostly due to the duration of pharmacokinetic sampling in that plasma samples were collected out to 24 hours post dose in **HP-01**, while plasma samples collection was extended out to 168 hours post dose in **TA-010**. In Study **TA-020**, the plasma samples were collected up to 24 hours post dose in 23 subjects following oral administration of the proposed commercial formulation (Formulation II, 2x100 mg tablets); avanafil t½ was approximately 3 to 5 hours. The avanafil T½ of 3 to 5 hours was verified by the fact that multiple-dose (QD or BID) administration of avanafil did not result in significant accumulation of avanafil (**TA-02 and TA-07**).

- **Metabolism**

In vitro metabolism studies indicated that avanafil was extensively metabolized by P450 isoforms, predominantly by CYP3A4, with a minor contribution by CYP2C.
In vivo, following single oral dose of 200 mg, avanafil was extensively metabolized and formed the major circulating metabolites, M4 and M16. Both M4 and M16 reached their maximum plasma levels at a median tmax of approximately 0.8 hours **(TA-014)**. The time course of the metabolites approximately paralleled avanafil. The metabolite/ parent ratios for M4 (22 to37%) and M16 (about 32%) across clinical pharmacology studies generally remained comparable and were not dose-dependent or affected by

hepatic impairment, renal impairment or age (M4 only). The ratios of M16/avanafil were slightly lower in young subject (32%) compared to elderly subjects (50 to 56%) (**TA-014**).
The M4 metabolite showed a phosphodiesterase selectivity profile similar to avanafil and an *in vitro* inhibitory potency for PDE5 at 18% of that for avanafil. Given its low plasma concentrations and lower potency against PDE5 compared to the parent compound, the contribution of M4 to the overall pharmacological activity against PDE5 after a single dose of avanafil was fairly limited, approximately 4% of total pharmacologic activity of the parent. The M16 metabolite was inactive against PDE5.
In the **TA-010** avanafil was extensively metabolized in humans; however, avanafil still represented the major radioactive component in plasma and accounted for approximately 37% of the total radioactive dose within the 0 to 12 hour interval after dosing. In pooled plasma samples, the major circulating metabolites identified were an open pyrrolidine ring carboxylic acid avanafil (M16) and monohydroxy avanafil (M4) which accounted for about 10.6% and 8.4%of the total radioactivity or 29% and 23% of the circulating concentration of unchanged avanafil, respectively. A third circulating metabolite, M27 (despyrrolidine avanafil), accounted for about 3.8% of the total radioactivity, or 10% of unchanged avanafil in humans.
Since avanafil undergoes significant and rapid metabolism, M27 is not considered a major circulating human metabolite (<10% radioactive dose). Plasma concentration-time profiles of the metabolites appeared to be similar to avanafil. The M10 and M16 metabolites were the major metabolites in faeces; and M16 was the major metabolite excreted in urine. About6% of the radioactive dose was excreted as unchanged avanafil in faecal samples. Unchanged avanafil was not detected in pooled urine samples, indicating that renal impairment might have little effect on systemic exposure to avanafil.
The chromatographic profile of the radioactivity in human plasma, urine, and faeces for this study revealed a metabolic pattern of primarily phase I metabolism, with only minor phase II metabolic species observed in the 3 matrices examined. The pyrrolidine ring appeared to be the active metabolic site because most biotransformation/structural modifications occurred on that ring. The major routes of biotransformation were proposed as the following: hydroxylation, oxidation, multiple *N*-dealkylation reactions, demethylation, and glucuronide conjugation.

Terminal elimination half live of avanafil could be estimated to be around 6 hours although different studies show a high variability, ranging from very short half-lives to up to 17 hours, with some subjects showing very long terminal half-lives (more than 50 hours).

- **Inter-conversion**

N/A.

- **Pharmacokinetics of metabolites**

See the comments of the pharmacokinetics of metabolites, in the section of metabolism.

- **Consequences of possible genetic polymorphism**

Avanafil is mainly metabolised through CYP3A4, with a minor contribution of CYP2C. Its limited contribution and the possibility to compensate lower metabolic rate via CYP3A4 make unlikely a relevant influence of genetic polymorphism on the elimination of avanafil and metabolites.

Data from food-interaction studies

A formal absolute oral bioavailability study has not been performed. The influence of food on the absorption of avanafil was studied in two studies. The **TA -020** was a Phase I, single-centre, open-label,

randomized, and four-period crossover study to assess the effect of food on the pharmacokinetics of avanafil. Subjects receiving treatment with food began eating a standardized high-fat breakfast 30 ± 5 minutes prior to dosing. Standard meals were provided uniformly to all subjects at approximately 4 and 9 hours after dosing, and an evening snack was provided approximately 12 – 13 hours after dosing. Blood samples for the determination of plasma avanafil and its metabolite concentrations were obtained from each subject at 0 (30 minutes predose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 8, 12, 18, and 24 hours postdose in each treatment period.

The absence of a food effect was concluded if the corresponding 90% CIs for the ratios of the geometric LS Means of Treatment B to Treatment A were contained within the equivalence range of 80% to 125% for each of the parameters.

Table 3. Arithmetic Mean (SD) and Geometric Mean (Geometric CV%) Pharmacokinetic Parameters for Plasma Avanafil

Group [a]	Geometric Mean PK Parameters (%CV [a])				% Geometric mean ratio (90% Confidence Interval)	
	t_{max} [b] (h)	C_{max} (ng/mL)	AUC_{0-inf} (ng.h/mL)	$t_{1/2}$ [b] (h)	C_{max}	AUC_{0-inf}
Avanafil, fasted (Treatment A)	0.75 (0.47-2.0)	2780 (34.3)	7960 (39.0)	5.1 (2.9)	Control	Control
Avanafil, fed (Treatment B)	2.0 (1.2-4.0)	1690 (32.0)	7920 (34.4)	4.5 (1.9)	61.00 (52.57-70.79)	96.20 (88.86-104.14)
Avanafil, fasted (Treatment C)	0.50 (0.50-1.3)	2930 (31.3)	7700 (35.5)	4.7 (2.9)	94.50 [c] (81.44-109.65)	106.56 [c] (97.78-116.13)
Avanafil, fasted (Treatment D)	0.50 (0.50-2.0)	635 (36.1)	1510 (39.1)	2.8 (1.7)	91.87[d] (78.26-107.84)	75.92[d] (69.58-82.85)

[a] Treatment A (2x100 mg, Formulation II, fasted); Treatment B (2x100 mg, Formulation II, fed; Treatment C (2x 100 mg, Formulation I, fasted) and Treatment D (1x50 mg, Formulation II, fasted)

[b] t_{max} is presented as median (minimum, maximum) and $t_{1/2}$ is presented as arithmetic mean (SD).

[c] Treatment C was used as the reference and Treatment A as the test.

[d] Treatment D was used as the reference and Treatment A as the test with parameters for Treatment D being dose-normalized to 200 mg avanafil.

Sources: TA-020 Post-text Tables 14.2.1.5-14.2.1.8 and 14.2.1.10-14.2.1.12

The statistical comparison of avanafil Cmax for Treatment B (fed) versus Treatment A (fasted) showed that the 90% CIs of the geometric LS Means ratio was outside the 80% to 125% range. The % mean ratio of avanafil untransformed Cmax of 61.00% suggested that mean maximum avanafil exposure was lower following avanafil administered under fed versus fasted conditions. The difference of Tmax between the treatment A (0, 75 (0, 47-2, 0)) and the treatment B (2, 0 (1, 2-4, 0)) is significantly different.

The other study for investigates the food effect on the pharmacokinetic of avanafil, after a high fat meal was the **HP-01**. Avanafil was given to the 6 volunteers who received 100 mg avanafil under fasting condition.

Absorption of avanafil was delayed in the presence of food with T max observed between 1.25 and 4 hours compared to 0.25 in the fasting state. The difference was not statically significant Cmax decreased by 24 %. This effect is supported by the 90 % confidence intervals (0.56-0.97) which are outside the (0.80-1.25) range. Conversely, food increased the mean AUC 0-t and AUC 0- inf, by the 25 % and 14 % respectively. This increase is supported by the 90 % confidence intervals, which are respectively (1.10-1.39) and (0.90-1.45). Mean terminal half-life of avanafil is lower after food intake (about 9 h) than in the fasted state (about 17 h). However, high mean value of T ½ in the fasted state can be mostly attributed to the high t ½ (49h) of one subject. When comparing the corresponding median values, which

are more suitable for the comparison between two treatments, it turns that the observed differences are weak (12h versus 10h).

Table 10. Summary statistics for pharmacokinetic parameters of TA-1790 after single oral administration of increasing doses of TA-1790 from 12.5 to 800 mg

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 (Fasted)	Mean	1156.73	0.63	16.69	2909.93	3451.09	6.0	0.037
	SD	128.24	0.25-1.25	16.51	480.60	844.74	4.7	0.035
200	Mean	2593.67	0.88	8.91	7688.58	8165.07	21.0	0.039
	SD	727.81	0.50-1.00	4.60	2606.78	3104.47	19.2	0.034
400	Mean	5993.67	0.75	19.84	14868.97	17363.12	33.1	0.037
	SD	1380.01	0.75-1.00	28.04	2924.20	6510.88	29.4	0.031
600	Mean	7248.50	0.75	11.78	20715.60	22388.05	62.8	0.051
	SD	987.87	0.50-1.25	5.34	6115.30	6695.51	40.7	0.034
800	Mean	6301.67	1.25	8.29	23481.27	24456.62	67.6	0.046
	SD	1211.59	0.50-1.50	4.78	3940.42	3778.23	70.3	0.048

* median and range

In conclusion, the Cmax values were approximately 39% lower under fed conditions and the median tmax was delayed from less than 1 hour in fasted conditions to 2 hours (range 1.2 - 4h) after food intake.

Given the type of medicinal product, route of administration, and target population the section 4.2 Posology in the PI was modified to advice of the delay on the onset of the effect if avanafil is taken with food, this was considered acceptable by the CHMP.

Dose proportionality and time dependencies in special populations

- **Impaired renal function**

The impaired renal function was studied in the **TA-013**. The study compared the PK of avanafil in subjects with mild and moderate renal impairment (24 in total) to subjects with normal renal function and the secondary objective was to assess the safety and tolerability of avanafil in subjects with mild and moderate renal impairment. The design was open-label, parallel-group, single dose, nonrandomized study. The study population consisted of adult male subjects, 52 – 78 years of age, who were medically healthy with no clinically significant screening results (except for renal insufficiency in subjects in Cohorts 2 and 3). Subjects with normal renal function (Cohort 1) were to have estimated CLcr of ≥ 80 mL/min. Subjects with renal impairment (Cohorts 2 and 3) met the following additional criteria: a) stable renal

impairment; b) subjects with mild renal impairment (Cohort 2) had a CLcr of ≥ 50 to < 80 mL/min; and c) subjects with moderate renal impairment (Cohort 3) had a CLcr of ≥ 30 to < 50 mL/min.

Statistical Comparisons of Plasma Avanafil, M4 Isomers, and M16 Isomers Pharmacokinetic Parameters for Mild Renal Impairment (Cohort 2) Versus Normal Renal Function (Cohort 1)

		Geometric LS Means [a]		Confidence Interval		
Parameter		Mild Renal Impairment	Normal Renal Function	(90% Confidence)		% Mean Ratio [a]
C_{max} (ng/mL)	Avanafil	2750	2650	(73.34, 147.53)		104.02
	M4	568	489	(85.51, 157.93)		116.21
	M16	1120	840	(91.76, 193.93)		133.40
AUC_{0-t} (ng*hr/mL)	Avanafil	7380	7950	(67.93, 126.74)		92.79
	M4	2510	2310	(86.31, 137.43)		108.91
	M16	3380	2450	(97.79, 195.24)		138.18
AUC_{0-inf} (ng*hr/mL) [b]	Avanafil	7300	8290	(61.43, 126.31)		88.09
	M4	2620	2440	(87.42, 131.90)		107.38
	M16	3640	2460	(104.44, 210.57)		148.30
		Treatment Median [c]		(95% CI)	Median Difference [d]	P-Value
t_{max} (hr)	Avanafil	0.50	0.63	(-0.25 , 0.00)	0.000	0.2954
	M4	0.75	0.75	(-0.75 , 0.25)	0.000	0.5680
	M16	0.75	0.88	(-0.50 , 0.25)	-0.125	0.3499
$t_{1/2}$ (hr) [b]	Avanafil	4.7	5.9	(-6.75 , 2.97)	-1.209	0.7768
	M4	5.8	7.4	(-3.39 , 1.05)	-0.967	0.7469
	M16	6.4	6.3	(-3.36 , 2.57)	-0.144	0.9431

Cohort 1: Normal renal function (CLcr ≥ 80 mL/min) (reference)
Cohort 2: Mild renal impairment (CLcr ≥ 50 to < 80 mL/min) (test)
[a.] C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented as geometric least-squares (LS) means with three significant figures, calculated by exponentiating the LS means from the ANOVA. Parameters were log-transformed prior to analysis. % Mean Ratio = 100*(test/reference)
[b.] The data for the following subjects were not included in the statistical analysis of AUC_{0-inf} or $t_{1/2}$, as the k_{el} values were not calculable due to one or more of the following: coefficient of determination (R^2 value) for k_{el} calculation was less than 0.8, slope was undefined, or $t_{1/2}$ was greater than half of the sampling interval: Avanafil: Subjects 1117, 1121, 1125, and 1126 (Cohort 1), Subject 1205 (Cohort 2); M4: Subjects 1121 and 1126 (Cohort 1); M16: Subjects 1121 and 1126 (Cohort 1), Subject 1229 (Cohort 2)
[c.] t_{max} and $t_{1/2}$ are presented with two significant figures.
[d.] The comparison was conducted using the Wilcoxon Rank Sum test. CI for the difference between two medians was calculated using the Hodges-Lehmann estimate.
Source: Tables 14.2.1.4, 14.2.1.5, 14.2.1.11.1, and 14.2.1.12, Tables 14.2.2.4, 14.2.2.5, 14.2.2.11.1, and 14.2.2.12, and Tables 14.2.3.4, 14.2.3.5, 14.2.3.11.1, and 14.2.3.12

Statistical Comparisons of Plasma Avanafil, M4 Isomers, and M16 Isomers Pharmacokinetic Parameters for Moderate Renal Impairment (Cohort 3) Versus Normal Renal Function (Cohort 1)

		Geometric LS Means [a]		Confidence Interval	
Parameter		Moderate Renal Impairment	Normal Renal Function	(90% Confidence)	% Mean Ratio [a]
C_{max} (ng/mL)	Avanafil	2650	2650	(70.48, 141.78)	99.96
	M4	490	489	(73.80, 136.29)	100.29
	M16	1050	840	(85.77, 181.27)	124.69
AUC_{0-t} (ng*hr/mL)	Avanafil	8960	7950	(82.53, 153.97)	112.72
	M4	2760	2310	(94.92, 151.14)	119.77
	M16	4480	2450	(129.74, 259.04)	183.33
AUC_{0-inf} (ng*hr/mL) [b]	Avanafil	9850	8290	(80.86, 174.92)	118.93
	M4	3300	2440	(109.66, 167.54)	135.55
	M16	5780	2460	(163.59, 338.66)	235.37

		Treatment Median [c]		(95% CI)	Median Difference [d]	P-Value
t_{max} (hr)	Avanafil	0.75	0.63	(0.00 , 0.25)	0.000	0.3094
	M4	0.88	0.75	(-0.25 , 1.00)	0.250	0.3785
	M16	1.0	0.88	(-0.25 , 0.50)	0.250	0.2538
$t_{1/2}$ (hr) [b]	Avanafil	6.0	5.9	(-6.47 , 3.35)	-0.488	0.7133
	M4	6.3	7.4	(-3.13 , 3.65)	0.166	0.9431
	M16	6.2	6.3	(-3.50 , 4.27)	0.749	0.6889

Cohort 1: Normal renal function (CLcr ≥ 80 mL/min) (reference)
Cohort 3: Moderate renal impairment (CLcr ≥ 30 to < 50 mL/min) (test)
[a.] C_{max}, AUC_{0-t} and AUC_{0-inf} are presented as geometric least-squares (LS) means with three significant figures, calculated by exponentiating the LS means from the ANOVA. Parameters were log-transformed prior to analysis. % Mean Ratio = 100*(test/reference)
[b.] The data for the following subjects were not included in the statistical analysis of AUC_{0-inf} or $t_{1/2}$, as the k_{el} values were not calculable due to one or more of the following: coefficient of determination (R^2 value) for k_{el} calculation was less than 0.8, slope was undefined, or $t_{1/2}$ was greater than half of the sampling interval: Avanafil: Subjects 1117, 1121, 1125, and 1126 (Cohort 1) and Subjects 1324, 1334, and 1335 (Cohort 3); M4: Subjects 1121 and 1126 (Cohort 1) and Subject 1324 (Cohort 3); M16: Subjects 1121 and 1126 (Cohort 1) and Subjects 1324 and 1335 (Cohort 3)
[c.] t_{max} and $t_{1/2}$ are presented with two significant figures.
[d.] The comparison was conducted using the Wilcoxon Rank Sum test. CI for the difference between two medians was calculated using the Hodges-Lehmann estimate.
Source: Tables 14.2.1.4, 14.2.1.6, 14.2.1.11.2, and 14.2.1.13, Tables 14.2.2.4, 14.2.2.6, 14.2.2.11.2, and 14.2.2.13, and Tables 14.2.3.4, 14.2.3.6, 14.2.3.11.2, and 14.2.3.13

There was no apparent effect of renal function on the pharmacokinetic parameters of avanafil and M4 metabolite, while C_{max} and AUC_{0-inf} of M16 were approximately 33% and 48% higher, respectively, in subjects with mild renal impairment compared to normal renal function. The M16 mean Cmax and AUC_{0-inf} were approximately 25% and 135% higher, respectively, in subjects with moderate renal impairment compared to normal renal function. The plasma concentration ratios of M4/avanafil or M16/avanafil were fairly similar among the subjects with or without renal impairment, suggesting that the mild or moderate renal impairment had little impact on the metabolite/avanafil ratios following a single oral dose of avanafil.

In conclusion, in mild renal impairment there was no apparent effect on avanafil pharmacokinetic parameters while C_{max} and AUC_{0-inf} of M16 were approximately 33% and 48% higher, respectively, in subjects with mild renal impairment compared to normal renal function. The M16 mean C_{max} and AUC_{0-inf} were approximately 25% and 135% higher, respectively, in subjects with moderate renal impairment compared to normal renal function. These results should be interpreted in light of the limited or absent activity of metabolites M4 and M16 respectively. The pharmacokinetics of avanafil in patients with severe renal disease has not been studied, and therefore the product is contraindicated to patients with severe renal impairment in the SmPC.

- **Impaired hepatic function**

The study **TA-012** was the primarily aimed to assess the single dose PK of avanafil in subjects with hepatic impairment and in healthy control subjects. The secondary objectives were to evaluate the safety

and tolerability of avanafil in subjects with hepatic impairment. The study design was an open label, nonrandomized, single-dose, parallel-cohort, matched-control study. In this study participated 27 subjects (nine subjects per cohort) were to be enrolled and dosed to achieve a total of 24 completed subjects (eight subjects per cohort).

The effect of hepatic impairment on the pharmacokinetics of avanafil was investigated in patients with mild (Childs-Pugh Class A) and moderate (Childs-Pugh Class B) hepatic impairment compared to healthy subjects following a 200 mg dose of avanafil.

Cohort	**No. of subjects**	**Hepatic function**	**Child-Pugh class (score)**
1	8	Normal	NA
2	8	Mild impairment	A (5-6)
3	8	Moderate impairment	B (7-9)

The Cmax and $AUC_{0\text{-}inf}$ of avanafil and M4 were similar between subjects with mild hepatic impairment and normal hepatic function, while C_{max} and $AUC_{0\text{-}inf}$ of M16 were higher by approximately 37% and 50%, respectively; in mild hepatic impairment subjects compared to subjects with normal hepatic function.

Mean avanafil, M4, and M16 Cmax was approximately 57%, 54% and 28%, respectively, lower in patients with moderate hepatic impairment compared to subjects with normal hepatic function, while $AUC_{0\text{-}inf}$ was mostly similar between the two groups of subjects. High protein binding for avanafil (>99%) and M4 (>96%) and moderate protein binding for M16 (81% to 84%) was observed in subjects with normal, mild and moderately impaired hepatic function, indicating that mild or moderate hepatic impairment did not affect the plasma protein binding of avanafil, M4 or M16.

Statistical Comparisons of Plasma Avanafil, M4, and M16 Isomers Pharmacokinetic Parameters: Mild Hepatic Impairment Versus Normal Hepatic Function

		Geometric Least-Squares Means[a]		Confidence Intervals	
Pharmacokinetic Parameters		**Mild Hepatic Impairment**	**Normal Hepatic Function**	**90% Confidence**	**% Mean Ratio***
C_{max} (ng/mL)	Avanafil	2390	2480	(62.61, 147.34)	96.05
	M4	442	456	(61.92, 151.60)	96.89
	M16	894	653	(89.65, 209.48)	137.04
AUC_{0-t} (ng*hr/mL)	Avanafil	8120	7730	(72.96, 151.55)	105.15
	M4	2140	2150	(72.06, 137.69)	99.61
	M16	2540	1960	(93.07, 180.54)	129.63
AUC_{0-inf} (ng*hr/mL)[b]	Avanafil	9050	9060	(67.08, 148.78)	99.90
	M4	2320	2290	(75.92, 134.41)	101.02
	M16	3050	2040	(102.74, 218.74)	149.91

		Treatment Median				
		Mild Hepatic Impairment	**Normal Hepatic Function**	**95% CI**	**Median Difference[c]**	**P-value**
t_{max} (hr)	Avanafil	0.50	0.50	(0.00 , 1.25)	0.000	0.5227
	M4	0.75	0.63	(-0.25 , 1.05)	0.000	0.6161
	M16	0.50	0.63	(-0.25 , 0.50)	0.000	1.0000
$t_{1/2}$ (hr)[b]	Avanafil	6.9	6.4	(-4.32 , 2.50)	0.012	1.0000
	M4	7.5	6.5	(-1.36 , 1.45)	0.880	0.3184
	M16	6.2	7.7	(-5.55 , 1.53)	-1.402	0.6366

Cohort 1: Normal hepatic function (reference)
Cohort 2: Mild hepatic impairment (test)
[a] C_{max} , AUC_{0-t} , and AUC_{0-inf} are presented as geometric least-squares (LS) means, calculated by exponentiating the LS means from the ANOVA. Parameters were log-transformed prior to analysis.
[b] The data for the following subjects were not included in the statistical analysis of AUC_{0-inf} , as the k_{el} values were not calculable due to one or more of the following: coefficient of determination (R^2 value) for k_{el} calculation was less than 0.8, slope was undefined, or $t_{1/2}$ was greater than half of the sampling interval.
Avanafil: Subjects 1116 and 1132 (Cohort 1), Subjects 1211 and 1223 (Cohort 2)
M16: Subject 1132 (Cohort 1), Subjects 1211, 1223, 1230, and 1236 (Cohort 2)
[c] The comparison was conducted using the Wilcoxon Rank Sum test. CI for the difference between two medians were calculated using the Hodges-Lehmann estimate.
% Mean Ratio = 100(test/reference).
C_{max}, $AUC_{0-t}$and AUC $_{0-inf}$, values are presented with three significant figures. $t_{1/2}$ is presented with two significant figures.
Source: Tables 14.2.1.11.1, 14.2.2.11.1, 14.2.3.11.1, 14.2.1.12, 14.2.2.12, and 14.2.3.12

Statistical Comparisons of Plasma Avanafil, M4, and M16 Isomers Pharmacokinetic Parameters: Moderate Hepatic Impairment Versus Normal Hepatic Function

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

Cohort 1: Normal hepatic function (reference)
Cohort 3: Moderate hepatic impairment (test)
[a.] C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented as geometric least-squares (LS) means, calculated by exponentiating the LS means from the ANOVA. Parameters were log-transformed prior to analysis.
[b.] The data for the following subjects were not included in the statistical analysis of AUC_{0-inf}, as the k_{el} values were not calculable due to one or more of the following: coefficient of determination (R^2 value) for k_{el} calculation was less than 0.8, slope was undefined, or $t_{1/2}$ was greater than half of the sampling interval.
Avanafil: Subjects 1116 and 1132 (Cohort 1), Subjects 1303, 1309, and 1335 (Cohort 3)
M4: Subjects 1303, 1309, and 1335 (Cohort 3)
M16: Subject 1132 (Cohort 1), Subjects 1301, 1303, 1305, 1309, and 1335 (Cohort 3)
[c.] The comparison was conducted using the Wilcoxon Rank Sum test. CI for the difference between two medians were calculated using the Hodges-Lehmann estimate.
% Mean Ratio = 100(test/reference).
C_{max}, AUC_{0-t},and AUC_{0-inf}, values are presented with three significant figures. $t_{1/2}$ is presented with two significant figures.
Source: Tables 14.2.1.11.2, 14.2.2.11.2, 14.2.3.11.2, 14.2.1.13, 14.2.2.13, and 14.2.3.13

In the study TA-012 the exposure to plasma avanafil and M4 was similar between subjects with mild hepatic impairment and those with normal hepatic function. Moreover, the time to reach Cmax (i.e. tmax) and t1/2 values were not statistically different between the two groups of subjects. Exposure to plasma M16 was approximately 30 to 50% higher in subjects with mild hepatic impairment compared to those with normal hepatic function.

The exposure to plasma avanafil, M4, and M16 as measured by Cmax was approximately 28 to 57% lower in moderate hepatic impairment subjects compared to those with normal hepatic function. However, mean AUC0-inf values were similar between the two groups of subjects and the differences in median tmax and t1/2 values for Avanafil between the two groups of subjects were not statistically significant.

Plasma protein binding was independent of hepatic function.

Therefore, dose adjustments are not required in patients with mild to moderate hepatic impairment.

Avanafil has not been studied in patients with severe hepatic impairment and therefore the product is contraindicated to patients with severe hepatic impairment in the SmPC.

- **Gender**

No studies were performed in women. Given the type of medicinal product, and target population this was considered acceptable by the CHMP.

- **Race**

No PK analysis were performed based on different races, this was considered acceptable by the CHMP.

- **Weight**

No PK analysis were performed based regarding body weight, this was considered acceptable by the CHMP.

- **Elderly**

Study **TA-014** was a single-center, open-label, non-randomized, two-cohort, single-dose PK study. Healthy young (18 - 45 years, inclusive) non-vasectomised male subjects (Cohort A, 18 enrolled to have at least 14 complete) and healthy elderly (65 year or older) male subjects (Cohort B, 14 enrolled to have at least 12 complete) were enrolled and given a single oral dose of 200 mg avanafil tablets following an overnight fast. Seminal fluid and plasma were collected from Cohort A, whereas only plasma samples were collected from Cohort B. All subjects were confined at the Clinical Research Unit approximately 12 - 16 hours prior to the avanafil administration and remained confined for approximately 24 hours following oral dosing (Day 1).

The primary objectives of this study were to determine avanafil semen exposure; to determine the acute effect of avanafil on sperm motility, count, density, morphology, vitality, ejaculate volume and viscosity; and to assess the effects of age on the PK of avanafil and its metabolites following a single oral dose of avanafil 200 mg.

	ELDERLY MALES (> 65)			YOUNG MALES (18-45)		
	Avanafil	M4	M16	Avanafil	M4	M16
C_{max} (µg/l)	2680	575	1330	2670	578	878
AUC0-t (ng*hr/mL)	7650	2730	3950	6810	2420	2150
AUC_{inf} (µg.h/l)	7630	2860	4240	7750	2760	2500
Tmax (hr)	0.75 (0.50,0.78)	0.78 (0.50,2.0)	0.78 (0.55,1.5)	0.56 (0.25, 1.0)	0.76 (0.50, 1.5)	0.57 (0.50, 1.0)
$t_{½}$ (h)	5.6 ± 3.1	6.9 ± 1.5	7.2 ± 1.5	6.5 ± 2.9	6.9 ± 1.9	7.9 ± 2.5

Systemic exposures to avanafil, M4 and M16 were generally comparable in elderly (65 years or over) and young (18-45 years) subjects. The absorption and metabolism of avanafil to M4 and M16 was not greatly affected by age, as the median tmax and mean t½ values for avanafil, M4 and M16 were comparable between elderly and young subjects. The plasma Cmax and AUC0-inf ratios of M4/avanafil were fairly similar among young and elderly subjects, while the ratios of M16/avanafil were slightly lower in young subject (32%) compared to elderly subjects (50 to 56%). Plasma protein binding of avanafil for the two age groups was high (~99%), and it was independent of age and avanafil plasma concentrations. Collectively, the pharmacokinetics of avanafil in healthy elderly subjects (65 years or over) were comparable to those of younger males (18-45 years of age). No dose adjustment is needed for avanafil based on age.

A single oral 200 mg dose of avanafil appeared to be similarly tolerated by the young male subjects (18 - 45 years, inclusive) and elderly male subjects (≥ 65 years) in this study.

The pharmacokinetics of avanafil and its metabolites were generally comparable in elderly and young subjects, but the studies were conducted with a few patients older than 75 or very old.

- **Children**

The Applicant has been granted a class waiver for the ED indication on the bases that the condition (ED) does not normally occur in the paediatric population.

Pharmacokinetic interaction studies

In vitro

Caco-2 and P-glycoprotein transporter (Pgp)

The purpose of the study was to evaluate the bidirectional Caco-2 permeability for avanafil, in the context of the Biopharmaceutics Classification System (BCS). For this purpose, BCS high permeability (Metoprolol) and low permeability (Ranitidine) were included, and results compared to those for avanafil. Digoxin was included as a positive P-glycoprotein substrate control.

In Caco-2 cell monolayers, avanafil was observed to have high passive permeability with a mean absorptive, apical to basolateral apparent permeability (Papp) value of 44.6 × 10-6 cm/sec. The mean, secretory, basolateral to apical, Papp value of 73.4 × 10-6 cm/sec and an efflux ratio (RE) <2.0 suggests that avanafil is a weak substrate of P-glycoprotein.

Additional studies conducted in multi-drug resistance gene (MDR1) and Madin-Darby canine kidney wild type (MDCK-WT) cells showed avanafil to be a weak PGP substrate. The efflux ratio of ratios (RE (MDR1)/RE (MDCK-WT), for avanafil was estimated to be 1.8, which is below the significance value of 2 suggested by the FDA to definitively declare it a human PGP substrate.

With regards to the potential for avanafil to act as a PGP inhibitor with digoxin as a substrate, the effect was relatively modest and there was no clear indication that avanafil is an inhibitor of PGP. With regards to the potential for drug-drug interactions *in vivo*, the possibility of interaction of avanafil with digoxin appeared to be remote.

Based on these *in vitro* results, *in vivo* clinical pharmacology studies of the effect of PGP inhibition on avanafil pharmacokinetics or the effect of avanafil on PGP substrates such as digoxin were not considered necessary, the observed effect was relatively modest and there is no clear indication that avanafil is an inhibitor of PGP. While the PGP activity precludes its definitive designation in the context of the BCS, its overall BCS classification is likely Class I or Class II, depending on dose administered compared to its solubility value at pH 7.

Human Cytochrome P450 isoforms

Two different *in vitro* methods (immunoinhibition and metabolism by recombinant human cytochrome P450) were used to assess metabolism of avanafil by P450 isoforms. The formation of the major metabolites of avanafil was catalysed primarily by CYP3A4, with a minor contribution by CYP2C.

For CYP1A1/2-, CYP2A6-, CYP2B6-, and CYP2E1-catalyzed reactions, no half maximal inhibitory concentration (IC50) could be determined for up to 100 µM avanafil. Based on the inhibition constants (Ki) and avanafil maximum observed plasma drug concentrations (Cmax) at 200 mg(2030 ng/mL or 4.2

μM), there is a low potential for drug interactions with substrates ofCYP1A1/2, CYP2A6, CYP2E1, and CYP2B6; likely interaction with substrates of CYP2C19; and possible interaction with substrates of CYP3A4, CYP2D6 and CYP2C8/9.

The metabolites of avanafil (M4, M16 and M27), also demonstrated a low potential to inhibit the activities of CYPs 1A, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4.

Based on these *in vitro* findings, clinical pharmacology studies of the effect of CYP3A4inhibitors on avanafil pharmacokinetics and the inhibitory effect of avanafil on the pharmacokinetics of CYP2C9, CYP2D6, CYP2C19, CYP2C8 and CYP3A4 substrates were therefore evaluated in the clinical pharmacology program.

In vivo

Studies of drug interactions

The study **TA-011** was a single-center, open-label, randomized, one sequence crossover, three parallel group study to evaluate the effect of the moderate (erythromycin) and strong CYP3A4 inhibitors (ketoconazole and ritonavir) on the safety and pharmacokinetics of avanafil in healthy male subjects. A total of 44 subjects (mean age 27.9 years; range 21.0 - 43.0 years) were enrolled and 41 subjects completed the study.

Avanafil plus Ketoconazole

Ketoconazole (400 mg daily), a selective and highly potent inhibitor of CYP3A4, increased avanafil 50 mg single dose exposure (AUC) and Cmax equal to 14-fold and 3-fold, respectively and prolonged the half-life of avanafil to approximately 9 hours.

Avanafil plus Erythromycin

Erythromycin (500 mg twice daily) increased avanafil 200 mg single-dose Cmax and AUC equal to approximately 2 fold and 3-fold, respectively, and prolonged the half-life of avanafil to approximately 8 hours.

Avanafil plus ritonavir

Ritonavir (600 mg twice daily), a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9, increased avanafil 50 mg single-dose Cmax and AUC equal to approximately 2-fold and 13-fold, and prolonged the half-life of avanafil to approximately 9 hours.

Avanafil is a substrate metabolised by CYP3A4. Therefore, a formal contraindication is included in the case of concomitant use of avanafil and potent CYP3A4 inhibitors in the SmPC. Precaution to patients taking moderate inhibitors of interaction between avanafil and moderate CYP3A4 inhibitors has been included in section 4.5 of the SmPC.

Study **TA-04** was a double-blind, randomized, 3-way crossover study to assess the hemodynamic response to sublingual glyceryltrinitrate in subjects receiving avanafil, sildenafil citrate, or placebo. Following a single oral dose of 100 mg sildenafil citrate, 200 mg avanafil, or placebo, subjects were challenged with 1 Nitrostat (glyceryltrinitrate tablet, USP) 0.4 mg (1/150 grain) administered sublingually.

Avanafil with glyceryltrinitrate

The conclusions of this study were avanafil and sildenafil were shown to potentiate the hypotensive effect of nitrates. Overall, 11 (12%) subjects with placebo, 15 (15%) subjects with avanafil, and 28 (29%) subjects with sildenafil had clinically significant drops in standing SBP (30 mmHg) after glyceryltrinitrate administration. Clinically significant drops of blood pressure (>30 mmHg) after a 0,4 mg glyceryltrinitrate tablet were more frequent if avanafil or sildenafil had been taken before. The number (%) of subjects with symptomatic hypotension AEs after administration of glyceryltrinitrate was 11 (11%) for placebo, 24 (24%) for avanafil, and 26 (27%) for sildenafil. Thus, the occurrence of symptomatic hypotension AEs in male subjects administered avanafil coadministered with a sublingual dose of glyceryltrinitrate appears comparable to that of sildenafil with glyceryltrinitrate.

The SmPC has in section 4.4 a special warning on the hypotensive effect of nitrates, furthermore in section 4.5 includes recommendation on the possible use of nitrates in case of a cardiovascular urgency patients that have taken a dose of avanafil. This advice also includes the possible duration of the hypotensive additive effect.

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

Groups 1, 2, 3, 4, and 5 = Glyceryl trinitrate at 12, 8, 4, 1, and 0.5 hrs post study drug administration, respectively.
N = 14-16, 15, 22-23, 21-23, and 23-24 for Groups 1, 2, 3, 4, and 5, respectively.
* significant difference from placebo
§ significant difference from sildenafil citrate
Sources: TA-04 Post-text Tables 14.2.1.1-14.2.1.8

The study **TA-016** was a single-center, double-blind, randomized, placebo-controlled, 2-way crossover study to assess the potential interaction between avanafil and warfarin in healthy male subjects. The primary objective of this study was to investigate the effect of avanafil on the pharmacokinetics and

pharmacodynamics (prothrombin time [PT] and international normalized ratio [INR]) of warfarin. The secondary objectives were to assess the effect of avanafil on platelet aggregation and to assess the safety and tolerability of co-administration of avanafil and warfarin. In addition, the effect of avanafil on colour discrimination was assessed. In total, 24 subjects were enrolled and 23 subjects completed the study.

Avanafil and warfarin

The Coax and AUC0-inf of R- and S-warfarin were not altered by co-administration with avanafil, as the 90% CI of the geometric LS mean ratios of warfarin + avanafil and warfarin + placebo were inside the 80% to 125% range. R- and S-warfarin tmax were not altered in the presence of avanafil.

The E_{MA} and AUEC0-168 of PT and INR changes from baseline were not altered by co administration with avanafil, as the 90% CI of the geometric LS mean ratios of warfarin + avanafil and warfarin + placebo were inside the 80% to 125% range.

The geometric LS mean ratios of platelet aggregation parameters M_{ein} and E_{MA} between warfarin + avanafil and warfarin + placebo were completely within the 80 to 125% range. Moreover, mean changes from baseline platelet aggregation, ranging from 2.6 to 11.8% following warfarin + avanafil and ranging from 2.3 to 14.4% following warfarin + placebo, were similar.

The analytical parameters of the Farnsworth-Mussel 100-Hue Test included total error score (a measure of the gross errors), square root transformed total error score, the C index (Confusion index, a measure of severity of a color loss), the S-index (Scatter index, a measure of degree of randomness or selectivity in observers' arrangement), and the Angle score (a measure of type of a color loss). There was no statistically significant result in comparisons of post-dose (0.67 hour) values between the two treatments. Comparisons on changes from baseline between the two treatments in untransformed total error score, C- and S-indices, and the Angle, did not reach statistical significance either. One marginally significant p-value was observed in mean change in square root transformed total error score in the analysis excluding an outlier. The overall results are well below any area of clinical concern. There were no suggestions of any subtle color deficiencies of any type following the warfarin+avanafil treatment compared to warfarin+placebo.

Co-administration of avanafil with warfarin had no effect on pharmacokinetics of R- or S warfarin or pharmacodynamics (PT, INR, and platelet aggregation) of warfarin. No impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-Hue Test was observed in this study. Once daily 200 mg oral dose of avanafil co-administered with a single 25 mg dose of warfarin was generally well tolerated by the healthy male subjects. In the TA-016, there was no significant effect of avanafil on the PK of R- or S-warfarin after a single dose of warfarin

The anticoagulation therapy has recently changed, and new drugs have been approved for the same or similar use, e.g. dabigatran, rivaroxaban and apixaban. Its metabolism is determined by the CYP3A4. A concern was raised regarding the possible interaction of avanafil with new anticoagulants and its clinical relevance. The Applicant discussed clopidogrel (an anti-platelet agent) and dabigatran (a direct thrombin inhibitor), concluding that currently there is no evidence to support any interaction of clinical relevance between either clopidogrel or dabigatran and any PDE5 inhibitor. Although specific interactions of avanafil with rivaroxaban and apixaban (both CYP3A4 substrates) have not been studied, an interaction is not expected. This was considered is acceptable by the CHMP.

The Study **TA-017** was a single-center, double-blind, randomized, placebo-controlled, two-cohort, two-period crossover study to assess the hemodynamic interactions between avanafil and two

α-adrenergic blockers (doxazosin and tamsulosin) in 48 (24 in each cohort) healthy male subjects (age 46.5 years; range 40 – 61 years).

Avanafil and doxazosin

Subjects who entered into Cohort A received oral doses of doxazosin QD in the morning:1 mg for 1 day (Day 1), 2 mg for 2 days (Days 2 to 3), 4 mg for 4 days (Days 4 to 7), and 8 mg for 11 days (Days 8 to 18). On Days 15 and 18, subjects also received a single oral dose of either avanafil 200 mg or placebo, according to the treatment randomization code. The avanafil or placebo doses were administered 1.3 hours after the doxazosin administration on Days 15 and 18, which would allow doxazosin (tmax ~2 hours) and avanafil(tmax ~0.7 hours) to reach their peak plasma concentrations at approximately the same time.

The largest mean standing SBP decreases following co-administration of doxazosin with avanafil occurred from Hours 0.5 to 1.75, ranging from -3.6 to 0.3 mmHg. Mean standing SBP changes from baseline following placebo ranged from -4.5 to +1.6 mmHg over the same period. The largest mean standing DBP changes following avanafil occurred from Hours 0.5 to 1.25, and ranged from -8.5 to -5.2 mmHg. Mean DBP changes from baseline following placebo ranged from -0.5 to +1.9 mmHg over the same period. The largest mean changes in standing pulse rate in the immediate post-dose period following avanafil occurred from hours 0.25 to 1.0, ranging from +6.4 to +10.2 bpm. Mean pulse rate changes from baseline following placebo ranged from -5.0 to -3.2 bpm over the same period.

No statistically significant differences were observed in the maximum change from baseline in standing SBP ($p = 0.2114$) or in the AUEC0-12 for standing SBP ($p = 0.9737$) following avanafil + doxazosin versus placebo + doxazosin. Statistically significant differences in the maximum change from baseline in standing DBP ($p = 0.0003$) and the AUEC0-12 for standing DBP ($p = 0.0137$) were observed following avanafil versus placebo. The differences in the LSM for maximum change in standing DBP and AUEC0-12 for standing DBP were -6.42 mmHg and -32.17 mmHg•h, respectively. Likewise, statistically significant differences in the maximum change from baseline in pulse rate ($p = 0.0002$) and the AUEC0-12 for standing pulse rate ($p = 0.0006$) were observed following avanafil versus placebo. The differences in the LSM for maximum change in standing pulse rate and AUEC0-12 for pulse rate were +7.21 bpm and +44.54 bpm•h, respectively.

A highly statistically significant difference in the maximum change from baseline in supine SBP ($p = 0.0005$) was observed following avanafil+doxazosin versus placebo+doxazosin. The difference in the LSM was -6.00 mmHg. No statistically significant difference was observed in the AUEC0-12 for supine SBP ($p = 0.0968$) following avanafil versus placebo; the 95% CI of the difference contained zero for this comparison. Highly statistically significant differences in the maximum change from baseline in supine DBP ($p = 0.0015$) and the AUEC0-12 for supine DBP ($p = 0.0034$) were observed following avanafil versus placebo. The differences in the LSM for maximum change in supine DBP and AUEC0-12 for supine DBP were -3.58 mmHg and -31.40 mmHg•h, respectively. No statistically significant difference was observed in maximum change from baseline in supine pulse rate ($p = 0.2564$) following avanafil versus placebo; the 95% CI of the difference contained zero for this comparison. However, a highly statistically significant difference in the AUEC0-12 for supine pulse rate ($p < 0.0001$) was observed. The difference in the LSM for supine pulse rate AUEC0-12 was +45.84 bpm•h.

A total of seven subjects in cohort experienced potentially clinically important absolute values or changes from baseline in standing SBP or DBP. Three subjects experienced standing SBP values <85 mmHg. One subject experienced a decrease from baseline in standing SBP >30 mmHg following avanafil. Two subjects experienced standing DBP values <45 mmHg following avanafil. Four subjects experienced decreases from baseline in standing DBP >20 mmHg following avanafil. One subject experienced such

decreases following placebo. There were no severe adverse events related to hypotension reported during the study. There were no cases of syncope.

Cohort A (Doxazosin)	LS Means		Comparison		
	Doxazosin + Avanafil	Doxazosin + Placebo	Mean Difference	95% CI	P-Value
Standing					
Maximum decrease in SBP (mmHg)	-14.46	-11.96	-2.50	-6.53 - +1.53	0.2114
Systolic $AUEC_{0-12}$ (mmHg•hr)	+23.54	+24.12	-0.58	-36.48 - +35.32	0.9737
Maximum decrease in DBP (mmHg)	-14.50	-8.08	-6.42	-9.54 - -3.30	0.0003
Diastolic $AUEC_{0-12}$ (mmHg•hr)	-24.23	+7.94	-32.17	-57.08 - -7.27	0.0137
Maximum increase in pulse rate (bpm)	+19.17	+11.96	+7.21	+3.82 - +10.60	0.0002
Pulse rate $AUEC_{0-12}$ (bpm•hr)	+54.70	+10.16	+44.54	+21.32 - +67.76	0.0006
Supine					
Maximum decrease in SBP (mmHg)	-13.21	-7.21	-6.00	-9.07 - -2.93	0.0005
Systolic $AUEC_{0-12}$ (mmHg•hr)	+12.26	+45.12	-32.86	-72.15 - +6.43	0.0968
Maximum decrease in DBP (mmHg)	-10.58	-7.00	-3.58	-5.63 - -1.53	0.0015
Diastolic $AUEC_{0-12}$ (mmHg•hr)	-23.90	+7.51	-31.40	-51.22 - -11.59	0.0034
Maximum increase in pulse rate (bpm)	+17.12	+13.37	+3.75	-2.92 - +10.42	0.2564
Pulse rate $AUEC_{0-12}$ (bpm•hr)	+59.48	+13.64	+45.84	+28.10 - +63.58	<0.0001

Cohort A: rising doses of doxazosin daily (Days 1-18) plus a single dose of 200 mg avanafil or placebo on Days 15 and 18. $AUEC_{0-12}$ = area under effect-time curve from hour 0 to hour 12; CI = confidence interval; DBP = diastolic blood pressure; LS = least squares; SBP = systolic blood pressure.

Source: TA-017 Post-text Tables 14.2.1.3.1 and 14.2.2.3.1

Avanafil and tamsulosin

Subjects who entered into cohort B received oral doses of tamsulosin (0.4 mg daily) in the morning for 11 consecutive days (Days 1 to 11). On Days 8 and 11, subjects also received a single oral dose of either avanafil 200 mg or placebo, according to the treatment randomization code. The avanafil or placebo doses were administered 3.3 hours after the tamsulosin administration on Days 8 and 11, which would allow tamsulosin (tmax ~4 hours) and avanafil (tmax ~0.7 hours) to reach their peak plasma concentrations at approximately the same time.

On the α-adrenergic blocker plus avanafil/placebo treatment days (Cohort A, Days 15 and 18; Cohort B, Days 8 and 11), supine and sitting blood pressure and pulse rate measurements were recorded before avanafil or placebo dosing (the baseline value was the mean of three consecutive measurements 30, 20, and 10 minutes before dosing), then every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, hourly for the next 4 hours, and again at 10, 12, 18, and 24 hours after the avanafil or placebo dosing. Measurements were taken after subjects had been supine for at least 5 minutes. Subjects then sat for 1 minute and stood for 2 minutes before measurement of standing blood pressure and heart rate.

The largest mean standing SBP changes following co-administration of tamsulosin with avanafil occurred from Hours 0.5 to 1.75, ranging from -6.3 to -2.3 mmHg. Mean standing SBP changes from baseline following placebo ranged from -2.6 to +1.2 mmHg over the same period. The largest mean standing DBP changes following avanafil occurred from Hours 0.75 to 1.25, ranging from -7.1 to -5.1 mmHg. Mean standing DBP changes from baseline following placebo ranged from -0.9 to +2.5 mmHg over the same period. The largest mean changes in standing pulse rate in the immediate post-dose period following avanafil occurred from Hours 0.25 to 1.25, ranging from +5.0 to +8.0 bpm. Mean pulse rate changes from baseline following placebo ranged from -2.9 to +1.8 bpm over the same period.

No statistically significant differences were observed in the maximum change from baseline in standing SBP ($p = 0.1101$) or DBP ($p = 0.0835$), the AUEC0-12 for standing SBP ($p = 0.8047$) or DBP ($p = 0.1094$), or the maximum change from baseline in standing pulse rate ($p = 0.1913$) following avanafil versus placebo. The 95% CIs of differences contained zero for all of these comparisons. Differences in the

AUEC0-12 for standing pulse rate following avanafil versus placebo were marginally statistically significant (p = 0.0471). The difference in the LSM for this parameter was +31.56 bpm•h, with a 95% CI of 0.44 - 62.68 bpm•h.

The largest mean supine SBP changes following avanafil occurred from hours 0.25 to 1.5, ranging from -4.9 to -3.3 mmHg. Mean supine SBP changes from baseline following placebo ranged from -0.2 to +1.8 mmHg over the same period. The largest mean supine DBP changes following avanafil occurred from hours 0.25 to 1.5, ranging from -4.5 to -3.2 mmHg. Mean supine DBP changes from baseline following placebo ranged from 0 to +1.9 mmHg over the same period. The largest mean changes in supine pulse rate in the immediate post-dose period following avanafil occurred from hours 0.25 to 1.0, ranging from +4.9 to +8.4 bpm. Mean pulse rate changes from baseline following placebo ranged from -1.8 to -0.2 bpm over the same period.

No statistically significant differences were observed in the maximum change from baseline in supine SBP (p = 0.0580), AUEC0-12 for supine SBP (p = 0.6023), or AUEC0-12 for supine DBP (p = 0.3439). The 95% CIs of differences contained zero for all of these comparisons. A statistically significant difference in the maximum change from baseline in supine DBP (p = 0.0392) was observed following avanafil versus placebo. The difference in the LSM was -3.33 mmHg. Statistically significant differences in the maximum change from baseline in supine pulse rate (p = 0.0344) and AUEC0-12 for supine pulse rate (p = 0.0013) were observed following avanafil versus placebo. The differences in the LSMs for these parameters were +4.67 bpm and +40.76 bpm•h, respectively.

A total of five subjects in Cohort B experienced potentially clinically important absolute values or changes from baseline in standing SBP or DBP. Two subjects experienced standing SBP values <85 mmHg following avanafil dosing. One subject experienced a decrease from baseline in standing SBP >30 mmHg following avanafil dosing. Two subjects experienced standing DBP values <45 mmHg following avanafil dosing. Four subjects experienced decreases from baseline in standing DBP >20 mmHg following avanafil dosing; one subject experienced such decreases following placebo. There were no severe adverse events related to hypotension reported during the study. There were no cases of syncope.

Cohort B (Tamsulosin)	LS Means		Comparison		
	Tamsulosin + Avanafil	Tamsulosin + Placebo	Mean Difference	95% CI	P-Value
Standing					
Maximum decrease in SBP (mmHg)	-14.50	-10.88	-3.63	-8.14 - +0.89	0.1101
Systolic $AUEC_{0-12}$ (mmHg•hr)	+11.71	+15.41	-3.70	-34.37 - +26.97	0.8047
Maximum decrease in DBP (mmHg)	-13.13	-9.46	-3.67	-7.86 - +0.53	0.0835
Diastolic $AUEC_{0-12}$ (mmHg•hr)	-24.40	-3.69	-20.71	-46.46 - +5.03	0.1094
Maximum increase in pulse rate (bpm)	+22.25	+19.79	+2.46	-1.32 - +6.24	0.1913
Pulse rate $AUEC_{0-12}$ (bpm•hr)	+97.82	+66.26	+31.56	+0.44 - +62.68	0.0471
Supine					
Maximum decrease in SBP (mmHg)	-11.00	-7.88	-3.13	-6.37 - +0.12	0.0580
Systolic $AUEC_{0-12}$ (mmHg•hr)	+20.86	+28.87	-8.01	-39.41 - +23.40	0.6023
Maximum decrease in DBP (mmHg)	-10.04	-6.71	-3.33	-6.49 - -0.18	0.0392
Diastolic $AUEC_{0-12}$ (mmHg•hr)	-16.52	-1.50	-15.02	-47.21 - +17.18	0.3439
Maximum increase in pulse rate (bpm)	+20.75	+16.08	+4.67	+0.37 - +8.96	0.0344
Pulse rate $AUEC_{0-12}$ (bpm•hr)	+92.65	+51.89	+40.76	+17.85 - +63.66	0.0013

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

$AUEC_{0-12}$ = area under effect-time curve from hour 0 to hour 12; CI = confidence interval; DBP = diastolic blood pressure; LS = least squares; SBP = systolic blood pressure.

Source: TA-017 Post-text Tables 14.2.2.3.2 and 14.2.1.3.2

Interaction study of avanafil with tamsulosin and doxazosine (study TA-017) did not show statistically significant effect on standing SBP but an effect was seen on decreasing DBP (supine and standing) and supine SBP, with increase in heart rate. Return to baseline was observed by 3 -5 hours post-avanafil.

A number of subjects in both cohorts (tamsulosin and doxazosine) experienced potentially clinically important absolute changes from baseline or low BP values in standing SBP or DBP (e.g. Decrease of > 30 mm Hg in SBP or DBP values <45 mm)

There is a warning in the SPC about avanafil co-administration with alpha-blockers. Patients should be stable on alpha-blocker therapy prior to initiating treatment with avanafil, avanafil should be initiated at the 50 mg dose and observation is needed because some patients could experience decreases of blood pressure clinically relevant.

Study TA-018 was a single-center, three-cohort, open-label, crossover study to determine the effect of avanafil on the pharmacokinetics of omeprazole (a 2C19 substrate), desipramine (a 2D6 substrate), and rosiglitazone (a 2C8 substrate) in healthy male subjects. In total, 60 subjects (20 per cohort, mean age 30.8 years; range 20 – 44 years) entered and 57 subjects completed the study. The potential effect of CYP inducers on the pharmacokinetics of avanafil was not evaluated. The concomitant use of avanafil and a CYP inducer is not recommended as it may decrease the efficacy of avanafil.

Based on *in-vitro* studies, avanafil is a potential inhibitor of CYP 2C19, 2C8, 2C9 and 2D6. Interaction studies have been performed evaluating the effect of avanafil on specific substrates (e.g. omeprazol, rosiglitazone, desipramine) as well as with digoxine to explore effect through pGp transporter. The studies evaluated the effect of single doses of avanafil 200 mg on other medicines pharmacokinetics, which is well in accordance with the expected use of avanafil but could have explored the full potential for interaction.

Avanafil and omeprazole

Subjects received oral doses of omeprazole 40 mg QD for 8 days (Days 1 to 8) plus a single oral dose of avanafil 200 mg on Day 8.

Co-administration of avanafil and omeprazole did not alter the omeprazole pharmacokinetic parameters AUC0-tau, as the 90% CI of the geometric LS mean ratios of omeprazole + avanafil versus omeprazole were inside the 80% to 125% range. A slight higher Cmax (16.7%; 90% CI 99.68-136.70) of omeprazole was observed in the presence of avanafil. Avanafil had no effect on omeprazole tmax or t1/2.

Statistical Comparisons of Plasma Omeprazole Pharmacokinetic Parameters Following Omeprazole Plus Avanafil Versus Omeprazole Alone (Cohort A)

Pharmacokinetic Parameters	Geometric LS Means [a]		Treatment O+A vs. Treatment O		
	Treatment O+A	Treatment O	90% CI	% Mean Ratio	
$C_{max,ss}$ (ng/mL)	1550	1330	(99.68, 136.70)	116.73	
AUC_{0-t} (ng*hr/mL)	4940	4420	(103.85, 120.60)	111.91	
	Treatment Median [b]		95% CI [c]	Median Difference	P-value
t_{max} (hr)	2.0	2.0	(-0.25 , 1.00)	0.2529	0.2292
$t_{1/2}$ (hr)	1.8	1.8	(-0.12 , 0.15)	0.0454	0.5791

Cohort A
Treatment O+A = Once daily 40 mg oral doses of omeprazole for 8 Days plus 200 mg avanafil (Day 8)
Treatment O = Once daily 40 mg oral doses of omeprazole for 7 days (Days 1-7)
[a.] $C_{max,ss}$ and AUC_{0-t} are presented as geometric least-squares means (LS Means) with three significant figures, calculated by exponentiating the LS Means from the ANOVA. Parameters were log-transformed prior to analysis.
% Mean Ratio = 100*(test/reference).
[b.] t_{max} and $t_{1/2}$ are presented with two significant figures.
[c.] The Confidence Interval (CI) is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks Test Statistic.
Source: Tables 14.2.1.5 and 14.2.1.6 and Appendix 16.1.9

Study TA-018 showed that a single avanafil 200 mg dose did not affect the AUC of omeprazole (40 mg daily), a CYP2C19 substrate. A 17% increase in omeprazole C_{max} was observed in the presence of avanafil. This slight change in omeprazole C_{max} is not considered clinically significant.

Avanafil and rosiglitazone

Subjects were randomized to receive a single oral dose of rosiglitazone 8 mg or a single oral dose of rosiglitazone 8 mg plus a single oral dose of avanafil 200 mg. The two treatments in Cohort B were separated by a washout period of at least 7 days.

The Cmax and AUC0-inf of rosiglitazone were not altered by co-administration with avanafil, as the 90% CI of the geometric LS mean ratios of rosiglitazone + avanafil versus rosiglitazone were inside the 80% to 125% range. Rosiglitazone tmax or t1/2 was not altered in the presence of avanafil.

Statistical Comparisons of Plasma Rosiglitazone Pharmacokinetic Parameters Following Rosiglitazone Plus Avanafil Versus Rosiglitazone Alone (Cohort B)

Pharmacokinetic Parameters	Geometric LS Means [a]		Treatment R+A vs. Treatment R		
	Treatment R+A	Treatment R	90% CI	% Mean Ratio	
C_{max} (ng/mL)	538	613	(80.40, 95.97)	87.84	
AUC_{0-t} (ng*hr/mL)	2970	2870	(100.41, 106.66)	103.49	
AUC_{0-inf} (ng*hr/mL)	3030	2920	(100.55, 106.68)	103.57	
	Treatment Median [b]		95% CI [c]	Median Difference	P-value
t_{max} (hr)	1.0	0.75	(-0.00 , 0.50)	0.1267	0.0898
$t_{1/2}$ (hr)	3.8	3.7	(-0.19 , 0.23)	0.0000	1.0000

Cohort B
Treatment R+A = Single oral dose of 8 mg rosiglitazone plus a single oral dose of 200 mg avanafil
Treatment R = Single oral dose of 8 mg rosiglitazone
[a.] C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented as geometric least-squares means (LS Means) with three significant figures, calculated by exponentiating the LS Means from the ANOVA. Parameters were log-transformed prior to analysis.
% Mean Ratio = 100*(test/reference).
[b.] t_{max} and $t_{1/2}$ are presented with two significant figures.
[c.] The Confidence Interval (CI) is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks Test Statistic.
Source: Tables 14.2.2.6 and 14.2.2.7 and Appendix 16.1.9

Avanafil and desipramine

Subjects were randomized to receive a single oral dose of desipramine 50 mg or a single oral dose of desipramine 50 mg plus a single oral dose of avanafil 200 mg. The two treatments in Cohort C were separated by a washout period of at least 10 days.

The Cmax and AUC0-inf of desipramine were not altered by co-administration with avanafil, as the 90% CI of the geometric LS means ratios of desipramine+avanafil versus desipramine were inside the 80% to 125% range. Desipramine t_{max} or t1/2 was not altered in the presence of avanafil.

Statistical Comparisons of Plasma Desipramine Pharmacokinetic Parameters Following Desipramine Plus Avanafil Versus Desipramine Alone (Cohort C)

Pharmacokinetic Parameters	Geometric LS Means [a]		Treatment D+A vs. Treatment D	
	Treatment D+A	Treatment D	90% CI	% Mean Ratio
$C_{max,ss}$ (ng/mL)	19.3	18.6	(97.10, 109.89)	103.30
AUC_{0-t} (ng*hr/mL)	448	431	(98.82, 109.62)	104.08
AUC_{0-inf} (ng*hr/mL)	468	451	(98.36, 109.27)	103.68

	Treatment Median [b]		95% CI [c]	Median Difference	P-value
t_{max} (hr)	6.0	6.0	(-0.01 , 1.00)	-0.0013	0.7012
$t_{1/2}$ (hr)	13	13	(-0.41 , 0.32)	-0.0639	0.8288

Cohort C
Treatment D+A = Single oral dose of 50 mg desipramine plus a single oral dose of 200 mg avanafil
Treatment D = Single oral dose of 50 mg desipramine
[a] C_{max}, AUC_{0-t}, and AUC_{0-inf} are presented as geometric least-squares means (LS Means) with three significant figures, calculated by exponentiating the LS Means from the ANOVA. Parameters were log-transformed prior to analysis.
% Mean Ratio = 100*(test/reference).
[b] t_{max} and $t_{1/2}$ are presented with two significant figures.
[c] The Confidence Interval (CI) is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks Test Statistic.
Source: Tables 14.2.3.6 and 14.2.3.7 and Appendix 16.1.9

Study **TA-019** was a double-blind, randomized, placebo-controlled, two-period, two-cohort crossover study to investigate the pharmacokinetic and hemodynamic interactions between avanafil and two common blood pressure medications, enalapril and amlodipine, in healthy male subjects. The study consisted of two independent cohorts. In total, 48 subjects (mean age 48.9 years; range 40 – 63 years) enrolled (24 subjects in each cohort) and 47 completed the study.

Avanafil and enalapril

Subjects received oral doses of enalapril 10 mg every 12 hours for 11 days. On Days 8 and 11, subjects also received a single oral dose of either avanafil 200 mg or matching placebo 2 hours after the morning dose of enalapril according to the randomization scheme.

A single dose of 200 mg avanafil co-administered with enalapril caused a mean maximum change in supine blood pressure of -1.75/-3.46 mmHg (compared to placebo), accompanied by a mean maximum change in pulse rate of +0.96 bpm.

Incidence of Potentially Clinically Important Hemodynamic Results (Cohort A: Enalapril)		
	Number of Subjects	
Parameter	Avanafil + Enalapril (N = 24)	Placebo + Enalapril (N = 24)
Standing SBP < 85 mmHg	0	0
Standing SBP decrease > 30 mmHg	0	0
Standing DBP < 45 mmHg	0	0
Standing DBP decrease > 20 mmHg	0	1
Supine SBP < 85 mmHg	0	0
Supine SBP decrease > 30 mmHg	1	0
Supine DBP < 45 mmHg	1	0
Supine DBP decrease > 20 mmHg	1	0
SBP= systolic blood pressure; DBP= diastolic blood pressure Cohort A: enalapril 10 mg BID on Days 1-11 plus a single dose of 200 mg avanafil or placebo on Days 8 and 11. Source: Tables 14.2.1.4.1, 14.2.1.4.2, 14.2.2.4.1, and 14.2.2.4.2		

Single doses of 200 mg avanafil co-administered with enalapril caused a mean maximum decrease in supine blood pressure of 2/3 mmHg (compared to placebo). A statistically significant difference in the maximum decrease from baseline in supine DBP (a secondary endpoint) was observed following co-administration of avanafil with enalapril versus placebo with enalapril. Supine DBP returned to baseline by 4 hours post-avanafil dosing. A syncope episode and a few potentially clinically important changes were observed in healthy volunteers who participated in this study.

Avanafil and amlodipine

Subjects received a single oral dose of avanafil 200 mg on Day 1. Beginning on Day 3, subjects received oral doses of amlodipine 5 mg QD in the morning for 18 days (Days 3 to 20). On Days 12 and 19, subjects also received either a single oral dose of avanafil 200 mg or matching placebo 2 hours after the dose of amlodipine according to the randomization scheme.

A single dose of 200 mg avanafil co-administered with amlodipine caused a mean maximum change in supine systolic blood pressure of -1.18 mmHg (compared to placebo), accompanied by a mean maximum change in pulse rate of +1.00 bpm; the mean maximum change in diastolic blood pressure was less than that observed in the placebo group.

Co-administration of avanafil with amlodipine did not alter the pharmacokinetics of amlodipine. Concomitant amlodipine was associated with 28% and 60% increases in Cmax and AUC0-inf, respectively, of avanafil. These increases in avanafil exposure in the presence of amlodipine at the 5 mg dose are considered of minimal clinical significance.

Incidence of Potentially Clinically Important Hemodynamic Results (Cohort B: Amlodipine)		
	Number of Subjects	
Parameter	Avanafil + Amlodipine (N = 23)	Placebo + Amlodipine (N=23)
Standing SBP < 85 mmHg	0	0
Standing SBP decrease > 30 mmHg	0	0
Standing DBP < 45 mmHg	0	0
Standing DBP decrease > 20 mmHg	0	1
Supine SBP < 85 mmHg	0	1
Supine SBP decrease > 30 mmHg	0	1
Supine DBP < 45 mmHg	0	3
Supine DBP decrease > 20 mmHg	1	3
SBP= systolic blood pressure; DBP= diastolic blood pressure Cohort B: amlodipine 5 mg QD on Days 3-20 plus a single dose of 200 mg avanafil or placebo on Days 12 and 19. Source: Tables 14.2.1.4.1, 14.2.1.4.2, 14.2.2.4.1 and 14.2.2.4.2		

Administration of avanafil 200 mg in healthy volunteers treated with amlodipine show a very little augmentation of the blood pressure decrease (-1,18 mmHg as compared to avanafil + placebo) with no symptomatic or relevant decreases of BP.

No pharmacokinetic interaction on amlodipine was seen after a single dose of avanafil, which could not be expected anyway.

Pharmacokinetics using human biomaterials

The results from *in vitro* information from human biomaterial studies established the basis of the clinical pharmacology studies of avanafil.

Avanafil and its major metabolites, M4 and M16, are highly and reversibly bound to plasma proteins (10-AVANAFIL-PK-12). Binding of avanafil is predominantly to albumin (99%), and less so to γ-globulin (43%) or α1-acid glycoprotein (66%).

Accordingly, drug-drug interactions via displacement of protein bound drugs are likely with avanafil and this was explored in specific human *in vivo* studies.

In vitro studies showed that avanafil is a weak substrate of P-glycoprotein (Pgp) (10-AVANAFIL-BCS-01) (10-AVANAFIL-PGP-01). In a study to examine the potential for avanafil to act as a Pgp inhibitor with digoxin as a substrate, there was no clear indication of an effect (10-AVANAFIL-PGP-01). Accordingly, interactions at the level of Pgp are not expected with avanafil and no specific *in vivo* studies were performed this was considered acceptable by the CHMP.

In vitro studies using pooled human liver microsomes demonstrated that avanafil has potential to inhibit CYP2C19 activity and possible potential to inhibit CYP3A4, CYP2C8, 300 mg) in the treatment of mild to moderate ED.

2.4.3. Pharmacodynamics

Primary pharmacology

The primary pharmacodynamics of avanafil was evaluated in a single-blind, randomized, crossover study in subjects with ED using the RigiScan device and visual sexual stimulation (VSS) **(TA-01)**. This is a validated method to evaluate the effect of avanafil on penile erection and allows the measurement of time to rigidity, duration, frequency, and degree of rigidity and tumescence of the penis. A cut-off of at least 60% rigidity was used for the efficacy endpoints as this is considered the minimum rigidity necessary for successful vaginal penetration and sexual intercourse.

Avanafil was superior to placebo on all measures, this reaching statistical significance for most efficacy endpoints. The results of this Phase 2 study demonstrated that avanafil is superior to placebo in the endpoints of time to ≥ 60% rigidity, duration of ≥ 60% rigidity, maximum rigidity, TAU, RAU, and responses to the 5-point EAS.

Statistical superiority of avanafil treatments compared to placebo was in general associated most frequently with the earliest time interval, 20–40 minutes after dosing. During this 20-40 minute interval the majority of efficacy endpoints for the 50 mg, 100 mg, and 200 mg avanafil treatments were statistically superior to placebo ($p < 0.05$). While all avanafil treatments showed some degree of efficacy during the middle (60–80 minute) interval, avanafil 200 mg continued to show superiority vs. placebo during the latest (100–120 minute) interval. There is a good concurrence among results for variables of effect.

Sildenafil arm showed also superiority to placebo and similar magnitude of effect than avanafil.

Secondary pharmacology

Visual Function

As a class, PDE5 inhibitors may have an effect on visual function, probably due to the fact that PDE6, which is involved in photo transduction in the retina, may be inhibited to a certain degree, particularly with less selective PDE5 inhibitors.

Non-clinical studies with avanafil showed weaker effects on photo transduction in isolated rabbit retina than those of sildenafil, no drug-induced changes in ERG waves in dogs, and no effect on flicker –induced ERG in anaesthetized dogs.

The **TA-016**was a single-center, double-blind, randomized, placebo-controlled, two-way crossover drug interaction study with at least a 21-day washout period.

One of the secondary objectives was to evaluate the effect of avanafil on color discrimination. The color vision test (Farnsworth-Munsell 100-Hue Test) was performed and the results are reported. The analytical parameters of Farnsworth-Munsell 100-Hue Test included total error score (a measure of the gross errors), square root transformed total error score, the C index (Confusion index, a measure of severity of a color loss), the S-index (Scatter index, a measure of degree of randomness or selectivity in observers' arrangement), and the Angle score (a measure of type of a color loss). There was no statistically significant result in comparisons of post dose (0.67 hour) values between the two treatments. Comparisons on changes from baseline between the two treatments in untransformed total error score, C- and S-indices, and the Angle, did not reach statistical significance either. One marginally significant p-value was observed in mean change in square root transformed total error score in the analysis excluding an outlier. The overall results do not lead to a clinical concern. Suitable cautionary statements in the SmPC regarding contraindication in patients with known hereditary retinal degenerative disorders, including those with disturbance in PDE, such as retinitis pigmentosa has been included in SmPC. Although the results of the trial demonstrated no impairment of colour discrimination this effect should be further investigated as described in the risk management plan.

Sperm Function

Some PDE5 inhibitors may have the potential to affect spermatogenesis. In non-clinical reproductive and developmental toxicity studies, a statistically significant decrease in sperm motility and an increase in percentage of abnormal sperm (primarily detached sperm tails) were observed. The sperm function was assessed in two studies in healthy adult male subjects **(TA-014) (TA-021)**.

The study **TA-014** was a single-center, open-label, non-randomized, two-cohort, single-dose PK study. Healthy young (18 - 45 years, inclusive) non-vasectomized male subjects (Cohort A, 18 enrolled to have at least 14 complete) and healthy elderly (65 year or older) male subjects (Cohort B, 14 enrolled to have at least 12 complete) were enrolled and given a single oral dose of 200 mg avanafil tablets following an overnight fast. Seminal fluid and plasma were collected from Cohort A, whereas only plasma samples were collected from Cohort B.

The primary objectives of this study were 1) to determine avanafil semen exposure; 2) to determine the acute effect of avanafil on sperm motility, count, density, morphology, vitality, ejaculate volume and viscosity.

The mean sperm motility did not change by ≥ 20% from baseline (Day -4) and there was no acute effect on morphological normal forms, sperm count, sperm concentrations and forward progress. Within the

context of this study design, no significant changes regarding sperm function in the majority of subjects were observed.

The **TA-021** was a single-center, double blind, two-period, placebo-controlled, randomized, crossover, and single-dose study. Eighteen (18) healthy (18 - 45 years, inclusive) non-vasectomized male subjects were planned to be enrolled. The objectives of this study were 1) to determine the acute effect of avanafil on sperm motility, count, density, morphology, vitality, ejaculate volume, and viscosity following a single oral dose of 200 mg avanafil in healthy male subjects and 2) to determine avanafil and metabolites semen and plasma exposure. Mean values for all semen parameters (sperm concentration, sperm motility, forward progression, total sperm count, sperm morphology, and total motile sperm count) were within normal limits at the Day 1 postdose assessment for both treatment groups. There were no subjects in either treatment group who experienced a ≥ 50% decrease from baseline in total motility, forward progression, or WHO calculated forward progression. Additionally, there was no statistically significant difference ($p > 0.05$) in the LS Means in change from baseline for total motility, forward progression, or WHO calculated forward progression percentages, comparing the avanafil and placebo treatments.

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.
Source: Tables 14.2.2.1 - 14.2.2.3, Tables 14.2.3.1 - 14.2.3.3, Tables 14.2.4.1 -14.2.4.3.

Summary of Semen Parameters by Time Point and Treatment					
Semen Parameter	Normal Range*	Screening (N = 17) Mean ± SD Median (Min, Max)	Predose (Day -2) (N = 17) Mean ± SD Median (Min, Max)	Avanafil (N = 17) Mean ± SD Median (Min, Max)	Placebo (N = 17) Mean ± SD Median (Min, Max)
Volume (mL)	2 - 6	3.1 ± 0.8 3.0 (2.0, 4.7)	3.3 ± 0.8 3.4 (2.0, 4.5)	2.8 ± 0.8 2.9 (1.1, 4.1)	3.1 ± 0.9 2.9 (1.9, 5.0)
Concentration (Mil/mL)	20 - 250	255 ± 158 200 (49, 570)	251 ± 129 200 (68, 519)	284 ± 166 227 (41, 564)	297 ± 163 231 (23, 624)
Total Sperm Count (Mil)	> 40	780 ± 520 604 (162, 1918)	859 ± 525 744 (238, 1907)	812 ± 550 681 (135, 1944)	937 ± 618 730 (44, 2145)
Normal Forms (%)	> 14	15 ± 5 14 (5, 27)	13 ± 5 14 (5, 22)	12 ± 4 13 (4, 17)	13 ± 5 13 (5, 22)
Total Motile Count (Mil)	> 20	584 ± 397 429 (113, 1362)	647 ± 420 610 (190, 1564)	607 ± 466 493 (55, 1672)	717 ± 510 562 (23, 1866)
Motility (%)	> 50	74 ± 6 74 (63, 88)	74 ± 8 73 (61, 89)	70 ± 10 73 (41, 86)	73 ± 9 74 (52, 89)
Forward Progression (%)@	> 50	95 ± 2 95 (91, 99)	95 ± 2 95 (90, 99)	94 ± 2 94 (88, 97)	94 ± 3 95 (86, 98)
WHO Calculated Forward Progression (%)#		71 ± 6 69 (60, 84)	70 ± 9 69 (55, 88)	66 ± 11 68 (38, 83)	69 ± 10 70 (45, 87)
Vitality (%)	> 50	91 ± 3 91 (85, 95)	93 ± 3 94 (85, 97)	91 ± 6 93 (72, 95)	91 ± 4 91 (82, 96)
* Normal ranges provided by Heartland Center for Reproductive Medicine Laboratories @ Forward progression (%) = forward moving sperm / total moving sperm (method used by Heartland) # WHO calculated forward progression (%) = forward moving sperm / total sperm (method using WHO criteria)					

No relevant effects on sperm motility, morphology, count or WHO calculated forward progression were observed after a single oral dose of 200 mg avanafil.

Effects on Blood Pressure and Heart Rate

The hypotensive effect of avanafil has been very modest in studies in healthy volunteers, with mean maximal decreases in systolic and diastolic blood pressure of 0.6mmHg and 2.4 mmHg, respectively.

Nevertheless attention should be paid on this hypotensive effect in special populations (e.g. elderly) and to possible relevant interactions with other hypotensive medicines or substances (see 2.2.6)

Effects on INR and Platelet Aggregation

Effect on platelet aggregation was studied as secondary objective in a sildenafil-warfarin interaction study, comparing the collagen-induced platelet aggregation after 3 days of avanafil 200 mg daily or after placebo. In both days this was assessed after a single dose of warfarin.

There was no apparent effect on platelet aggregation.

QT Prolongation

A thorough QT/QTc study was performed that conformed to the requirements of ICH E14 –"The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" **(TA-140)**.

The **TA-140** was performed in a double-blind (except for the use of moxifloxacin), randomized, single site, and four-arm crossover design in healthy male subjects. The central electrocardiogram (ECG) laboratory (eResearchTechnology, Inc. [eRT], Philadelphia, Pennsylvania USA) was blinded to treatment. The primary objective of this study was to assess whether treatment with a therapeutic (100 mg) or supratherapeutic (800 mg) dose of avanafil had the potential to cause QT/QTc prolongation in healthy volunteers.

In the pharmacodynamics analysis, the primary QT to QTc correction formula was determined for each subject by iterating the QT-RR relationship using the 48 pre-treatment baseline ECGs and all of the posttreatment placebo period ECGs in order to find an estimate for the exponent such that the slope of this relationship was closest to zero.

QTcI is the individually determined QT correction, and the goal is to find β such that QTcI is a constant, where QTcI = QT / (RR) β. This implies log (QTcI) = log (QT) - β×log (RR). Because log (QTcI) is a constant, one can re-write this equation as log QT = α +β×log (RR). Therefore, the exponent estimate can be obtained by numerical iteration such that slope for QT-RR relationship is closest to zero or using regression analysis on log-transformed data based on the least squares approach.

Additional correction formulae included but considered secondary are QTcF and QTcB.

The results pharmacodynamics were that the placebo baseline adjusted change for HR using a time-averaged basis showed a +0.6 bpm increase for moxifloxacin and a +0.5 bpm change for the clinical dose of avanafil, all clinically not significant. For the supratherapeutic dose of avanafil there was an average +5.3 bpm increase with a marked increase in the first 1 to 3 hours exceeding 10 bpm, which is clinically important. There were also 3 (5%) tachycardic outliers demonstrated only for the supratherapeutic avanafil dose again highlighting this effect. This change can affect the QTc determination. The mean change from baseline placebo corrected for the 2 avanafil doses demonstrated a -0.4 msec and -1.9 msec decrease in PR duration and +0.1 msec and +0.2 ms for QRS duration. No outliers were identified. These changes are of no clinical relevance.

Avanafil with alcohol

The concomitant use of alcohol (0,5g/Kg of weight) with avanafil produces in healthy volunteers a small additive effect on the hypotensive effect of avanafil (around 3mm Hg more decrease with the combination than with avanafil alone). It appears reasonable to advice in the SPC and the PIL about the increase of potential for symptomatic hypotension if avanafil is taken with alcohol.

Relationship between plasma concentration and effect

Not applicable

Pharmacodynamic interactions with other medicinal products or substances

The hypotensive effect of avanafil has been very modest in studies in healthy volunteers, with mean maximal decreases in systolic and diastolic blood pressure of 0.6mmHg and 2.4 mmHg, respectively. Nevertheless attention should be paid on this hypotensive effect in special populations (eg. elderly) and to possible relevant interactions with other hypotensive medicines or substances. For specific considerations on nitrates, doxazosin, tamsulosin, enalapril and amlodipine refer to the above section on drug interactions.

2.4.4. Discussion on clinical pharmacology

Avanafil has a good oral bioavailability and after oral administration, avanafil Tmax is around 30- 45 min. Avanafil is extensively metabolized by P450 isoforms, predominantly by CYP3A4, with a minor contribution by CYP2C. Mean terminal half-life is around 6 hours, although different studies show a high variability, ranging from very short half-lives to up to 17 hours. There is influence of the food intake in the absorption of avanafil in the sense of delaying absorption, this information is included in the SPC and PIL as it could modify the time to reach the effect after dosing. The pharmacokinetics of avanafil and its metabolites were generally comparable in elderly and young subjects, but the studies were conducted with few patients older than 75 or very old patients.

Based on the data from the dedicated hepatic study (TA-012), which included subjects with mild (n=8) and moderate (n=8) hepatic impairment, PK in subjects with mild-moderate hepatic impairment was comparable to those with normal liver function, with the exception of a 28-57% lower Cmax for subjects with moderate impairment. No significant differences in AE profile were noted.

The applicant provided as well a discussion on the observed decreased efficacy in subjects with mild renal impairment. The Applicant hypothesized that the observed differences are likely related to greater impairment of vascular or nerve function in this subset of patients compared to the general study population, in a manner similar to diabetics or prostatectomized subjects, making them less responsive to pharmacological treatment for ED. This explanation seemed reasonable.

The applicant performed thorough QT/QTc study accordingly with the ICH topic E14 ”Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrythmic potential for non antiarrhytmic drugs (CHMP/ICH/2/04)” in order to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation. The threshold level of regulatory concern, discussed further below, is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.

As the QT interval has an inverse relationship to heart rate, the measured QT intervals are generally corrected for heart rate in order to determine whether they are prolonged relative to baseline. Various correction formulae have been suggested, of which Bazett’s and Fridericia’s corrections are the most widely used and the preferred method.

A single dose of 100 mg, or a supratherapeutic dose of 800 mg avanafil, were investigated for their ability to cause QT/QTc prolongation. No adverse effects were observed for 100 mg avanafil. There were marked increases in heart rate over 10 bpm in subjects receiving 800 mg for 1-3 hours after dosing that confounded interpretation of the effects of this dose due to invalidation of QTcB as well as individual QTc correction during this time. Nevertheless, there was no specific evidence for an effect of this high dose of avanafil on cardiac repolarisation except at the 3 hour time point which had an upper CI of 10.2 msec.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of avanafil and its metabolites were generally comparable in elderly and young subjects, but the studies were conducted with few patients older than 75 or very old patients.
Based on the limited data available, it is recommended to start with the minimum efficacious dose and adjusting posology based on tolerance and this is reflected in the SPC.
Furthermore, the observed decrease in efficacy in subjects with renal impairment is reflected in the SPC.
The Applicant presented data using QTcI. To rule out any effect of Avanafil on QTc, the Applicant has been recommended at post-authorisation to present data for each quartile of QTc values.

2.5. *Clinical efficacy*

Introduction

The Phase 3 clinical studies included one study in the general population with ED (TA-301), one study in diabetic men with ED (TA-302), one study in males with ED following nerve-sparing radical prostatectomy (TA-303) and one open label extension study to assess the long-term safety and tolerability of avanafil (TA-314). Collectively, these studies randomized a total of 1334 subjects.

Dose-response study

The **TA-05** study was a multicentre, double-blind, randomized, parallel-design phase 2 study designed to evaluate the safety and efficacy of various doses of avanafil in the treatment of mild to moderate ED.

Subjects were eligible for inclusion if they had a history of mild to moderate ED with duration of at least 6 months and who were in a monogamous heterosexual relationship for at least 3 months. Subjects with diabetes and subjects with ED caused by spinal cord injury or radical prostatectomy were excluded from participation.

The study consisted of a 4-week (non-treatment) run-in period, followed by a 12-week treatment period. Eligible subjects were assigned randomly in a 1:1:1:1:1 ratio to one of the following treatments: placebo, avanafil 50 mg, avanafil 100 mg, avanafil 200 mg, or avanafil 300 mg. During the treatment period, subjects were instructed to take 1 dose (2 capsules) of study drug with water approximately 30 minutes prior to initiation of sexual activity. Subjects were instructed to refrain from large meals, alcohol, or grapefruit juice consumption from 2 hours before study drug until 2 hours after dosing.

Subjects were instructed to complete a diary entry for each attempt at sexual activity during both the run-in and active treatment periods. Subject in the pivotal phase III studies were to complete the same diary questions, which included the following 7 items:

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

- 7. Were you satisfied overall with your sexual experience? (Yes or no).

Subjects also completed the IIEF questionnaire at baseline (prior to randomization) and at each follow-up visit during treatment.

The main objective of study TA-05 was to evaluate the safety and efficacy of various dose levels of avanafil in subjects with mild to moderate ED.

The three primary efficacy endpoints were:

- Success rate of subject's responses to SEP2: "Were you able to insert your penis into your partner's vagina?"
- Success rate of subject's responses to SEP3: "Did your erection last long enough for you to have successful intercourse?"
- EFS of the IIEF Questionnaire.

The secondary efficacy endpoints included assessments of the following: responses to secondary Subject Diary questions, responses to individual questions from the IIEF questionnaire, responses to the GAQ.

The safety assessments included AEs, vital sign changes, laboratory results, and physical examination findings.

Efficacy analyses were performed on the ITT (subjects who attempted and reported at least one sexual encounter with study medication) and PPP (all subjects who reported using at least 6 doses of study medication during treatment) populations. The efficacy analyses based on the ITT population were considered the primary analysis. Safety analyses were performed on the ITT population.

The statistical analyses were reported using summary tables and data listings. Statistical testing (including testing of statistical assumptions) other than interaction testing were two-sided and performed at the 0.05 alpha level. Interaction testing was performed at the 0.10 alpha level. Tests were declared statistically significant if the calculated p-value was ≤ 0.10 for interaction testing and ≤ 0.05 for all other tests. All analyses and tabulations were performed using SAS® Version 8.2 on a PC platform. Continuous variables were summarized with means, standard deviations (SD), medians, minimums, and maximums. Categorical variables were summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the CRFs, as well as any derived data, were included in data listings.

For Subject Diary-based endpoints, the desired sample size of at least 50 subjects in each of the 5 dose groups would provide 90% power for detecting a difference between proportions characterized by a variance of 0.154 and an average proportion of 0.5 among the dose groups using the Chi-square test at a two-sided alpha level of 0.05. For EFS, a one-way analysis of variance would have 90% power to detect an effect size across the 5 dose groups. It was estimated that approximately 17% of subjects might have some degree of incomplete data. Therefore, the total sample size was determined to be 250 to 300 subjects.

Results

A total of 460 subjects were screened for study TA-05. Two hundred ninety-five (n=295) subjects were randomized, including 59, 57, 61, 59, and 59 subjects in the placebo, and 50 mg, 100 mg, 200 mg, and 300 mg avanafil treatment groups, respectively. A total of 284 (96.3%) subjects attempted and reported at least one sexual encounter with study medication and were included in the ITT population. This

population included 55 (93.2%), 56 (98.2%), 60 (98.4%), 56 (94.9%), and 57 (96.6%) subjects in the placebo, and 50 mg, 100 mg, 200 mg, and 300 mg avanafil treatment groups, respectively. A total of 263 (89.2%) subjects used at least 6 doses of study medication during treatment and were included in the PPP population.

Prior to randomization, 165 subjects were considered screen failures. Of the 295 subjects randomized, 249 (84.4%) completed the treatment protocol. Forty-six (15.6%) subjects did not complete the protocol. The reasons for discontinuation included withdrawal by subject (26, 8.8% subjects), AE (5, 1.7% subjects), protocol violation (1, <1% of subjects), non-compliance (2, 0.7% subjects), lost to follow-up (10, 3.4% subjects), and lack of efficacy (2, 0.7% subjects). There were no deaths.

In regards to demographic and baseline characteristics, subjects in the ITT population were predominantly Caucasian (85.6%) with a mean age of 56.1 years (range 32 to 70 years). Demographic profile was similar across treatment groups, with exception of a higher percentage of Caucasians in the placebo group compared with the avanafil 200 mg group (94.5% Caucasians vs.76.8% Caucasians, respectively). The mean weight and height for the ITT population were 93.7 kg and 178.5 cm, respectively, and were similar across treatment groups. The mean duration of ED was 66.7 months (range = 6 months to 30 years) and was similar across treatment groups. The aetiology of ED for most subjects was organic (57.7%), with 5.3% due to a psychological aetiology and 36.6% having ED of a mixed aetiology. The majority of subjects experienced ED of moderate severity (84.9% subjects) with a gradual onset (94.0% subjects).

At least 40% of subjects in the ITT population had a medical history for the following body systems: urogenital (76.1%); head, ears, eyes, nose, and throat (55.6%), musculoskeletal (54.2%), and gastrointestinal system (47.9%). The majority of subjects (251 subjects, 88.4%) in the ITT population had previously been treated for ED; these treatments included oral medication (87.3%), intracavernosal injections (12.3%), vacuum pump/band (4.9%), and Muse® (4.6%).

The demographic and Baseline (Screening) characteristics of the PPP population were similar to those of the ITT population and no statistically significant differences in Baseline characteristics between treatment groups were identified.

Co-primary endpoints results

The percentage level of attempts where subjects achieved erections enabling vaginal penetration (SEP2) during the Treatment Period was: 76.1% for avanafil 50 mg, 79.2% for 100 mg, 79.8% for 200 mg, and 83.7% for 300 mg, versus 60.5% for placebo. For each avanafil dose, penetration success rates during treatment were statistically significant when compared to placebo. Change from Baseline in penetration success rates were 8.4% for avanafil 50 mg, 17.5% for 100 mg, 13.0% for 200 mg, and 20.9% for 300 mg, versus 4.2% for placebo. Only the 100 mg and 300 mg avanafil doses had statistically significant changes from baseline in penetration success rates compared to placebo.

Table 6 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.

The percentage level of attempts resulting in erections lasting long enough for successful intercourse (SEP3) during the treatment period was: 53.4% for avanafil 50 mg, 58.6% for 100 mg, 62.1% for 200 mg, and 64.3% for 300 mg, versus 28.9% for placebo. For each dose of avanafil, intercourse success rates were statistically significant when compared to placebo. Change from Baseline in intercourse success rates were 32.2% for avanafil 50 mg, 39.6% for 100 mg, 41.7% for 200 mg, and 46.1% for 300 mg, versus 12.1% for placebo. For each dose of avanafil, the change from baseline in intercourse success rate during treatment was statistically significant when compared to placebo.

Table 7 Overall Erectile Function Domain Score (ITT Population)

	Placebo (N=55)	Avanafil			
		50 mg (N=56)	100 mg (N=60)	200 mg (N=56)	300 mg (N=57)
EFS from IIEF Questionnaire					
Baseline (Run-in)					
Mean (SD)	15.8 (4.0)	16.1 (3.5)	16.2 (4.1)	16.5 (3.8)	16.5 (3.8)
Median	15.0	16.0	16.0	16.0	16.0
Min-Max	11 - 24	11 - 25	11 - 25	11 - 25	11 - 25
Pairwise P-value vs. Placebo [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.

EFS scores at the end of treatment were 19.4 for avanafil 50 mg, 22.3 for 100 mg, 22.4 for 200 mg, and 22.5 for 300 mg, versus 16.9 for placebo. Change from baseline in EFS scores were 3.2 for avanafil 50 mg, 6.1 for 100 mg, 5.9 for 200 mg, and 6.0 for 300 mg versus 1.1 for placebo. For each dose of avanafil, the change from Baseline in EFS score was statistically significant when compared to placebo.

Results of the secondary endpoints generally supported the co-primary endpoints results.

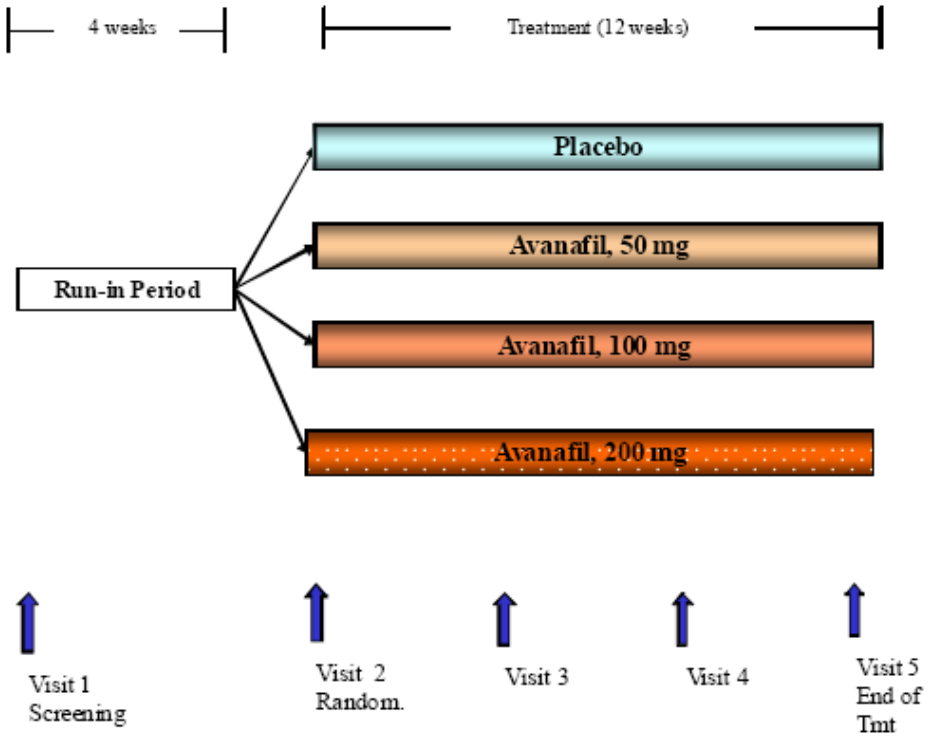
In regards to safety, the observed AE profile was generally consistent with results noted in previous studies. The AE most frequently reported by each avanafil group was headache. Headache and flushing occurred more frequently in avanafil groups than in placebo and tended to increase in frequency with increasing dose. Headache (the most frequently reported treatment-related AE) was considered treatment related for 2 (3.6%) subjects in the placebo group and 4 (7.1%), 7 (11.7%), 7 (12.5%), and 15 (26.3%) subjects in the avanafil 50 mg, 100 mg, 200 mg, and 300 mg groups, respectively.

Main studies

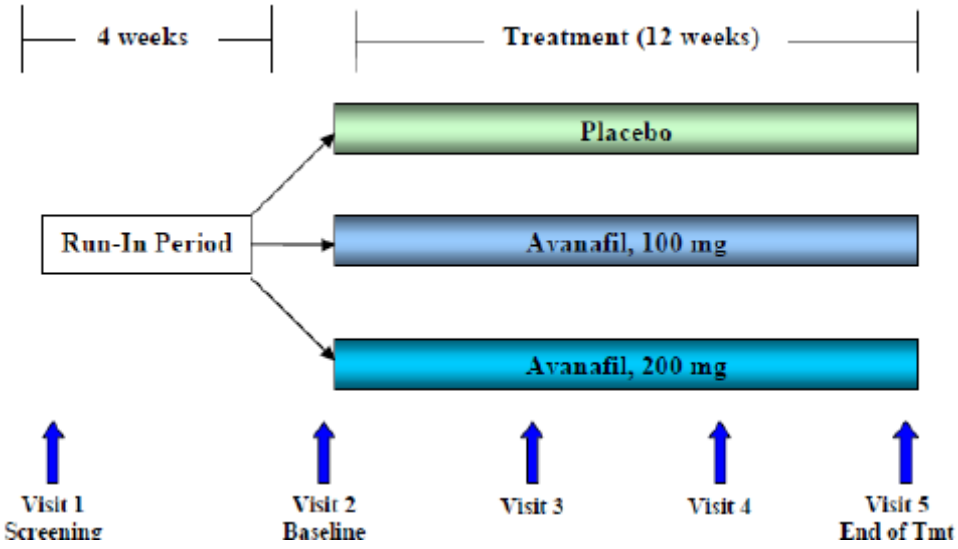
Methods

The efficacy and safety of avanafil on an as needed basis in men with ED has been evaluated in three pivotal randomised, double-blind, placebo-controlled, 12-week, parallel-design studies (studies TA-301, TA-302 and TA-303). Of the 3 pivotal studies, 2 of them were performed in specific populations: study TA-302 enrolled diabetic subjects (T1DM or T2DM) with mild to severe ED; study TA-303 enrolled subjects with mild to severe ED following bilateral nerve sparing radical prostatectomy. The designs of the three studies are similar hence they will be described together.

Study Design Schematic (TA-301)



Study Design Schematic (Studies TA-302 and TA-303)



In all studies, there was a 4-week baseline period without ED therapy, followed by a 12-week treatment period. Subjects who met the initial eligibility criteria entered the 4-week, non-treatment run-in period and were instructed to record information on each of their attempts at sexual intercourse. At the end of the run-in period, subjects were eligible for randomization to treatment if they met the following criteria: documented at least 4 attempts at sexual intercourse during the run-in period; failed to maintain an

erection of sufficient duration to have successful intercourse (as documented in the subject diary during the run-in period) for at least 50% of their attempts; and had an IIEF erectile function domain score of 5 to 25, inclusive. Subjects that met eligibility criteria were randomized to placebo or different doses of avanafil (100mg or 200mg in TA-302 and TA-303; 50mg or 100mg or 200mg in TA-301).

Study participants

Inclusion Criteria

The pivotal studies enrolled males 18-70 years of age at the time of screening; with mild to severe ED of at least 6 months duration, defined as the 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; with willingness and ability to provide informed consent; willingness and ability to comply with all study requirements; agreement to make at least 4 attempts at intercourse per month; and agreement not to use any other treatments for ED during the study. Because the response to treatments for ED in patients with diabetes or prostatectomy may differ from those in the general ED population, diabetics and the post-prostatectomy population were studied separately (Studies TA-302 and TA-303, respectively).

In the post-prostatectomy study (TA-303), additional inclusion criteria were: patients with a history of ED of at least 6 months following bilateral nerve-sparing radical prostatectomy; history of bilateral nerve-sparing 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); PSA level at screening consistent with the absence of residual prostate cancer; and history of sexual potency prior to radical prostatectomy (not needing treatment/product or device for ED).

Exclusion criteria

General exclusion criteria common to the 3 phase III pivotal studies included: patients with cardiovascular illnesses within the preceding 6 months (such as myocardial infarction, stroke, high-risk arrhythmia or ECG judged by the investigator to be clinically significant, coronary revascularization, unstable angina, angina with sexual intercourse, congestive heart failure, clinically significant cardiomyopathy, moderate or severe cardiac valvular disease) were excluded from the studies. Other key exclusion criteria included: retinitis pigmentosa or non-arteritic anterior ischemic optic neuropathy; advanced neurologic degenerative disease; ED after spinal cord injury, penile anatomic abnormalities; uncontrolled hypertension, hypotension, orthostatic hypotension or evidence of cerebral hypoperfusion upon standing from a seated position; treatment with nitrates, CYP3A4 inhibitors, antiandrogen therapy, androgen replacement therapy not stable for at least 3 months, or initiation or dose change of an alpha-adrenergic antagonist within 14 days prior to randomization; patients with abnormal liver function test (AST, ALT >2 × ULN), or severe renal failure (serum creatinine >2.5 mg/dl, estimated creatinine clearance <60 mL/min [Cockcroft-Gault]) were also excluded. Patients with history of hypersensitivity to avanafil or other PDE5 inhibitors; dose-limiting AEs with a PDE5 inhibitor or history of treatment failure with other PDE5 inhibitors were not eligible for inclusion in the 3 main efficacy studies.

In protocol TA-302, which included diabetics, patients with a history of 3 or more episodes of hypoglycaemia requiring assistance within the last 2 years; uncontrolled diabetes (haemoglobin A1c [HbA1c] >9%); fasting blood glucose >270 mg/dL were excluded. Patients with diabetic complications, such as proliferative diabetic retinopathy and/or diabetic autonomic neuropathy with clinically significant gastroparesis were not excluded from participation.

In protocol TA-303 (patients with history of radical prostatectomy) additional exclusion criteria were: history of severe ED requiring routine medical therapy prior to bilateral nerve-sparing radical prostatectomy; history of previous pelvic surgery, brachytherapy, or cryotherapy of the prostate.

Treatments

Different doses of avanafil or placebo were to be taken on demand, approximately 30 minutes before sexual activity. No restrictions were placed on the timing of avanafil dosing relative to the consumption of food or alcohol. Subjects were permitted to take up to two doses of study drug in a 24-hour period at least 12 hours apart. Subjects were not to take more than two doses of study drug in a 24-hour period.

Antidepressants, other than trazodone, were permitted during the study. Subjects on hormone replacement therapy or alpha-adrenergic antagonists were required to be on a stable regimen for at least 3 months and 14 days prior to entry into the study, respectively. However, if alpha blocker therapy was initiated during the study, treatment was to begin with the lowest available dose.

During the course of the study, subjects were not allowed to take the following medications: nitrates; trazodone; any drugs known to interfere with metabolism by the CYP3A4 enzyme (such as Ketoconazole, Erythromycin, protease inhibitors, Cimetidine); Spironolactone; Phentolamine; Papaverine; Alprostadil; other PD5 inhibitors; and any prescription, over-the-counter, herbal, or naturopathic products for "male enhancement" or the treatment of ED.

In the post-prostatectomy study, subjects may have been previously treated with alprostadil and/or PDE5 inhibitors following prostatectomy but such treatments must have been discontinued prior to beginning the 4-week run-in period of the study. The use, duration, and end date of any such treatments were to be recorded in the subject's medical history.

Objectives

The objectives of the pivotal studies were to evaluate the safety and efficacy of avanafil in subjects with mild to severe ED in the general population (TA-301), diabetics (TA-302) or post-prostatectomy (TA-303).

Outcomes / endpoints

- **Primary endpoints**

Three co-Primary efficacy parameters were used in the pivotal studies:

Change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which subjects were able to maintain an erection of sufficient duration to have successful intercourse (question 3 of the Sexual Encounter Profile [SEP3]: "Did your erection last long enough for you to have successful intercourse?");

Change in the percentage of sexual attempts between the run-in period and the 12-week treatment period in which subjects were able to insert the penis into the partner's vagina (question 2 of the Sexual Encounter Profile [SEP2]: "Were you able to insert your penis into your partner's vagina?");

Change in International Index of Erectile Function (IIEF) erectile function domain score from baseline to the end of the 12-week treatment period.

The IIEF is a 15-item questionnaire, self-administered measure of erectile function. The 15 items cover five domains: erectile function (6 items), orgasmic function (2 items), sexual desire (2 items), intercourse satisfaction (3 items), and overall sexual satisfaction (2 items). This questionnaire was completed at each study visit and subjects were to self-evaluate their erectile function over the previous 4-week period. Depending on the responses, each question could be scored from 0 to 5, or 1 to 5, with 0 for no attempt at sexual intercourse.

- **Secondary endpoints**

The main secondary efficacy variables were the same in the pivotal studies:

- 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;
- Subjects assessed their overall response to treatment by answering Global Assessment and Future Use questions at the end of treatment (Visit 5, Week 12 or Early Termination). The questions pertained to effectiveness of treatment ("Has the treatment you have been taking over the past study interval improved your erections?") and future product use ("If the study treatment were available today, would you buy it?").

Sample size

The sample size estimation was based on the three co-primary efficacy endpoints for the Phase 3 pivot studies. Estimates from the results of study TA-05 were used for sample size calculation. In study TA-05, the average standard deviation for the change in the percentage of subjects able to insert their penis into their partner's vagina was approximately 32. It was calculated that with 125 (in TA-302) or 150 subjects (in TA-301) in each treatment group, the studies had more than 90% power to detect a mean difference of 13% by a two-tailed t-test with a 5% type I error. In study TA-05, the average standard deviation in the change in the percentage of subjects with an erection of sufficient duration to have successful intercourse was approximately 33. With 125 (in TA-302) and 150 subjects (in TA-301) in each treatment group, it was estimated that the studies had more than 90% power to detect a 13% difference in response rate between two treatment groups. In TA-05, the average standard deviation in the change in IIEF erectile function domain score was approximately 7.0 points. With 125 (in TA-302) 150 subjects (in TA-301) in each treatment group, the studies had more than 90% power to detect a mean difference of 3 (TA-301) to 5 (TA-302) points in ED domain score between two treatment groups.

In study TA-303 (post-prostatectomy study), the sample size estimation was also based on all three primary efficacy endpoints for the study, and conservative estimates from the results of a previous study with vardenafil in patients with either bilateral or unilateral nerve-sparing prostatectomy were used for sample size calculation. Due to difference between the two studies, the standard deviations from the vardenafil study results were increased (by 40%) in the sample size calculation for study TA-303, and the calculations were based on a two-sided test with a 5% type I error. In the vardenafil study, a mean difference of 25.7% in the percentage of successful insertions during the 12-week treatment period was observed, with a standard deviation of 41. For study TA-303, a sample size of 100 subjects per group should have more than 86% power to detect a mean difference of 25.7% for the change in the percentage of successful insertions between the run-in period and the 12-week treatment period, given a standard

deviation of 57.4 (41×1.4). In the vardenafil study, a mean difference of 24.3% in the percentage of successful intercourse attempts during the 12-week treatment period was observed, with a standard deviation of 40. For study TA-303, a sample size of 100 subjects per group, should have more than 86% power to detect a mean difference of 24.3% for the change in the percentage of successful intercourse attempts between the run-in period and the 12-week treatment period, given a standard deviation of 56.0 (40×1.4). In the vardenafil study, a mean difference of 6.1 in the IIEF erectile function domain score at Week 12 was observed, with a standard deviation of 8.4. For study TA-303, a sample size of 100 subjects per group should have more than 86% power to detect a mean difference of 6.1 in the change from baseline to the end of treatment in the erectile function domain score, given a standard deviation of 11.8 (8.4×1.4).

Randomisation

In the general population study (TA-301), eligible subjects were randomized in a 1:1:1:1 ratio to one of the following treatments: placebo, avanafil 50 mg, avanafil 100 mg, or avanafil 200 mg. In the other 2 pivotal studies (TA-302 and TA-303), eligible subjects were randomized in a 1:1:1 ratio to one of the following treatments: placebo, avanafil 100 mg, or avanafil 200 mg.

In the 3 pivotal studies, randomization was stratified using a centralized, computer-generated randomization system by disease severity as determined by IIEF erectile function domain scores at the randomization visit.

Blinding (masking)

The 3 pivotal studies were double-blind studies, in which investigators and subjects were blinded to treatment assignment. Blinding was not to be broken during the study unless considered necessary by the investigator or medical monitor for management of an adverse event or other medical emergency.

Statistical methods

The analysis population for all efficacy evaluations is the Intent-to-Treat (ITT) Population. The ITT Population included all randomized subjects who took at least 1 dose of study drug (as reported in the subject diary) and had at least one post-dosing efficacy assessment.

The evaluable Population (per-protocol population) was defined as all subjects in the ITT Population who reported using at least 6 doses of study drug during the treatment period and had at least 4 attempts at sexual intercourse during the non-treatment run-in period.

The Safety Population was defined as all subjects who took at least one dose of study drug and had safety data available. The Safety Population was used for all safety analyses.

Analysis of each primary efficacy variable was performed using an analysis of covariance (ANCOVA) model with treatment, baseline erectile dysfunction severity category, and study as factors and baseline value as the covariate. For each treatment group, the least-squares (LS) mean, corresponding standard error, and two-sided p-value for the change in each primary efficacy variable were obtained. For each treatment comparison of interest, the difference in LS mean, corresponding standard error, two-sided 95% confidence interval, and two-sided p-value were derived from the ANCOVA model.

A step-down, multiple-comparison procedure was used to compare the efficacy of each avanafil dose group with placebo. In the 3 pivotal studies, comparison started with the high-dose group (avanafil 200 mg). If the statistical comparison of the high-dose treatment with placebo was statistically significant at the 5% significance level using a two-tailed test for all three co-primary efficacy variables, then the efficacy of the lower dose(s) was tested. If more than one avanafil dose was significantly better than placebo, then those avanafil doses were compared.

The same methodology used for the analyses of the primary efficacy variables was used for the analyses of secondary efficacy variables derived from subject diaries and IIEF responses. The number and percentage of subjects in each treatment group with an improvement in IIEF erectile function domain score were summarized.

Regarding the handling of dropouts or missing data, in the analysis of primary endpoints the last observation carried forward convention was used. No adjustments were made for missing data in secondary efficacy analyses or safety analyses.

Results

Study TA-301

Participant flow

A total of 1509 subjects were enrolled in the study and 646 of them were randomized to treatment (162 to placebo, 161 to avanafil 50mg, 161 to avanafil 100mg, and 162 to avanafil 200mg). Of the 646 randomized subjects, 550 (85.1%) completed the study and 96 (14.9%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was similar across the treatment groups (25 [15.4%] in the placebo group, 30 [18.6%] in the 50 mg avanafil, 20 [12.4%] in the avanafil 100mg, and 21 [13.0%] in the avanafil 200mg). The most common reasons for discontinuation from the study were protocol non-compliance (which also includes subjects who withdrew consent) (n=53, 8.2%), loss to follow-up (n= 22, 3.4%), and adverse event (n= 17, 2.6%). The ITT population included 622 subjects, 155 in the placebo group, 154 in the 50mg avanafil, 157 in the 100mg avanafil, and 156 in the 200mg avanafil groups. No information on previous PD5E inhibitors usage has been provided.

Baseline data

With regards to demographic and baseline characteristics, the majority of subjects were white (85.6%), with a mean age of 55.7 years. Similar proportions of subjects with mild, moderate, and severe ED were randomized to treatment. At baseline, mean duration of ED was 77.4 months and the majority of subjects had a duration of ED ≥24 months. With the exception of race, the treatment groups were comparable with respect to demographic and baseline characteristics.

Overall, 233 (36.2%) subjects reported a history of hypertension, 73 (11.3%) subjects reported a history of depression, and 61 (9.5%) subjects reported a history of coronary artery disease. With the exception of depression (reported in a lower proportion of subjects in the avanafil 100mg group), the treatment groups were comparable with respect to medical history of special interest.

In total, 187 (29.0%) subjects took antihypertensive medications, 49 (7.6%) subjects took antidepressants, and 38 (5.9%) subjects took alpha blockers. A lower proportion of subjects in the avanafil 50 mg group took antihypertensive medications than in the other treatment groups. A higher

proportion of subjects in the avanafil 50 mg group took antidepressants than in the other treatment groups. The proportion of subjects who took alpha blockers was similar in each treatment group.

Mean treatment duration in placebo group was 10.41 weeks versus 10.20 to 10.93 weeks in the avanafil groups. The mean number of total doses taken in the placebo group was 16.84 vs. 18.52-19.96 in the avanafil groups.

Based on the patient's diary responses, mean time from drug intake until the start of sexual activity was 53.38 min for the placebo group, and 63.05 min, 56.89 min and 58.62 min in the avanafil 50mg, 100mg and 200 mg groups, respectively. Mean time from drug intake to the start of sexual activity was 59.50 min for all avanafil groups and 57.97 min for all treatment groups.

From across various time periods after taking the study drug, all avanafil doses had higher success rates than the placebo group.

Outcomes and estimation

The result of the primary efficacy endpoints (changes from baseline to the end of treatment in the percentage of sexual attempts in which the subject was able to maintain an erection, in the percentage of sexual attempts in which the subject was able to achieve successfully penetration and in the IIEF erectile function domain) are presented in tables 9-11 below:

Table 9. Change in the Percentage of Sexual Attempts between the Run-in Period and the Treatment Period in Which the Subject Was Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) –ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	155	12.6 (17.82)	27.0 (31.41)	14.4 (27.63)	14.1 (2.57)	<0.0001
Avanafil 50 mg	154	13.5 (18.58)	41.3 (35.94)	27.8 (33.86)	27.8 (2.58)	<0.0001
Avanafil 100 mg	157	13.9 (18.87)	57.1 (36.05)	43.2 (33.86)	43.4 (2.56)	<0.0001
Avanafil 200 mg	156	12.4 (18.52)	57.0 (37.78)	44.6 (35.67)	44.2 (2.57)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [4]		
	LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)	30.2 (3.63)	(23.0 , 37.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)	29.3 (3.63)	(22.2 , 36.5)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)	13.8 (3.64)	(6.6 , 20.9)	0.0002
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	16.4 (3.64)	(9.3 , 23.6)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	15.6 (3.63)	(8.5 , 22.7)	<0.0001
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)	0.8 (3.62)	(-6.3 , 7.9)	0.8198

Table 10. 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) – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	155	46.7 (36.34)	53.8 (37.88)	7.1 (32.07)	7.1 (2.33)	0.0025
Avanafil 50 mg	154	45.4 (36.72)	64.3 (37.21)	18.9 (35.51)	18.2 (2.34)	<0.0001
Avanafil 100 mg	157	46.6 (38.24)	73.9 (32.26)	27.3 (35.17)	27.2 (2.32)	<0.0001
Avanafil 200 mg	156	48.3 (38.22)	77.3 (31.44)	29.0 (35.90)	29.8 (2.33)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [4]		
	LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)	22.7 (3.30)	(16.3 , 29.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)	20.1 (3.29)	(13.6 , 26.5)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)	11.1 (3.31)	(4.6 , 17.6)	0.0009
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	11.7 (3.30)	(5.2 , 18.1)	0.0004
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	9.0 (3.29)	(2.5 , 15.5)	0.0064
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)	2.6 (3.28)	(-3.8 , 9.1)	0.4221

Table 11. Change in IIEF Erectile Function Domain Score From Baseline to End of Treatment – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	152	12.4 (5.11)	15.3 (7.79)	2.9 (6.38)	2.9 (0.57)	<0.0001
Avanafil 50 mg	152	12.6 (5.20)	18.1 (7.94)	5.4 (7.54)	5.4 (0.57)	<0.0001
Avanafil 100 mg	156	12.6 (5.39)	20.9 (7.90)	8.3 (7.67)	8.3 (0.56)	<0.0001
Avanafil 200 mg	155	12.8 (5.00)	22.2 (7.73)	9.5 (7.03)	9.5 (0.56)	<0.0001

Treatment Comparison	Difference (Tmt 1 – Tmt 2) [4]		
	LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)	6.7 (0.80)	(5.1 , 8.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)	5.5 (0.80)	(3.9 , 7.0)	<0.0001
Avanafil 50 mg (Tmt 1) vs. Placebo (Tmt 2)	2.6 (0.80)	(1.0 , 4.2)	0.0014
Avanafil 200 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	4.1 (0.80)	(2.5 , 5.6)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Avanafil 50 mg (Tmt 2)	2.9 (0.80)	(1.3 , 4.5)	0.0003
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)	1.2 (0.79)	(-0.4 , 2.7)	0.1366

Differences between avanafil groups and placebo increased with dose, especially for changes in SEP3 and SEP2. At end of treatment, for each of the primary endpoints, there was a statistically significant difference over placebo for all three avanafil dosing groups. In addition, the treatment comparisons of avanafil 200 mg and avanafil 100 mg with avanafil 50 mg were statistically significant for all primary endpoints. However, there was no statistically significant difference between avanafil 200 and 100 mg.

Results of the per-protocol analyses (not shown in this AR) for all 3 primary efficacy endpoints were similar to those for the ITT population.

Analyses of the secondary efficacy endpoints in the ITT population were statistically significant for the Change in IIEF Questionnaire Scores and Change in Secondary Subject Diary Responses for all avanafil doses. The treatment comparisons of each avanafil dose with placebo were statistically significant as well. No the treatment comparisons between avanafil doses for secondary efficacy endpoints has been provided.

The responses to the Global Assessment (subjects that answer that the study treatment improved their erections) for the ITT population at the end of treatment were affirmative in 26.6% of subjects in the placebo group, in 52.1% of subjects in the avanafil 50 mg group, 61.2% of subjects in the avanafil 100 mg group, and in 72.5% of subjects in the avanafil 200 mg group. The treatment comparisons of each avanafil dose with placebo were statistically significant.

The responses to the Future Use Questions (they would buy the study treatment if it were available today) for the ITT population at the end of treatment were affirmative in 26.6% of subjects in the placebo group, in 45.1% of subjects in the avanafil 50 mg group, 58.5% of subjects in the avanafil 100 mg group, and 67.1% of subjects in the avanafil 200 mg group. The treatment comparisons of each avanafil dose with placebo were statistically significant.

Other Efficacy Analyses

Regarding successful or satisfied subject diary responses (question SEP 3 and SEP 2) by time interval, the proportion of attempts resulting in successful intercourse was higher for all three avanafil doses than placebo at any time of assessment (Tables 20 and 21), with very similar percentage of success across all time intervals. After 4 hours, the number of attempts reported was too low to reach any conclusion.

Overall, all avanafil doses were better than placebo for the rest of efficacy analyses, including: Improvement in IIEF Erectile Function Domain Score, Normalized IIEF Erectile Function Domain Score at End of Treatment, Number of Successful Sexual Attempts, and Mean Number of Sexual Attempts Per Week.

Table 20. 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)

Table 21. Summary of Attempts in Which Subjects Were Able to Insert Their Penis Into Their Partner's Vagina by Time Interval (SEP2) – 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 (%)	31 (41.9)	45 (73.8)	93 (84.5)	48 (87.3)
>15 minutes and ≤30 minutes				
Number of attempts	973	1014	1008	1071
Successful erections [1] n (%)	564 (58.0)	748 (73.8)	767 (76.1)	876 (81.8)
>30 minutes and ≤45 minutes				
Number of attempts	648	825	953	776
Successful erections [1] n (%)	343 (52.9)	578 (70.1)	729 (76.5)	637 (82.1)
>45 minutes and ≤60 minutes				
Number of attempts	500	499	537	494
Successful erections [1] n (%)	300 (60.0)	324 (64.9)	422 (78.6)	389 (78.7)
>60 minutes and ≤120 minutes				
Number of attempts	347	336	447	386
Successful erections [1] n (%)	169 (48.7)	201 (59.8)	341 (76.3)	307 (79.5)
>120 minutes and ≤240 minutes				
Number of attempts	73	88	107	100
Successful erections [1] n (%)	50 (68.5)	53 (60.2)	73 (68.2)	79 (79.0)
>240 minutes and ≤360 minutes				
Number of attempts	8	18	12	23
Successful erections [1] n (%)	6 (75.0)	15 (83.3)	6 (50.0)	17 (73.9)
>360 minutes				
Number of attempts	12	22	23	23
Successful erections [1] n (%)	6 (50.0)	16 (72.7)	22 (95.7)	23 (100.0)

- **Study TA-302**

Participant flow

A total of 1378 subjects were enrolled in the study and 390 of them were randomized to treatment (130 to placebo, 129 to avanafil 100mg, and 131 to avanafil 200mg). Of the randomized subjects, 330 (85.4%) completed the study and 57 (14.6%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was similar across the treatment groups (15.4% in the placebo group, 15.5% in the avanafil 100mg, and 13% in the avanafil 200mg). The most common reasons for discontinuation from the study were protocol non-compliance (which also includes subjects who withdrew consent) (n=36, 9.2%), loss to follow-up (n= 15, 3.8%), and adverse event (n= 4, 1.0%).

Baseline data

The majority of subjects were white (80.5%) with a mean age of 58.0 years. Overall, the ED severity was mild for 21.8% of subjects, moderate for 31.3% of subjects, and severe for 46.9% of subjects. At baseline, the mean duration of ED was 72.3 months, with a longer mean duration of ED was for the placebo and avanafil 100 mg groups than for the avanafil 200 mg group. Overall, 89.5% of subjects had type II diabetes and 10.5% of subjects had type I diabetes and the mean duration of diabetes was 11.3 years.

Overall, 260 (67.0%) subjects reported a history of hypertension, 54 (13.9%) subjects reported a history of coronary artery disease, and 34 (8.8%) subjects reported a history of depression (a higher proportion of them in the avanafil 100 mg group).

In total, 239 (61.6%) subjects took antihypertensive medications, 24 (6.2%) subjects took alpha blockers, and 23 (5.9%) subjects took antidepressants. A higher proportion of subjects in the avanafil 100 mg group took antihypertensive medications and alpha blockers than in the other treatment groups.

Approximately 40% of the patients (n=154) reported treatment with insulin analogs.

Mean treatment duration in placebo group was 10.64 weeks versus 10.33 to 10.91 weeks in the avanafil groups. The mean number of total doses taken in the placebo group was 17.29 vs. 18.12-19.06 in the avanafil groups.

Based on the patient's diary responses, mean time from drug intake until the start of sexual activity for successful attempts was 49.89 min for the placebo group, and 54.57 min and 68.96 min in the avanafil 100mg and 200 mg groups, respectively. Mean time from drug intake to the start of sexual activity for unsuccessful attempts was 60.74 min for the placebo group and 54.19 min and 58.83 min. for the 100mg and 200mg avanafil groups respectively.

Numbers analysed

The ITT population included 379 subjects, 127 in the placebo group, 126 in the 100mg avanafil, and 126 in the 200mg avanafil groups.

Outcomes and estimation

The result of the primary efficacy endpoints (changes from baseline to the end of treatment in the percentage of sexual attempts in which the subject was able to maintain an erection, in the percentage of sexual attempts in which the subject was able to achieve penetration successfully and in the IIEF erectile function domain) are presented in tables 9-11 below:

Table 9. Change in the Percentage of Sexual Attempts between the Run-in Period and the Treatment Period in Which the Subject Was Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	127	10.0 (16.41)	20.5 (29.10)	10.5 (27.73)	13.6 (2.77)	<0.0001
Avanafil 100 mg	126	8.2 (17.42)	34.4 (36.37)	26.2 (33.71)	28.7 (2.78)	<0.0001
Avanafil 200 mg	126	8.0 (14.91)	40.0 (36.34)	32.1 (32.94)	34.0 (2.76)	<0.0001
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				20.4 (3.84)	(12.9 , 28.0)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				15.2 (3.84)	(7.6 , 22.7)	<0.0001
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				5.3 (3.84)	(-2.3 , 12.8)	0.1724

Table 10. 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) – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	127	36.0 (36.63)	42.0 (39.34)	5.9 (31.16)	7.5 (2.85)	0.0088
Avanafil 100 mg	126	32.5 (35.19)	54.0 (39.40)	21.5 (37.19)	21.5 (2.85)	<0.0001
Avanafil 200 mg	126	41.5 (37.66)	63.5 (38.67)	22.0 (35.00)	25.9 (2.90)	<0.0001
Treatment Comparison				Difference (Tmt 1 – Tmt 2) [4]		
				LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				18.4 (3.95)	(10.6 , 26.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				14.0 (3.94)	(6.3 , 21.8)	0.0004
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				4.4 (3.97)	(-3.4 , 12.2)	0.2719

Table 11. Change in IIEF Erectile Function Domain Score From Baseline to End of Treatment – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	125	11.4 (5.01)	13.2 (7.72)	1.8 (6.24)	1.8 (0.64)	0.0066
Avanafil 100 mg	125	11.2 (4.78)	15.8 (8.26)	4.6 (7.00)	4.5 (0.64)	<0.0001
Avanafil 200 mg	125	12.0 (5.10)	17.3 (8.65)	5.3 (7.50)	5.4 (0.66)	<0.0001
Treatment Comparison				Difference (Tmt 1 – Tmt 2) [4]		
				LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				3.6 (0.87)	(1.9 , 5.3)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				2.8 (0.87)	(1.1 , 4.5)	0.0017
Avanafil 200 mg (Tmt 1) vs. Avanafil 100 mg (Tmt 2)				0.8 (0.88)	(-0.9 , 2.6)	0.3387

Differences between avanafil groups and placebo increased with dose, especially for changes in SEP3 and SEP2. At end of treatment, for each of the primary endpoints, there was a statistically significant difference over placebo for all the avanafil dosing groups. However, there was no statistically significant difference between avanafil 200 and 100 mg.

Results of the per-protocol analyses (not shown in this AR) for all 3 primary efficacy endpoints were similar to those for the ITT population.

Analyses of the secondary efficacy endpoints in the ITT population were statistically significant for the Change in IIEF Questionnaire Scores and Change in Secondary Subject Diary Responses for all avanafil doses. The treatment comparisons of each avanafil dose with placebo were statistically significant as well. No the treatment comparisons between avanafil doses for secondary efficacy endpoints has been provided.

The responses to the Global Assessment (subjects that answer that the study treatment improved their erections) for the ITT population at the end of treatment were affirmative in 20.8% of subjects in the placebo group, 45.7% of subjects in the avanafil 100 mg group, and in 55% of subjects in the avanafil 200 mg group. The treatment comparisons of each avanafil dose with placebo were statistically significant.

The responses to the Future Use Questions (they would buy the study treatment if it were available today) for the ITT population at the end of treatment were affirmative in 22.5% of subjects in the placebo group, in 40.5% of subjects in the avanafil 100 mg group, and 47.9% of subjects in the avanafil 200 mg group. The treatment comparisons of each avanafil dose with placebo were statistically significant.

Other Efficacy Analyses

Regarding successful or satisfied subject diary responses (question SEP 3 and SEP 2) by time interval, the proportion of attempts resulting in successful intercourse was higher for all three avanafil doses than placebo across all time intervals. The percentage of success was very similar across different time periods of taking avanafil as shown in the tables below (Tables 20 and 21). This puts into question the sensibility of the tool to identify an optimum window for successful attempts. After 3 hours, the number of attempts reported was too low to reach any conclusion. Overall, all avanafil doses were better than placebo for the rest of efficacy analyses, including: Improvement in IIEF Erectile Function Domain Score, Normalized IIEF Erectile Function Domain Score at End of Treatment, Number of Successful Sexual Attempts, and Mean Number of Sexual Attempts Per Week.

Table 20. Summary of Attempts in Which Subjects Maintained an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) by Time Interval –ITT Population

Time Interval From Dose to Attempt Statistic	Placebo	Avanafil 100 mg	Avanafil 200 mg
≤15 minutes			
Number of attempts	46	53	45
Successful intercourse [1] n (%)	12 (26.1)	33 (62.3)	16 (35.6)
>15 minutes and ≤30 minutes			
Number of attempts	719	749	797
Successful intercourse [1] n (%)	218 (30.3)	322 (43.0)	358 (44.9)
>30 minutes and ≤45 minutes			
Number of attempts	722	616	711
Successful intercourse [1] n (%)	166 (23.0)	223 (36.2)	298 (41.9)
>45 minutes and ≤60 minutes			
Number of attempts	369	420	387
Successful intercourse [1] n (%)	69 (18.7)	161 (38.3)	137 (35.4)
>60 minutes and ≤120 minutes			
Number of attempts	331	336	348
Successful intercourse [1] n (%)	94 (28.4)	160 (47.6)	168 (48.3)
>120 minutes and ≤240 minutes			
Number of attempts	62	59	102
Successful intercourse [1] n (%)	12 (19.4)	20 (33.9)	60 (58.8)
>240 minutes and ≤360 minutes			
Number of attempts	13	8	22
Successful intercourse [1] n (%)	2 (15.4)	2 (25.0)	9 (40.9)
>360 minutes			
Number of attempts	21	12	31
Successful intercourse [1] n (%)	1 (4.8)	6 (50.0)	21 (67.7)

Table 21. Summary of Attempts in Which Subjects Were Able to Insert Their Penis Into Their Partner's Vagina (SEP2) by Time Interval – ITT Population

Time Interval From Dose to Attempt Statistic	Placebo	Avanafil 100 mg	Avanafil 200 mg
≤15 minutes			
Number of attempts	46	53	45
Successful insertions [1] n (%)	28 (60.9)	36 (67.9)	28 (62.2)
>15 minutes and ≤30 minutes			
Number of attempts	719	749	797
Successful insertions [1] n (%)	386 (53.7)	438 (58.5)	542 (68.0)
>30 minutes and ≤45 minutes			
Number of attempts	722	616	711
Successful insertions [1] n (%)	316 (43.8)	359 (58.3)	472 (66.4)
>45 minutes and ≤60 minutes			
Number of attempts	369	420	387
Successful insertions [1] n (%)	151 (40.9)	231 (55.0)	238 (61.5)
>60 minutes and ≤120 minutes			
Number of attempts	331	336	348
Successful insertions [1] n (%)	157 (47.4)	215 (64.0)	241 (69.3)
>120 minutes and ≤240 minutes			
Number of attempts	62	59	102
Successful insertions [1] n (%)	19 (30.6)	40 (67.8)	74 (72.5)
>240 minutes and ≤360 minutes			
Number of attempts	13	8	22
Successful insertions [1] n (%)	4 (30.8)	7 (87.5)	17 (77.3)
>360 minutes			
Number of attempts	21	12	31
Successful insertions [1] n (%)	1 (4.8)	8 (66.7)	26 (83.9)

- **Study TA-303**

Participant flow

A total of 528 subjects were enrolled in the study and 298 of them were randomized to treatment (100 to placebo, 99 to avanafil 100mg, and 99 to avanafil 200mg). Of the randomized subjects, 252 (7684.6%) completed the study and 46(15.4%) subjects discontinued from the study. The percentage of subjects who discontinued from the study was higher in the placebo group (24 subjects, 24%) than the avanafil groups (14 subjects [14.1%] in the avanafil 100mg, and 8 subjects [8.1%] in the avanafil 200mg). The most common reasons for discontinuation from the study were withdrawal of consent (n=23, 7.7%), loss to follow-up (n= 10, 3.4%), protocol non-compliance (n=7, 2.3%), and adverse event (n= 5, 1.7%). The ITT population included 286 subjects, 196 in the placebo group, 194 in the 100mg avanafil, and 96 in the 200mg avanafil groups.

Baseline data

The majority of subjects were White (81.5%) with a mean age of 58.4 years. Across all treatment groups, the ED severity at baseline was mild for 9.1% of subjects, moderate for 19.5% of subjects, and severe for 71.5% of subjects. At baseline, the mean duration of post-surgery ED for all subjects was 18.7 months, with a mean duration of ED similar between the treatment groups. The majority of subjects had robotic

surgical technique for their radical prostatectomy (80.5%), and most subjects had initiated previous penile rehabilitation treatment within 3 months of their prostatectomy (78.2%).

In total, 125 (41.9%) subjects reported a history of hypertension, 38 (12.8%) subjects reported a history of other cardiovascular disease, and 35 (11.7%) subjects reported a history of depression. With the exception of hypertension (lower proportion of subjects in the avanafil 100mg group reported a history of it), the treatment groups were comparable with respect to medical history category.

In total, 118 (39.6%) subjects took antihypertensive medications, 28 (9.4%) subjects took antidepressants, and 4 (1.3%) subjects took alpha blockers. Overall, the usage of concomitant medications was similar between the treatment groups. No information on previous PD5E inhibitors usage has been provided.

All subjects included in this study had undergone bilateral nerve sparing; no subjects with unilateral nerve sparing were included in the study. Mean treatment duration in placebo group was 10.24 weeks versus 10.72 to 11.35 weeks in the avanafil groups. The mean number of total doses taken in the placebo group was 15.35 vs. 15.54 -17.58 in the avanafil groups.

Outcomes and estimation

The result of the primary efficacy endpoints (changes from baseline to the end of treatment in the percentage of sexual attempts in which the subject was able to maintain an erection, in the percentage of sexual attempts in which the subject was able to achieve penetration successfully and in the IIEF erectile function domain) are presented in tables 9-11 below:

Table 9. Change in the Percentage of Sexual Attempts Between the Run-in Period and the Treatment Period in Which the Subject Was Able to Maintain an Erection of Sufficient Duration to Have Successful Intercourse (SEP3) – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	96	4.1 (12.57)	8.9 (20.54)	4.8 (19.89)	13.9 (3.42)	<0.0001
Avanafil 100 mg	94	5.1 (14.31)	23.4 (35.03)	18.3 (30.18)	28.0 (3.54)	<0.0001
Avanafil 200 mg	96	5.3 (13.42)	26.4 (35.03)	21.1 (31.83)	29.4 (3.33)	<0.0001
				Difference (Tmt 1 – Tmt 2) [4]		
Treatment Comparison				LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				15.6 (3.90)	(7.9 , 23.2)	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				14.2 (3.92)	(6.4 , 21.9)	0.0004

Table 10. 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) – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	96	20.1 (33.78)	19.7 (32.58)	-0.4 (21.59)	7.5 (3.68)	0.0417
Avanafil 100 mg	94	17.2 (30.06)	32.5 (38.74)	15.3 (32.21)	22.3 (3.66)	<0.0001
Avanafil 200 mg	96	19.9 (33.77)	40.8 (40.79)	20.8 (31.78)	27.7 (3.48)	<0.0001
Treatment Comparison				Difference (Tmt 1 – Tmt 2) [4]		
				LS Mean (SE)	95% CI	P-value
Avanafil 200 mg (Tmt 1) vs. Placebo (Tmt 2)				20.1 (3.99)	12.3, 28.0	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				14.8 (4.00)	6.9, 22.7	0.0003

Table 11. Change in IIEF Erectile Function Domain Score From Baseline to End of Treatment – ITT Population

Treatment	n [1]	Baseline [2] Mean (SD)	End of Treatment [3] Mean (SD)	Change From Baseline [4]		
				Mean (SD)	LS Mean (SE)	P-value
Placebo	95	9.1 (4.47)	9.3 (5.51)	0.1 (3.56)	1.2 (1.16)	0.2964
Avanafil 100 mg	94	9.1 (4.38)	12.6 (8.08)	3.6 (7.04)	4.7 (1.18)	<0.0001
Avanafil 200 mg	96	9.5 (4.42)	14.7 (8.65)	5.2 (7.00)	6.2 (1.11)	<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)				5.0 (0.89)	3.3, 6.8	<0.0001
Avanafil 100 mg (Tmt 1) vs. Placebo (Tmt 2)				3.5 (0.89)	1.7, 5.2	0.0001

Differences between avanafil groups and placebo increased with dose, especially for changes in SEP3 and SEP2. At end of treatment, for each of the primary endpoints, there was a statistically significant difference over placebo for all the avanafil dosing groups. However, no the treatment comparisons between avanafil doses for the primary efficacy endpoints has been provided.

Analyses of the secondary efficacy endpoints in the ITT population were statistically significant for the Change in IIEF Questionnaire Scores and Change in Secondary Subject Diary Responses for all avanafil doses. The treatment comparisons of each avanafil dose with placebo were statistically significant as well.

The responses to the Global Assessment (subjects that answer that the study treatment improved their erections) for the ITT population at the end of treatment were affirmative in 10.7% of subjects in the placebo group, 31.3% of subjects in the avanafil 100 mg group, and in 41.3% of subjects in the avanafil 200 mg group. The treatment comparisons of each avanafil dose with placebo were statistically significant.

The responses to the Future Use Questions (they would buy the study treatment if it were available today) for the ITT population at the end of treatment were affirmative in 27.7% of subjects in the placebo group, in 39.8% of subjects in the avanafil 100 mg group, and 57.6% of subjects in the avanafil 200 mg group. The treatment comparison of each avanafil dose with placebo was statistically significant only for the 200mg avanafil dose.

Other Efficacy Analyses

Regarding successful or satisfied subject diary responses (question SEP 3 and SEP 2) by time interval, the proportion of attempts resulting in successful intercourse was higher for all three avanafil doses than placebo. After 2 hours, the number of attempts reported was too low to reach any conclusion.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis of efficacy data from 2 of the Phase 3 pivotal studies (TA-301 and TA-302) and study TA-05 (phase 2 dose-finding study) has been provided. The other phase III pivotal study (TA-303) has not been included in the integrated analysis set and its results have been analysed separately. This can be acceptable, since from an efficacy point of view, the population from that study (subjects with ED post bilateral nerve sparing radical prostatectomy) can be considered different.

The majority of subjects in the integrated analysis population were white (84%), 56.6 years of age on average and with a mean IIEF erectile function domain score of 12.9 (moderate severity). Regarding weight, height and BMI, the mean measurements in the integrated population were 94.3 Kg, 178.1 cms and 29.7 kg/m2, respectively. Those measurements are not in line with those expected to be the average measurements in multiple zones of the EU. Adding the fact that all the clinical phase III trials for avanafil have been carried out in the USA, extrapolation of the observed results to the EU population needed further discussion from the Applicant. Additional data provided indicated an increase in exposure (by means of Cmax and AUC) in subjects with lower body weight, which is in line with the increase in AEs frequency observed in subjects with normal BMI (≥ 18.5-<25kg/m2), when compared to overweight and/or obese subjects..

Prior use of PDE5 inhibitors in the pivotal studies, ranged from 71.9% (study TA-301) to 75.3% (in the diabetic study, TA-302), with similar percentages across all treatment arms. This percentage is similar to those observed with other PDE5 inhibitors. Taking into consideration that these data were not provided originally and that patients with a prior history of treatment failure with other PD5E inhibitors were excluded from the pivotal trials, it was questioned whether the population included was an enriched population, favouring the observed efficacy results. The Applicant argued that by defining treatment failure as “the failure to respond to two or more specific PDE5 inhibitors, with each used on multiple attempts”, the Applicant tried to identify subjects unresponsive to PDE5 inhibitor therapy as a class, rather than to a single agent. It is noted that the implementation of this criterion resulted in the exclusion of only 4 subjects in study TA.301 (general population with ED). Therefore, based on the data and arguments provided by the Applicant, the possible impact of the enrichment of the population on the observed efficacy can be considered not relevant.

Table 1 Summary of Results for Primary Efficacy Endpoints (Studies TA-05, TA-301, TA-302, and TA-303) –ITT Population

Treatment	Study TA-05			Study TA-301			Study TA-302			Study TA-303		
	Baseline Mean (SD)	Treatment Mean (SD)	Change LS Mean (SE)	Baseline Mean (SD)	Treatment Mean (SD)	Change LS Mean (SE)	Baseline Mean (SD)	Treatment Mean (SD)	Change LS Mean (SE)	Baseline Mean (SD)	End of Treatment Mean (SD)	Change LS Mean (SE)
Percentage of Attempts Resulting in Successful Intercourse (SEP3)												
Placebo	16.9 (19.62)	28.9 (30.16)	11.2 (4.21)	12.6 (17.82)	27.0 (31.41)	14.1 (2.57)	10.0 (16.41)	20.5 (29.10)	13.6 (2.77)	4.1 (12.57)	8.9 (20.54)	13.9 (3.42)
Avanafil 50 mg	21.2 (19.61)	53.4 (33.89)	34.4* (4.19)	13.5 (18.58)	41.3 (35.94)	27.8* (2.58)	-	-	-	-	-	-
Avanafil 100 mg	19.1 (20.38)	58.6 (33.61)	40.0* (4.03)	13.9 (18.87)	57.1 (36.05)	43.4* (2.56)	8.2 (17.42)	34.4 (36.37)	28.7* (2.78)	5.1 (14.31)	23.4 (35.03)	28.0* (3.54)
Avanafil 200 mg	20.4 (18.92)	61.9 (32.99)	43.0* (4.18)	12.5 (18.52)	57.0 (37.78)	44.2* (2.57)	8.0 (14.91)	40.0 (36.34)	34.0* (2.76)	5.3 (13.42)	26.4 (35.03)	29.4* (3.33)
Avanafil 300 mg	18.6 (20.51)	64.3 (32.28)	46.0* (4.14)	-	-	-	-	-	-	-	-	-
Percentage of Attempts Resulting in Successful Vaginal Penetration (SEP2)												
Placebo	56.6 (36.06)	60.5 (36.55)	-0.2 (3.53)	46.7 (36.34)	53.8 (37.88)	7.1 (2.33)	36.0 (36.63)	42.0 (39.34)	7.2 (2.85)	20.1 (33.78)	19.7 (32.58)	7.5 (3.68)
Avanafil 50 mg	67.8 (29.71)	76.1 (29.97)	11.5* (3.51)	45.4 (36.72)	64.3 (37.21)	18.2* (2.34)	-	-	-	-	-	-
Avanafil 100 mg	61.6 (34.68)	79.2 (26.51)	16.7* (3.37)	46.6 (38.24)	73.9 (32.26)	27.2* (2.32)	32.5 (35.19)	54.0 (39.40)	21.5* (2.85)	17.2 (30.06)	32.5 (38.74)	22.3* (3.66)
Avanafil 200 mg	66.8 (31.02)	79.8 (27.90)	15.4* (3.50)	48.3 (38.22)	77.3 (31.44)	29.8* (2.33)	41.5 (37.66)	63.5 (38.67)	25.9* (2.90)	19.9 (33.77)	40.8 (40.79)	27.7* (3.48)
Avanafil 300 mg	62.8 (32.59)	83.7 (20.52)	20.8* (3.46)	-	-	-	-	-	-	-	-	-

Statistically significant p-value for the treatment comparison between avanafil and placebo is indicated by an asterisk (*).

Table 1 Summary of Results for Primary Efficacy Endpoints (Studies TA-05, TA-301, TA-302, and TA-303) –ITT Population (cont.)

Treatment	Study TA-05			Study TA-301			Study TA-302			Study TA-303		
	Baseline Mean (SD)	Treatment Mean (SD)	Change LS Mean (SE)	Baseline Mean (SD)	Treatment Mean (SD)	Change LS Mean (SE)	Baseline Mean (SD)	Treatment Mean (SD)	Change LS Mean (SE)	Baseline Mean (SD)	End of Treatment Mean (SD)	Change LS Mean (SE)
IIEF Erectile Function Domain Score												
Placebo	15.8 (4.04)	16.9 (7.32)	0.9 (0.95)	12.4 (5.11)	15.3 (7.79)	2.9 (0.57)	11.4 (5.01)	13.2 (7.72)	1.8 (0.64)	9.1 (4.47)	9.3 (5.51)	1.2 (1.16)
Avanafil 50 mg	16.1 (3.46)	19.4 (7.54)	3.2 (0.94)	12.6 (5.20)	18.1 (7.94)	5.4* (0.57)	-	-	-	-	-	-
Avanafil 100 mg	16.2 (4.08)	22.3 (7.00)	6.1* (0.90)	12.6 (5.39)	20.9 (7.90)	8.3* (0.56)	11.2 (4.78)	15.8 (8.26)	4.5* (0.64)	9.1 (4.38)	12.6 (8.08)	4.7* (1.18)
Avanafil 200 mg	16.5 (3.82)	22.4 (7.41)	6.0* (0.94)	12.8 (5.00)	22.2 (7.73)	9.5* (0.56)	12.0 (5.10)	17.3 (8.65)	5.4* (0.66)	9.5 (4.42)	14.7 (8.65)	6.2* (1.11)
Avanafil 300 mg	16.5 (3.83)	22.5 (7.17)	6.1* (0.94)	-	-	-	-	-	-	-	-	-

Statistically significant p-value for the treatment comparison between avanafil and placebo is indicated by an asterisk (*).

In general, results from the integrated analyses are in line with those observed in the individual studies, with a slightly lower magnitude of the effect for all 3 co-primary endpoints in the integrated analyses. Differences between avanafil 100mg and 200mg with avanafil 50mg and placebo were statistically significant, while comparison between avanafil 100mg and 200mg did not reach statistical significance, as previously seen in the individual studies.

In the integrated population as well as the individual studies TA-302 and TA-303, the magnitude of changes for all 3 co-primary endpoints observed among prostatectomisedsubjects was similar to those reported for diabetics; when compared with those observed among general population subjects (TA-301) the magnitude observed in both subpopulations was smaller than those observed in the general population subjects. These findings were the grounds for a MO. New analysis of the data confirms these findings. The applicant stated that the smaller improvements in diabetics and prostatectomised subjects was also observed in other marketed PDE5 inhibitors and concluded that the SPC should set appropriate expectations for obtaining a satisfactory response.

Overall, discontinuations were higher in the avanafil 50mg group (31 subjects, 14.8%) then the placebo group (47 subjects, 13.9%), and the other two avanafil treatment groups (38 subjects, 11.1% in the 100mg dose and 31 subjects, 9.2% in the 200mg dose). A substantial percentage of discontinuations were due to "withdrawn consent/protocol non-compliance" and "lost for follow-up.

Mean EF domain scores at baseline was in the moderate ED range (12.6-13.6) for all subjects. At the end of treatment, mean EF domain scores for patients in placebo group stayed in the same category (14.8) of ED severity, while patients in avanafil groups showed mean values of about 18.4-20.4.

With regards to time from dose to start of action, findings are in line with those previously mentioned for the individual studies, with very small differences on the percentage of success at the different time periods.

With regards to time from dose to start of action, based on data collected by the subjects on their diaries (after the sexual encounter) in all 3 pivotal studies, all avanafil doses had higher success rates than the placebo group. However, the percentage of success was very similar across the different time periods. This finding questions the sensibility of this tool to identify an optimum window for success and precludes from reaching sound conclusions about the start of action.

Clinical studies in special populations

Diabetic subjects or subjects with ED as a result of a bilateral nerve sparing radical prostatectomy have been included in the clinical avanafil studies (TA-302 and TA-303, respectively). With regards to age, the studies allowed inclusion of males with no upper age limit in 2 of the pivotal studies. Due to the low number of very elderly subjects (≥75 years old) enrolled, the efficacy and safety profiles have not been described in depth. Adequate post-marketing pharmacovigilance measures have been proposed to allow more a better characterization.

Certain subpopulations have not been included in the avanafil clinical development program; therefore the efficacy of avanafil has not been demonstrated. These populations include: patients with ED due to spinal cord injury or other neurological disorders and subjects with severe renal or hepatic impairment. The lack of data in these subpopulations has been adequately reflected in the SPC.

Data from subjects with mild-moderate renal impairment included in the phase III pivotal studies showed dose-related improvements and an unexpected decrease in efficacy (in subjects with mild renal impairment) when compared to subjects with normal function. The Applicant hypothesizes that the observed differences are likely related to greater impairment of vascular or nerve function in this subset of patients compared to the general study population, in a manner similar to diabetics or

prostatectomized subjects, making them less responsive to pharmacological treatment for ED. The observed decrease in efficacy in this population is reflected in the SPC.

Supportive study

- **TA-314**

In order to assess long term efficacy, the Applicant chose an open-label design study (phase III open label extension study TA-314) with a 52-week treatment period.

All eligible subjects were initially assigned to treatment with avanafil 100 mg (regardless of the dose taken during the qualifying trial). Subjects who has tolerance issues with avanafil 100 mg could request a dose reduction to 50 mg. Subjects who tolerated treatment with avanafil 100 mg could request a dose increase to 200 mg, based on self-determined need. Like in the pivotal studies, subjects were instructed to take 1 dose of study drug approximately 30 minutes prior to initiation of sexual activity, without restrictions on the timing consumption of food or alcohol. Subjects were requested to make at least 4 attempts per month at sexual intercourse and for each attempt, they were instructed to record information regarding the administration of study drug and sexual experience in a subject diary.

Allowed and prohibited medications were similar to those in the phase III pivotal studies.

Methods

The objective of this study was to evaluate the long-term safety, tolerability, and efficacy of avanafil in men with mild to severe ED.

The 3 co-primary efficacy endpoints were the following: percentage of sexual attempts during the 52-week treatment period in which subjects were able to maintain an erection of sufficient duration to have successful intercourse (SEP3); percentage of sexual attempts during the 52-week treatment period in which subjects were able to insert the penis into their partner's vagina (SEP2); and mean IIEF erectile function domain score at the end of the 52-week treatment period.

Other efficacy endpoints included: changes in the three co-primary efficacy variables from the end of the qualifying study (TA-301 or TA-302) to the end of the extension study; percentages of sexual attempts resulting in successful intercourse (SEP3) and successful vaginal penetration (SEP2) by dose for subjects who took at least 4 doses of avanafil 100 mg consecutively and at least 4 doses of avanafil 200 mg consecutively in study TA-301, TA-302, and/or TA-314; mean IIEF domain scores at the end of treatment and changes from baseline to end of treatment; percentage of subjects with an improvement in IIEF erectile function domain score from baseline to end of treatment; percentage of subjects with an IIEF erectile function domain score in the normal range at the end of treatment; and counts and percentages of positive responses to diary questions by time interval between dose administration and attempt.

The primary population for efficacy analyses was the ITT Population (subjects who took at least 1 dose of study drug and had at least one post-dose efficacy assessment). The last observation carried forward convention was used to adjust for missing data.

An "a priori" definition of success was established study 314 as a positive change from baseline for diary question 5 (SEP3) between the run-in period and the first 30 days of the TA-314 treatment period. Additionally, "responders" were defined as subjects who were on active treatment and were successful in the qualifying study or subjects who were successful during the first month of TA-314. However, the applied definition had limitations, since the magnitude of that "positive" change considered clinically relevant was not defined.

Results

Overall, 536 (75.3%) subjects voluntarily increased their dose from 100 mg to 200 mg during study TA-314; 171 (24.0%) subjects remained at 100 mg; 3 (0.4%) subjects voluntarily decreased their dose from 100 mg to 50 mg; 1 (0.1%) subject was dispensed all three doses of avanafil; and 1 (0.1%) subject was not dispensed study drug during this study.

The majority of subjects were white (85.7%) with an average age of 56.4 years. Overall, the ED severity was mild for 29.1% of subjects, moderate for 33.4% of subjects, and severe for 37.5% of subjects. The mean baseline IIEF erectile function domain score was 12.2 and at baseline of the qualifying study, the mean duration of ED was 75.9 months. Subjects who received avanafil 100 mg and 200 mg had lower mean IIEF erectile function domain scores at baseline, indicating a greater degree of ED, and a longer mean duration of erectile dysfunction than subjects who received avanafil 100 mg only.

Of the 712 enrolled subjects, 492 (69.1%) subjects completed the study and 220 (30.9%) subjects discontinued from the study. After achievement of planed enrolment numbers that ensured retention of at least 300 subjects through 6 months and 100 subjects through 12 months, the Sponsor decided to close enrolment. The primary reasons for discontinuation from the study were subject withdrawal of consent (13.8%), lost to follow-up (9.4%), protocol non-compliance (4.2%), and adverse event (2.8%). For the overall discontinuations and discontinuations due to AEs, the percentages of discontinuations were lower in the avanafil 100 mg-200 mg group (25.9% and 1.5%, respectively) than the avanafil 100 mg only group (46.2% and 6.4%, respectively).

Overall, the mean percentage of sexual attempts resulting in successful intercourse (SEP3) was 66.6% during the 52-week treatment period and the mean change from baseline was 54.8%. For subjects who received avanafil 100 mg only, the mean percentage of sexual attempts resulting in successful intercourse was 67.7% during the 52-week treatment period and the mean change from baseline was 54.4%. For subjects who received avanafil 100 mg and 200 mg, the mean percentage of sexual attempts resulting in successful intercourse was 66.3% during the 52-week treatment period and the mean change from baseline was 54.9%.

Overall, the mean percentage of sexual attempts resulting in successful vaginal penetration (SEP2) was 80.2% during the 52-week treatment period and the mean change from baseline 36.9%. For subjects who received avanafil 100 mg only, the mean percentage of sexual attempts resulting in successful vaginal penetration was 83.3% during the 52-week treatment period and the mean change from baseline was 39.2%. For subjects who received avanafil 100 mg and 200 mg, the mean percentage of sexual attempts resulting in successful vaginal penetration was 79.4% during the 52-week treatment period and the mean change from baseline was 36.4%.

Overall, the mean IIEF erectile function domain score was 12.3 at baseline and 22.6 at the end of treatment; the mean change in IIEF erectile function domain score from baseline to end of treatment was 10.3. For subjects who received avanafil 100 mg only, the mean IIEF erectile function domain score was 22.2 at the end of treatment and the mean change in IIEF erectile function domain score from baseline was 8.7. For subjects who received avanafil 100 mg and 200 mg, the mean IIEF erectile function domain score was 22.7 at the end of treatment and the mean change in IIEF erectile function domain score from baseline 10.8.

Dose-response relationship

Across all pivotal studies, there was a superiority trend of avanafil 100mg and 200mg over avanafil 50mg, with statistically significant differences of all 3 avanafil doses over placebo. However, differences between 100mg and 200mg were minimal, not reaching statistical significance or clinical relevance in the double-blind controlled studies. The Applicant supports the superiority of the avanafil 200mg mostly in the open label extension study and the benefits observed in patients who voluntarily elected to increase

their avanafil dose from 100mg to 200mg. Due to the nature of its design, its results are methodologically more difficult to interpret, especially taking into account that the decision to increase the dose was made (subjectively) by the own subjects. Additionally, the Applicant states that it could be reasonable to allow patients with an unsatisfactory response to the 100 mg dose to try the 200 mg dose and that certain subpopulations of patients could benefit from the higher avanafil dose. However, the population subgroup(s) candidate for the avanafil 200mg still remain to be clearly identified and safety data should also have to be taken into consideration. Of note, the comparison of avanfil 200mg and 100mg in diabetics and prostatectomized subjects, subpopulations with possible poor response, was not statistically significant or clinically relevant. The avanafil 200mg dose has not shown statistical or clinical superiority over the 100mg and it has not been study enough in certain subpopulations, such as very elderly patients (≥75 years old), or patients with low BMI.

Responder Analysis

A responder analysis (based on the definition provided by the Applicant) was performed for subjects in study TA-314. The mean age of responders was 55.5 years and the mean age of non-responders was 61.0 years. The responder group had a lower proportion of subjects with diabetes than the non-responder group (26.7% vs. 56.3%). Responders had a shorter mean duration of ED than non-responders (73.6 months vs. 88.9 months) and a lower proportion of subjects with severe ED at baseline than the non-responder group (32.3% vs. 63.0%). Of the subjects who were non-responders to 100 mg (n=172), 112 (65.1%) subjects were responders to 200 mg.

Maintenance of the effect

Mean percentage of sexual attempts resulting in successful intercourse was 42.1% during the final month of the qualifying study and 66.6% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful intercourse was 24.5%. For subjects who received avanafil 100 mg only during study TA-314, the mean percentage of sexual attempts resulting in successful intercourse was 54.5% during the final month of the qualifying study and 67.7% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful intercourse was 13.2%. For subjects who received avanafil 100 mg and 200 mg during study TA-314, the mean percentage of sexual attempts resulting in successful intercourse was 38.7% during the final month of the qualifying study and 66.3% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful intercourse was 27.6%.

Overall, the mean percentage of sexual attempts resulting in successful vaginal penetration was 63.5% during the final month of the qualifying study and 80.2% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful vaginal penetration was 16.7%.

For subjects who received avanafil 100 mg only during study TA-314, the mean percentage of sexual attempts resulting in successful vaginal penetration was 74.5% during the final month of the qualifying study and 83.3% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful vaginal penetration was 8.8%. For subjects who received avanafil 100 mg and 200 mg during study TA-314, the mean percentage of sexual attempts resulting in successful vaginal penetration was 60.5% during the final month of the qualifying period and 79.4% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful vaginal penetration was 18.9%.

Mean IIEF erectile function domain score was 18.2 at endpoint of the qualifying study and 22.6 at the end of treatment of the open-label study; the mean change in IIEF erectile function domain score from endpoint of the qualifying study was 4.3. For subjects who received avanafil 100 mg only during study TA-314, the mean IIEF erectile function domain score was 20.9 at endpoint of the qualifying study and

22.2 at the end of treatment of the open-label study; the mean change in IIEF erectile function domain score from endpoint of the qualifying study was 1.4. For subjects who received avanafil 100 mg and 200 mg during study TA-314, the mean IIEF erectile function domain score was 17.5 at endpoint of the qualifying study and 22.7 at the end of treatment of the open-label study; the mean change in IIEF erectile function domain score from endpoint of the qualifying study was 5.2.

Overall, efficacy was maintained during the 52-week observation period, with increasing efficacy results as time passed, which is expected.

- **TA-03**

Study TA-03 was a Phase 2, double-blind, randomized, crossover study in 51 adult male subjects who were in a monogamous, heterosexual relationship for at least 3 months and who had a subjective complaint of erectile dysfunction and had been experiencing unsatisfactory sexual intercourse during the past 3 months. Subjects were treated with avanafil 200mg or sildenafil 100mg in random order during various treatment periods and were instructed to initiate sexual activity at defined intervals after dosing. Each treatment period was 3 to 4 weeks in duration. Subjects were to maintain a diary of all treatments and to record the time between treatment and initiation of sexual activity and the effectiveness of treatment in a diary. Subjects completed the IIEF questionnaire and global evaluation questions at the end of each treatment period. Avanafil 200 mg treatment improved primary endpoints of erectile function and was similar to sildenafil 100 mg treatment for SEP2 and time from dosing to achieve an erection sufficient for intercourse. The mean percentages of sexual attempts resulting in successful intercourse for avanafil 5- to 10-minute, sildenafil 5- to 10-minute, and avanafil 2-hour treatment were 56%, 69%, and 75%, respectively. The mean percentages of sexual attempts resulting in successful vaginal penetration for avanafil 5- to 10-minute, sildenafil 5- to 10-minute, and avanafil 2-hour treatment were 79%, 85%, and 88%, respectively.

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program to assess the efficacy and safety of avanafil in men with ED included 18 Phase 1 studies, 3 Phase 2 studies, and 4 Phase 3 studies. These studies evaluated the pharmacokinetics, efficacy, and safety of avanafil at doses ranging from 12.5 mg to 800 mg. The doses for which the applicant is seeking approval are 50 mg, 100 mg, and 200 mg. All of the studies of the clinical development program were conducted in various centres in the United States, with exception of one phase 1 PK study (HP-01), which included 65 young (ages 18-35 years) healthy volunteers and it was conducted in France.

A total of 460 subjects were screened for study TA-05, and 295 of them were randomized. A total of 284 (96.3%) subjects attempted and reported at least one sexual encounter with study medication and were included in the ITT population. Of the 295 subjects randomized, 249 (84.4%) completed the treatment protocol. The reasons for discontinuation included withdrawal by subject (26, 8.8% subjects), AE (5, 1.7% subjects), protocol violation (1, <1% of subjects), non-compliance (2, 0.7% subjects), lost to follow-up (10, 3.4% subjects), and lack of efficacy (2, 0.7% subjects).

At the end of the treatment period (12 weeks), for each of the co-primary endpoints, there was a statistically significant difference from placebo for all avanafil dose groups. In the study, the superiority of avanafil 200mg over 100mg did not reach statistical significant or clinical relevance. This finding is in line with the results observed across the pivotal studies.

Based on results from study TA-05, the Applicant chose avanafil 50mg, 100mg and 200mg to be used in the phase III pivotal studies. There were minimal differences in efficacy between avanafil 200mg and 300mg with a less favourable safety profile for the higher avanafil dose; the Applicant concluded that no additional benefit was obtained from the avanafil 300mg and did not include the higher dose in the phase III clinical program .

The Phase 3 clinical studies included one study in the general population with ED (TA-301), one study in diabetic men with ED (TA-302), one study in males with ED following nerve-sparing radical prostatectomy (TA-303) and one open label extension study to assess the long-term safety and tolerability of avanafil (TA-314). Collectively, these studies randomized a total of 1334 subjects.

Prior to the start of the phase III clinical program, the selection of doses to be used in the clinical trials was defined in a dose-finding phase II study. Based on its results, the avanafil 50mg, 100mg and 200mg doses were chosen.

The overall design of the phase III pivotal studies (parallel, double blind placebo controlled studies, with measurement of efficacy at 12 weeks and the chosen efficacy parameters) is considered appropriate. In fact, the clinical development performed for avanafil is similar to those performed with previous PDE5 inhibitors already authorized for ED. The CHMP noted that no active comparison of avanafil with other PDE5 inhibitors has been done, which would have allowed contextualizing the efficacy results in the current clinical setting of ED treatment. However, although this information would have been useful, the study design of the pivotal trials is considered acceptable to demonstrate the efficacy of this medicinal product.

Efficacy data and additional analyses

The majority of subjects included in the pivotal studies were white (84%), an average age around 56 years and a mean IIEF erectile function domain score in the moderate severity range.

Prior use of PDE5 inhibitors in the pivotal studies, ranged from 71.9% (study TA-301) to 75.3% (in the diabetic study, TA-302), with similar percentages across all treatment arms. This percentage is similar to those observed with other PDE5 inhibitors. Based on the data and arguments provided by the Applicant, the possible impact of the enrichment of the population on the observed efficacy can be considered not relevant.

With regards to weight, height and BMI, it was noted that the mean measurements in the integrated population (94.3 Kg, 178.1 cms and 29.7 kg/m2, respectively) are not the expected average measurements in multiple zones of the EU. A subgroup analysis based on the subjects´ BMI was not originally performed. The Applicant was requested to further discuss the extrapolation of the observed results to the EU population. With regards to weight, additional data provided indicated an increase in exposure (by means of Cmax and AUC) in subjects with lower body weight, which is in line with the increase in AEs frequency observed in subjects with normal BMI (⩾18.5-<25kg/m2), when compared to overweight and/or obese subjects.

In the pivotal studies, for each of the co-primary endpoints at the end of treatment, there was a statistically significant difference from placebo for all three avanafil doses. Additionally, comparisons of both avanafil 100 mg and 200 mg with avanafil 50mg (TA-301) were statistically significant for all 3 co-primary endpoints. However, when a comparison was done between avanafil 100 mg and 200mg doses, there was no statistically significant difference. The Applicant argued that this finding could be due to several factors, such as an insufficient sample size or inter-subject variability. While this can be agreed on, the superiority of the avanafil 200mg over 100mg rests on an open label extension study (TA-314) in which the decision to increase the dose was made by the own subjects and not based on a more objective basis. However, it can be argued that both doses (100mg and 200mg) have proven superiority over placebo and it can be left open for the healthy young subject and their doctor to decide on the need to increase the dose.

Results in special populations such as diabetics and subjects with nerve sparing prostatectomy were smaller than those in the general population study and further justification about the clinical relevance of the observed effects was requested. The applicant stated that the smaller improvements in diabetics and prostatectomised subjects were also observed in other marketed PDE5 inhibitors. This information is reflected in the SPC.

The lack of a pre-planned definition of “responders” and “clinically significant” change from baseline for the 3 co-primary endpoints was raised by the Committee during the assessment. In response to this, the Applicant provided a post-hoc analysis defining the minimum threshold for a clinically relevant change from baseline for SEP 3, SEP2 and IIEF as an improvement of 23%, 21% and >4 points, respectively. These values were adopted from data recently published in scientific literature (Rosen et al). Responder data from this post-filing analysis showed that all doses of avanafil were statistically superior to placebo for all three co-primary endpoints (p⩽0.0343) and across all three individual pivotal studies. Clinically relevant improvements, as defined above, were observed for the general population as well as the diabetic and post-prostatectomy populations. Findings also confirmed a smaller effect in diabetics and prostatectomized patients, as previously observed. These data has been reflected in the relevant section of the SmPC in order to give to the prescriber a correct appraisal of the drug effectiveness in populations with these co-morbidities.

To assess the maintenance of the effect beyond 12 weeks, the Applicant has chosen an open-label design study (phase III open label extension study TA-314) with a 52-week treatment period. Although the chosen design is not the most robust to demonstrate long term efficacy, the uncontrolled open extension with active treatment suggests the maintenance of the effect.

Overall, the mean percentage of sexual attempts resulting in successful intercourse was 42.1% during the final month of the qualifying study and 66.6% during the 52-week treatment period; the mean

change in the percentage of attempts resulting in successful intercourse was 24.5%.

There were little differences of results for the avanafil 100mg only group and 100-200mg group. These data seems to suggest that subjects who respond successfully with avanafil treatment are likely to continue responding over time.

Across all pivotal studies, there was a superiority trend of avanafil 100mg and 200mg over avanafil 50mg, with statistically significant differences of all 3 avanafil doses over placebo. However, differences between 100mg and 200mg were minimal, not reaching statistical significance or clinical relevance in the double-blind controlled studies. In addition, the avanafil 50mg dose showed small improvement for all 3 co-primary endpoints.

The time from drug intake to the start of the sexual activity was not well defined during the clinical trials. Based on the patient's diary responses, the percentage of success at different time periods are very similar (from earliest times up to 4-6 hours post-dose), which questions the sensibility of this tool to identify an optimum window for success and precludes from reaching sound conclusions about the start of action.

Overall, the change from baseline for all 3 co-primary endpoints seemed larger in the subgroup of younger subjects (<50 years), for all avanafil doses. In older patients, due to the low number of them enrolled in the pivotal studies and the lack of robust PK data, the efficacy (and safety) profile (s) have not been described in depth, especially for the elderly subjects ($\geqslant$ 70 years old). Adequate post-marketing pharmacovigilance measures have been proposed to allow a better characterization.

In diabetic subjects, the magnitude of changes observed for all 3 co-primary endpoints was smaller in all treatment groups, when compared with those observed among general population subjects. The same trend is observed in the subjects with a radical prostatectomy, which showed even smaller improvements. No comparison between both avanafil doses has been performed for these 2 populations.

Based on ED severity and duration at baseline, the end-of-treatment measurements generally decreased as severity of ED increased.

2.5.2. Conclusions on the clinical efficacy

Clinical efficacy of avanafil in males with ED is supported by three phase III pivotal studies and an open-label extension study. All avanafil doses showed superiority over placebo with statistical significance and clinically relevant improvements from baseline.

As insufficient data was available to support a maximum daily administration frequency of twice a day, the maximum daily administration frequency was restricted to once daily, which has been reflected in section the SmPC.

The number and percentage of subjects $\geqslant$ 70 years of age across the clinical studies is rather small. Ideally, a larger dataset in patients $\geqslant$ 70 years old would have been preferred in order to better characterize the clinical profile of avanafil in this population. The SmPC reflects the limited data available in elderly patients.

2.6. *Clinical safety*

Two analysis cohorts were defined for the safety analyses: the Double-Blind Cohort (the primary safety population for analysis), which included subjects from the double-blind, placebo-controlled studies

(TA-05, TA-301 and TA-302) who received avanafil 50 mg, 100 mg, 200 mg, or placebo; and the phase 3 Double-Blind Cohort, which consists of all subjects from two of the phase III, double-blind, placebo-controlled studies (TA-301 and TA-302). Safety data from the other phase III study TA-303 are presented separately.

The long-term safety analysis set is based on the safety data from the 52 week open-label extension study TA-314.

Patient exposure

Overall, 2144 subjects were exposed to avanafil: 644 subjects in Phase 1 studies, 360 subjects in Phase 2 studies and 1140 subjects in Phase 3 studies. The number of subjects exposed to a dose of ≤50 mg, 100 mg, and 200 mg, was 326, 547, and 1010, respectively. A total of 137 subjects were exposed to higher doses than those proposed for marketing (300-800 mg).

In the phase 1 studies, 644 subjects were exposed to avanafil: 83 subjects received a dose of avanafil ≤50 mg, 73 subjects received avanafil 100 mg, 485 subjects received avanafil 200 mg and 80 subjects received a dose of avanafil >200 mg.

In the Double-Blind Cohort, the mean duration of exposure was 12.1 weeks with an overall mean time on treatment of 10.6 weeks and an overall median time on treatment of 11.3 weeks. The mean total number of doses taken was 17.8 (16.7 doses for the placebo group, 17.5 doses for the avanafil 50 mg group, 18.5 doses for the avanafil 100 mg group and 18.4 doses for the avanafil 200 mg group). In this cohort, 629 of the 1267 subjects (49.6%) took two doses of study drug within 24 hours (171 of the 349 [49.0%] subjects in the placebo group, 113 of the 217 [52.1%] subjects in the avanafil 50 mg group, 179 of the 349 [51.3%] subjects in the avanafil 100 mg group and 166 of the 352 [47.2%] subjects in the avanafil 200 mg group). For subjects who took two doses of study drug within 24 hours (n=629), the mean number of times during the study that two doses were taken within 24 hours was 3.2.

In the Phase III Double-Blind Cohort, the exposure to the study drug was similar to that seen for the Double-Blind Cohort. The mean duration of exposure was 12.2 weeks with an overall mean time on treatment of 10.6 weeks and an overall median time on treatment of 11.3 weeks. The mean total number of doses taken was 18.6 (17.5 doses for the placebo group, 18.6 doses for the avanafil 50 mg group, 19.3 doses for the avanafil 100 mg group and 19.2 doses for the avanafil 200 mg group). In this cohort, 549 of the 1032 (53.2%) took two doses of study drug within 24 hours (158 of the 291 [54.3%] subjects in the placebo group, 88 of the 160 [55.0%] subjects in the avanafil 50 mg group, 151 of the 288 [52.4%] subjects in the avanafil 100 mg group and 152 of the 293 [51.9%] subjects in the avanafil 200 mg group). For subjects who took two doses of study drug within 24 hours (n=549), the mean number of times during the study that two doses were taken within 24 hours was 3.4.

In the long-term safety analysis set (TA-314), the mean duration of exposure to avanafil was 35.3 weeks and the median duration of exposure was 38.1 weeks. Overall, 493 subjects were exposed to avanafil for ≥6 months (26 weeks) and 153 subjects were exposed to avanafil for ≥12 months (52 weeks). Mean and median duration of exposure were longer for subjects who received avanafil 100 mg and 200 mg than for those who received avanafil 100 mg only. In total, 536 (75.3%) subjects were dispensed avanafil 100 mg and 200 mg during the study; 171 (24.0%) subjects were dispensed avanafil 100 mg only; 3 (0.4%) subjects were dispensed avanafil 100 mg and 50 mg; 1 (0.1%) subject was dispensed all three doses of avanafil; and 1 (0.1%) subject was not dispensed study drug during this study.

Overall, the mean total number of doses taken was 68.6: 47.5 doses for subjects who received avanafil 100 mg only during this study; 75.4 doses for subjects who received avanafil 100 mg and 200 mg during this study; and 58.2 doses for subjects in the “other” doses group.

Demographic and baseline characteristics in both of the safety cohorts are comparable to those from the integrated analysis efficacy population, which has already been assessed previously in the efficacy section, along with data from individual studies TA-303 and TA-314.

Adverse events

The overall safety profile for avanafil seems to be in line with that known for other PDE5 inhibitors already authorised and no new safety signals have been observed. In the largest safety cohort provided by the Applicant (double-blind cohort), approximately a third (n=425 [33.5%]) of the subjects reported a TEAE, with a higher incidence in the avanafil treatment groups, although a clear dose-related trend could not be identified. With regards to severity, the majority of the events were mild-moderate in severity, including the drug-related TEAEs.

In the Integrated Double-Blind Cohort (Table 18), 425 (33.5%) subjects reported at least one TEAE during the study. The incidence of TEAEs was higher in the avanafil groups (31.3% to 40.1%) than in the placebo group (25.5%). Overall, 149 (11.8%) subjects had a TEAE that was considered by the investigators to be related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (10.6% to 17.3%) than in the placebo group (4.3%). Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups. The percentage of subjects who discontinued study drug due to an adverse event was similar across all treatment groups. In total, 22 (1.7%) subjects discontinued study drug due to an AE and 6 (0.5%) subjects due to a drug-related TEAE.

The most common system organ classes of TEAEs were infections and infestations (9.2%), nervous system disorders (7.8%) and musculoskeletal and connective tissue disorders (5.1%).

The incidences of TEAEs were higher in the avanafil groups than in the placebo group in the following system organ: nervous system disorders (placebo, 3.4%; avanafil 50 mg, 6.9%; avanafil 100 mg, 8.9%; and avanafil 200 mg, 11.6%); vascular disorders (placebo, 0.6%; avanafil 50 mg, 3.7%; avanafil 100 mg, 6.3%; and avanafil 200 mg, 4.0%); and gastrointestinal disorders (placebo, 2.6%; avanafil 50 mg, 4.1%; avanafil 100 mg, 4.3%; and avanafil 200 mg, 5.4%).

The incidences of the following TEAEs were higher in the avanafil groups than in the placebo group: upper respiratory tract infection (placebo, 0.3%; avanafil 50 mg, 1.8%; avanafil 100 mg, 1.1%; and avanafil 200 mg, 1.4%); influenza: (placebo, 0.0%; avanafil 50 mg, 0.5%; avanafil 100 mg, 1.7%; and avanafil 200 mg, 0.3%); headache (placebo, 1.7%; avanafil 50 mg, 5.1%; avanafil 100 mg, 6.9%; and avanafil 200 mg, 10.5%); nasal congestion (placebo, 1.1%; avanafil 50 mg, 1.8%; avanafil 100 mg, 2.9%; and avanafil 200 mg, 2.0%); sinus congestion (placebo, 0.3%; avanafil 50 mg, 0.5%; avanafil 100 mg, 0.9%; and avanafil 200 mg, 1.7%); flushing (placebo, 0.0%; avanafil 50 mg, 3.2%; avanafil 100 mg, 4.3%; and avanafil 200 mg, 4.0%); and dyspepsia (placebo, 0.0%; avanafil 50 mg, 0.5%; avanafil 100 mg, 0.6%; and avanafil 200 mg, 1.4%).

In study TA-05, the incidence of headache was higher in the avanafil 300 mg group (26.3%) than the other treatment groups (placebo [3.6%], avanafil 50 mg [7.1%], avanafil 100 mg (11.7%), and avanafil 200 mg [12.5%]). No major differences in the incidences of other specific TEAEs were observed between avanafil 300 mg and the other treatment groups.

In the Phase III double-blind cohort, 343 (33.2%) subjects had a TEAE, being the incidence of TEAEs higher in the avanafil groups (32.5% to 39.2%) than in the placebo group (25.1%). Overall, 103 (10.0%) subjects had a TEAE that was considered related to study drug. The incidence of drug-related TEAEs was higher in the avanafil groups (8.8% to 15.7%) than in the placebo group (3.1%).

Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups. Overall, 22 (2.1%) subjects discontinued study drug due to an AE.

The percentage of subjects who discontinued study drug was similar for the treatment groups. In total, 6 (0.6%) subjects discontinued study drug due to a drug-related TEAE.

The incidences of TEAEs in the following system organ classes were higher in the avanafil groups than in the placebo group: infections and infestations (placebo, 6.5%; avanafil 50 mg, 8.1%; avanafil 100 mg, 10.1%; and avanafil 200 mg, 9.6%); nervous system disorders (placebo, 3.1%; avanafil 50 mg, 5.6%; avanafil 100 mg, 7.6%; and avanafil 200 mg, 11.6%); gastrointestinal disorders (placebo, 2.4%; avanafil 50 mg, 5.6%; avanafil 100 mg, 4.2%; and avanafil 200 mg, 5.1%); vascular disorders (placebo, 0.3%; avanafil 50 mg, 4.4%; avanafil 100 mg, 6.3%; and avanafil 200 mg, 3.8%); and respiratory, thoracic and mediastinal disorders (placebo, 1.7%; avanafil 50 mg, 2.5%; avanafil 100 mg, 4.9%; and avanafil 200 mg, 5.1%).

The incidences of the following TEAEs were higher in the avanafil groups than in the placebo group: influenza (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 1.7%; and avanafil 200 mg, 0.3%); headache (placebo, 1.4%; avanafil 50 mg, 4.4%; avanafil 100 mg, 5.9%; and avanafil 200 mg, 10.2%); dyspepsia (placebo, 0.0%; avanafil 50 mg, 0.6%; avanafil 100 mg, 0.3%; and avanafil 200 mg, 1.4%); and flushing (placebo, 0.0%; avanafil 50 mg, 3.8%; avanafil 100 mg, 4.2%; and avanafil 200 mg, 3.8%).

In study TA-303, 106 (35.6%) subjects had a TEAE: 23 (23.0%) subjects in the placebo group, 38 (38.4%) subjects in the avanafil 100 mg group and 45 (45.5%) subjects in the avanafil 200 mg group. Forty (13.4%) subjects had a TEAE that was considered related to study drug: 4 (4.0%) subjects in the placebo group, 13 (13.1%) subjects in the avanafil 100 mg group and 23 (23.2%) subjects in the avanafil 200 mg group. Most of the TEAEs were mild or moderate in severity. The distributions of TEAEs by maximum severity were similar for the treatment groups. Six (2.0%) subjects discontinued study drug due to an AE: 1 (1.0%) subject in the placebo group, 3 (3.0%) subjects in the avanafil 100 mg group and 2 (2.0%) subjects in the avanafil 200 mg group. For 2 (2.0%) subjects in the avanafil 100 mg group and 1 (1.0%) subject in the avanafil 200 mg group, the AE that led to discontinuation was considered to be related to study drug.

For the placebo group in study TA 303, the most common system organ classes of TEAEs were infections and infestations (7.0%), investigations (4.0%) and injury, poisoning and procedural complications (4.0%). For the avanafil 100 mg group, the most common system organ classes of TEAEs were infections and infestations (10.1%), nervous system disorders (10.1%) and vascular disorders (7.1%). For the avanafil 200 mg group, the most common system organ classes of TEAEs were investigations (14.1%), nervous system disorders (13.1%), and vascular disorders (11.1%).

The incidences of TEAEs in the following system organ classes were higher in both of the avanafil groups than in the placebo group: infections and infestations (placebo, 7.0%; avanafil 100 mg, 10.1%; and avanafil 200 mg, 9.1%); nervous system disorders (placebo, 2.0%; avanafil 100 mg, 10.1%; and avanafil 200 mg, 13.1%); investigations (placebo, 4.0%; avanafil 100 mg, 6.1%; and avanafil 200 mg, 14.1%); vascular disorders (placebo, 0.0%; avanafil 100 mg, 7.1%; and avanafil 200 mg, 11.1%); musculoskeletal and connective tissue disorders (placebo, 2.0%; avanafil 100 mg, 3.0%; and avanafil 200 mg, 6.1%); and eye disorders (placebo, 0.0%; avanafil 100 mg, 1.0%; and avanafil 200 mg, 2.0%).

For the placebo group, the most frequently reported TEAE (preferred term) was bronchitis (4.0%), while for the avanafil 100 mg group, the most frequently reported TEAEs were headache (8.1%), flushing (5.1%), nasopharyngitis (3.0%), back pain (3.0%) and nasal congestion (3.0%). For the avanafil 200 mg group, the most frequently reported TEAEs were headache (12.1%), flushing (10.1%),

nasopharyngitis (5.1%), electrocardiogram abnormal (3.0%) and upper respiratory tract infection (3.0%).

The incidences of the following TEAEs were higher in both avanafil groups than in the placebo group and increased with dose: headache (placebo, 1.0%; avanafil 100 mg, 8.1%; and avanafil 200 mg, 12.1%); flushing (placebo, 0.0%; avanafil 100 mg, 5.1%; and avanafil 200 mg, 10.1%); nasopharyngitis (placebo, 0.0%; avanafil 100 mg, 3.0%; and avanafil 200 mg, 5.1%); electrocardiogram abnormal (placebo, 0.0%; avanafil 100 mg, 1.0%; and avanafil 200 mg, 3.0%); upper respiratory tract infection (placebo, 0.0%; avanafil 100 mg, 2.0%; and avanafil 200 mg, 3.0%); and dizziness (placebo, 0.0%; avanafil 100 mg, 1.0%; and avanafil 200 mg, 2.0%).

In the long-term safety analysis set (study TA-314), 275 (38.7%) subjects had a TEAE and 79 (11.1%) subjects had a TEAE that was considered to be related to study drug. Most of the TEAEs were mild or moderate in severity, 21 (3.0%) subjects had a TEAE that was considered severe in severity. Twenty (2.8%) subjects discontinued study drug due to a TEAE, and for 10 (1.4%) of these subjects, the AE that led to discontinuation was considered to be related to study drug. The most common system organ classes of TEAEs were infections and infestations (12.2%), nervous system disorders (7.9%), musculoskeletal and connective tissue disorders (5.5%), vascular disorders (5.3%), gastrointestinal disorders (5.1%) and respiratory, thoracic and mediastinal disorders (4.2%). The most frequently reported TEAEs (preferred terms) were headache (5.6%), flushing (3.5%), nasopharyngitis (3.4%), nasal congestion (2.1%), upper respiratory tract infection (1.5%), influenza (1.5%) and back pain (1.5%). The incidence of these events was higher in the avanafil 200 mg group than in the avanafil 100 mg group.

Drug-Related Treatment-Emergent Adverse Events

In the double-blind cohort (Table 20), the incidences of TEAEs were higher in the avanafil groups than in the placebo group in the following system organ classes: nervous system disorders (placebo, 1.1%; avanafil 50 mg, 4.6%; avanafil 100 mg, 6.3%; and avanafil 200 mg, 9.1%); vascular disorders (placebo, 0.3%; avanafil 50 mg, 2.8%; avanafil 100 mg, 4.6%; and avanafil 200 mg, 4.0%); and respiratory, thoracic and mediastinal disorders (placebo, 1.1%; avanafil 50 mg, 1.8%; avanafil 100 mg, 2.9%; and avanafil 200 mg, 3.7%).

The incidences of the following drug-related TEAEs were higher in the avanafil groups than in the placebo group: headache (placebo, 1.1%; avanafil 50 mg, 4.6%; avanafil 100 mg, 5.7%; and avanafil 200 mg, 8.8%); flushing (placebo, 0.0%; avanafil 50 mg, 2.8%; avanafil 100 mg, 4.3%; and avanafil 200 mg, 4.0%); and nasal congestion (placebo, 0.9%; avanafil 50 mg, 1.8%; avanafil 100 mg, 2.0%; and avanafil 200 mg, 1.7%).

In the Phase III double-blind cohort, the incidences of drug-related TEAEs were similar to those in the double-blind cohort.

In study TA 303, for the avanafil 100 mg group, the most frequently reported drug-related TEAEs were flushing (5.1%), headache (5.1%), nasal congestion (3.0%) and hot flush (2.0%). For the avanafil 200 mg group, the most frequently reported drug-related TEAEs were flushing (10.1%), headache (8.1%) and electrocardiogram abnormal (2.0%). All other drug-related TEAEs were reported by only 1 subject in a treatment group.

The incidences of the following drug-related TEAEs were higher in one or both avanafil groups than in the placebo group and increased with dose: headache (placebo, 1.0%; avanafil 100 mg, 5.1%; and avanafil 200 mg, 8.1%) and flushing (placebo, 0.0%; avanafil 100 mg, 5.1%; and avanafil 200 mg, 10.1%).

In the long-term safety analysis set (study TA-314), the most frequently reported drug-related TEAEs were headache (4.4%), flushing (3.4%), nasal congestion (1.5%), dizziness (0.7%), dyspepsia (0.6%) and nausea (0.4%).

Treatment-Emergent Adverse Events by Severity

Overall, most of the TEAEs were mild or moderate in severity and showed a similar distribution by maximum severity across treatment groups. In the double-blind cohort, 19 (1.5%) subjects had a severe TEAE: 4 (1.1%) subjects in the placebo group, 2 (0.9%) subjects in the avanafil 50 mg group, 9 (2.6%) subjects in the avanafil 100 mg group and 4 (1.1%) subjects in the avanafil 200 mg group. The most frequently reported severe TEAE was headache (2 subjects).

Distributions of TEAEs by maximum severity in the Phase III double-blind cohort were similar to those in the double-blind cohort.

In study TA-303, 3 (1.0%) subjects had a severe TEAE: 1 (1.0%) subject in the placebo group with gastroesophageal reflux disease, 1 (1.0%) subject in the avanafil 100 mg group with dyspepsia and 1 (1.0%) subjects in the8 avanafil 200 mg group with cataract and epistaxis. One subject taking avanafil 100 mg had 3 TEAEs (dyspepsia) that were considered to be severe and related to study drug. The events resolved after the subject was permanently discontinued from study drug.

In the long-term safety analysis set (study TA-314), most of the TEAEs were mild or moderate in severity, and 21 (2.9%) subjects had a severe TEAE. Two (0.3%) of these subjects had 1 or more severe drug-related TEAEs. Of these 2 subjects, one of them discontinued the study drug. The TEAEs for both subjects resolved.

Regarding targeted medical events, the reporting of cardiovascular events was low and similar across treatment groups. Special sensory (vision or hearing) events were reported with low frequency, which is expected, since the known incidence of these events is low and with other PDE5 inhibitors has been mostly reported in the post-marketing setting.

In the double-blind cohort, the incidence of upper respiratory TEAEs was higher in the avanafil 100 mg (12.6%) and avanafil 200 mg (12.2%) groups than in the avanafil 50 mg (6.6%) and placebo (6.6%) groups. The incidences hemodynamic changes TEAEs, major cardiac events and special sensory effects were low and similar across treatments. One subject (in study TA-301) had an acute myocardial infarction 4 days after the last dose of study drug (avanafil 50mg). The subject recovered from the event and was discontinued from the study. The investigator considered the event of myocardial infarction as severe and not related to study drug (the subject had a long history of non-compliance with hypertension treatment and severe multi-vessel coronary artery disease). No TEAE of hypotension or priapism were reported.

In the Phase III double-blind cohort, the incidence of upper respiratory events (6.2% placebo, 8.1% avanafil 50 mg, 11.1% avanafil 100 mg and 10.9% avanafil 200 mg) was similar to those seen in the double blind cohort. The incidences of reported hemodynamic changes TEAEs, major cardiac events and special sensory effects were low and similar for the treatments. No TEAE of hypotension or priapism was reported in this cohort.

In study TA-303, the incidence of upper respiratory events was higher in the avanafil 100 mg and 200 mg groups (10.1% and 11.1%, respectively) than in the placebo group (7.0%). The most common upper respiratory event was nasopharyngitis, which appeared to be a dose-related TEAE (0.0% in the placebo group, 3.0% in the avanafil 100 mg group and 5.1% in the avanafil 200 mg group), as well as upper respiratory tract infections (0.0% in the placebo group, 2.0% in the avanafil 100 mg group and 3.0% in the avanafil 200 mg group).

Four subjects had a TEAE categorized as hemodynamic changes (dizziness for 3 avanafil subjects [one in the 100mg group, 2 in the 200mg group] and syncope for one placebo subject). Three subjects had TEAEs categorized as special sensory effects (vision blurred for one subject on avanafil 100 mg and cataracts for 2 subjects on avanafil 200 mg). No subject had a TEAE categorized as priapism or major cardiac events.

In study TA-314, 80 (11.3%) subjects had 1 or more upper respiratory TEAEs, with higher incidence in the avanafil 200 mg group (11.5%) than in the avanafil 100 mg group (4.1%), most of the, of mild or moderate in severity, with the exception of 4 of subjects who had severe TEAEs. The most common upper respiratory TEAEs were nasopharyngitis (3.4%) and nasal congestion (2.1%).

Ten (1.4%) subjects had a haemodynamic change TEAE (9 subjects with dizziness and 1 subject with syncope vasovagal). No differences were observed between the avanafil 100 mg group and the avanafil 200 mg group in the incidence of these events. All of the TEAEs of dizziness were mild or moderate in severity and the TEAE of syncope vasovagal was a SAE moderate in severity (the subject developed symptoms after administration of mepivacaine local anesthesia at the dentist's office, the events resolved within 1 hour; the investigator considered the event not related to study drug and the subject continued in the study).

Four (0.6%) subjects had a special hearing sensory TEAE (2 subjects with vertigo, 1 subject with motion sickness and 1 subject with tinnitus). The TEAEs of vertigo and tinnitus were mild in severity and the TEAE of motion sickness was moderate in severity. Three (0.4%) subjects had a TEAE categorized as special vision sensory effects (1 subject with photophobia, 1 subject with blurred vision and 1 subject with cyanopsia). The TEAEs of photophobia, blurred vision and cyanopsia were mild in severity.

Three (0.4%) subjects had a TEAE categorized as "priapism" while taking avanafil 200 mg (2 subjects with increased erection of mild severity and 1 subject with spontaneous penile erection). One of the TEAEs of increased erection was mild in severity and the other was moderate in severity; the TEAE of spontaneous penile erection was mild in severity. These events did not meet the clinical definition of priapism (i.e., an erection lasting longer than 4 hours).

No subject had a TEAE of hypotension or a major cardiac event in study TA-314.

Subgroup safety analyses based on certain special groups (age and race) and situations (diabetic status, hypertension status, alpha-blocker usage and coronary artery disease status) have been performed. No subgroup analysis based on weight/BMI was provided with the initial submission. Taking into consideration that the average anthropometric measures were not those expected for European subjects, the Applicant was asked to provide safety data based on the several BMI subgroups. It is noted that the overall AEs and drug-related AEs for the avanafil-treated subjects were more frequent in subjects with a BMI<25 (normal BMI subjects), and a dose-related increase was observed. Adequate wording should be included in the SPC regarding the expected increase in AE frequency in subjects with a BMI below 25.

In the age-based subgroup analysis, AE incidences per dose are similar across all age groups, with exception of avanafil 200mg in ≥65 years old subjects. In this age group, an increase in AE frequency was observed.

In the race-based subgroup analysis, incidence of TEAE seemed to be higher in non-black subjects incidence of targeted medical events were similar for both race subgroups.

With regards to diabetic status at baseline, the incidence of reported AEs was higher in the non-diabetics for all treatment groups (including placebo), then in the diabetics. A similar trend was observed based on hypertension status at baseline.

Based on coronary artery disease history at baseline, more subjects with coronary artery disease treated with avanafil 200 mg reported an SAE than those without a history of coronary disease.

Among subjects with concomitant alpha-blocker use, the subjects assigned to avanafil 200mg reported a higher incidence of TEAEs, drug-related TEAEs and SAEs, as it would be expected due to the additive hypotensive effects of both drugs.

Serious adverse event and deaths

One death was reported in the entire avanafil clinical program (subject was assigned to avanafil100 mg group of study TA-301); the event was considered not related to study drug (self-inflicted gunshot wound). In total, in the double-blind cohort, 18 (1.4%) subjects had a SAE. The incidence of SAEs was similar across all treatment groups, none of the SAEs were considered by the investigators to be related to study drug. In total, 22 (1.7%) subjects discontinued study drug due to an AE.

Laboratory findings

With regards to laboratory values and vital signs abnormalities, no new or unexpected signals have been identified.

Vital Signs

In the Double-Blind Cohort, the incidences of abnormal increases/decreases in SBP or DBP in the double-blind cohort were low and similar across treatment groups. Similar incidences were observed in the Phase 3 double-blind cohort. In study TA-303, one subject in the avanafil 200 mg group (Subject 337-005) had an adverse event of hypertension that led to discontinuation of study drug. The event was moderate in severity and was not considered to be related to study drug. The outcome of the event was not resolved.

Electrocardiogram (ECG) parameters and physical examination findings were not summarized for the integrated cohorts.

Safety in special populations

Subjects with severe renal or hepatic failure were excluded from the clinical studies; therefore no safety data is available for this subpopulation of patients. Further safety (as well as efficacy) data from patients with impaired hepatic/renal function included in the pivotal studies or the open label extension study TA-314 was provided and did not show any new safety signals. However, no clinical data are available from subjects with mild-moderate hepatic impairment.

With regards to age, the number and percentage of subjects ≥ 70 years of age across the clinical studies is rather small. The small number of subjects precludes from making a specific recommendation at this time.

Immunological events

This was regarded as not applicable and accepted by the CHMP.

Safety related to drug-drug interactions and other interactions

Avanafil metabolism is principally mediated by the CYP isoforms 3A4 (major route) and 2C9 (minor route). *In vivo* studies have shown a relevant decrease of avanafil metabolism with up to 13-14 fold increase in AUC and 3 fold increase in C_{max} of avanafil in presence of potent CYP3A4 inhibitors such as ketoconazol or ritonavir. Therefore, the use of avanafil is contraindicated with the concomitant use of potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). With regards to less moderate CYP3A4 inhibitors inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of avanafil should not exceed 100 mg as advised in the SPC on a minimum interval interdoses (e.g. 48 hours).

After *in vitro* studies, avanafil is a potential inhibitor of CYP 2C19, 2C8, 2C9 and 2D6. Interaction studies have been performed evaluating the effect of avanafil on specific substrates (e.g. omeprazol, rosiglitazone, and desipramine) as well as with digoxine to explore effect through pGp transporter. The studies evaluated the effect of single doses of avanafil 200 mg on other medicines pharmacokinetics, which is well in accordance with the expected use of avanafil but could have not explored the full potential for interaction. Nevertheless, no safety concerns are expected from avanafil affecting other medicinal products of possible common use in this population through those mechanisms.

With regard to pharmacodynamic interactions, there is a safety concern due to the potential addition of hypotensive effects when avanafil is taken concomitantly with nitrates or hypotensive medicines, as well as acute intake of alcohol. Interaction studies in healthy volunteers with nitrates, alpha-blockers, amlodipine and enalapril have shown different magnitudes of effect, in general of little relevance. Nevertheless attention should be paid on this hypotensive effect in real cardiovascular patients, elderly or with polimedication. A contraindication has been established for concomitant use of nitrates and several precautions are also set with regards to concomitant use of hypotensive medicines and alcohol.

Discontinuation due to adverse events

No important differences in the incidence of adverse events that resulted in study drug discontinuation were observed between the following subgroups: age, race, diabetic status, baseline hypertension, concomitant alpha-blocker use.

Four (8.0%) subjects with coronary artery disease at baseline treated with avanafil 200 mg experienced adverse events resulting in study drug discontinuation compared to 2 (0.7%) subjects without coronary artery disease at baseline treated with avanafil 200 mg. No other differences in the incidences of adverse events resulting in study drug discontinuation were observed between the baseline coronary artery disease status subgroups.

Post marketing experience

Avanafil is not yet marketed in any country and no post-marketing data are available.

2.6.1. Discussion on clinical safety

For the safety analysis, the Applicant has defined two analysis cohorts for safety analyses: the Double-Blind Cohort (subjects from the double-blind, placebo-controlled studies TA-05, TA-301 and TA-302) and the phase III Double-Blind Cohort (subjects from two of the phase III, double-blind,

placebo-controlled studies TA-301 and TA-302). Safety data from the other phase III pivotal study (TA-303) and the open-label extension study (TA-314) were presented separately. The most relevant target population for safety analysis should be the cohort consisting of subjects who were included in all three phase III placebo-controlled pivotal studies, which consists of the largest placebo-controlled pool and comprises the primary population for safety analysis considered to be representative of the main target population. Therefore, the Applicant was requested to provide a new safety analysis based on this new double-blind cohort (including all three phase III trials and the dose-finding phase II study TA-05), which is considered to be the primary population for safety analysis. On the basis of the new double-bling cohort analysis, the incidence of TEAEs was higher in the avanafil groups (31.3% to 39.7%) than in the placebo group (24.9%). In total in the Avanafil-treated groups, 15.2% of patients had a TEAE that was considered related to study drug compared to 4.2% in the placebo group; the distribution of TEAE related to study drug showed a dose-dependent trend (from 10.6% to 18.6%). Most of drug-related TEAEs were mild to moderate and severity tended to increase with the dose. The incidence of SAEs in the new double-blind cohort was low (from 0.9% to 1,6% in the avanafil groups). There was no SAE considered related to study drug. In total, 28 (1.8%) subjects discontinued study drug due to an adverse event. Discontinuation due to drug-related TEAEs was less than 1%.

The most common system organ classes of TEAEs in the avanafil groups were infections and infestations (9.1%), nervous system disorders (7.9%), vascular disorders (5.6%), musculoskeletal and connective tissue disorders (4.8%), and gastrointestinal (4.7%), all AEs known to be associated with the drug class of PDE inhibitors. The incidences of TEAEs in each of these system organ classes was higher in the avanafil groups than in the placebo group, with the exception of infections and infestations where similar incidences were observed for the placebo and the 50 mg avanafil dose. The most commonly reported TEAEs were: Headache (8.2%), Flushing (4.6%), Nasal congestion (2.2%) and Back pain (2.1%).

The most common AEs, headache, flushing, nasal congestion, and dyspepsia occurred more than once in roughly half of the patients who experienced them. Discontinuation due to AEs was low (2% in the avanafil group vs. 1.3 % in the placebo group), for drug-related TEAE the percentage of discontinuation was less 0.8% in the avanafil group vs. 0% in the placebo group. There were 7 withdrawals due to headache considered related to avanafil: 1 in the 50 mg dose group, 3 in the 100 mg group, 4 in the 200 mg group, and 1 in the 300 mg group. Two withdrawals were caused by cardiovascular AEs (angina pectoris and decreased energy and shortness of breath).

The percentage of severe TEAEs increased in the group of patients with Hypertension, Diabetes, or Benign Prostatic Hypertrophy treated with avanafil compared with the general patient population (3.1% vs. 1.7), whereas no change was observed in the placebo group (2.0 general population vs. 2.1 co-morbidity population). From the data submitted by the applicant it is not possible to evaluate which severe TEAE increased in frequency compared to the general population. The specific TEAEs showing a trend towards increased frequency, independently of severity, were upper respiratory tract infections (2.9 % avanafil vs. 1.6% placebo), sinus congestion (1.6 vs. 0.9%), and nasopharyngitis (3.3% vs. 2.8%).

In conclusion, no relevant differences were observed between the safety profile derived from the new double-blind cohort and that identified on the basis of the original safety cohort proposed by the applicant. However, an increased frequency of severe TEAEs was observed in the group of patients with Hypertension, Diabetes, or Benign Prostatic Hypertrophy treated with avanafil compared with the general patient population. Based on additional analyses provided by the Applicant, which showed that the frequencies of severe events were low and not dose related, it is not expected that this sub-population would be at greater risk with use of avanafil.

Demographic and baseline characteristics in both of the safety cohorts and the individual studies

(TA-303 and TA-314) are comparable to those from the integrated analysis efficacy population, which have already been assessed in the efficacy section. No subgroup analysis based on weight/BMI was provided with the initial submission. Taking into consideration that the average anthropometric measures were not those expected for European subjects, the Applicant was asked to provide safety data based on the several BMI subgroups. It is noted that the overall AEs and drug-related AEs for the avanafil-treated subjects were more frequent in subjects with a BMI<25 (normal BMI subjects), and a dose-related increase was observed. The expected increase in AE frequency in subjects with a BMI below 25 has been included in section 4.8 of the SPC.

The overall safety profile for avanafil seems to be in line with that known for other PDE5 inhibitors already authorised and no new safety signals have been observed. In the largest safety cohort provided by the Applicant (double-blind cohort), approximately a third of the subjects reported a TEAE, with a higher incidence in the avanafil treatment groups, although a clear dose-related trend could not be identified. With regards to severity, the majority of the events were mild-moderate in severity, including the drug-related TEAEs.

Regarding targeted medical events, the reporting of cardiovascular events was low and similar across treatment groups. Special sensory (vision or hearing) events were reported with low frequency, which is expected, since the known incidence of these events is low and with other PDE5 inhibitors has been mostly reported in the post-marketing setting.

No subjects reported hypotension TEAEs. Events possibly related to hypotension (dizziness, hypotension, syncope or orthostatic hypotension) were also reported with low frequency across all treatment groups, including placebo. Taking into account that hypotension is a known class effect for PDE5 inhibitors, it is uncertain whether the population included would be a “lower cardiovascular” risk population. Therefore, special attention should be paid to cardiovascular events (hemodynamic changes, major cardiovascular events and other relevant cardiovascular events), as described in the RMP.

Incidence of SAEs reported across the individual studies and in the integrated safety cohorts was low and generally considered by the investigators not related with the study drug.

Subgroup analyses based on certain special groups (age and race) and situations (diabetic status, hypertension status, alpha-blocker usage and coronary artery disease status) have been performed. Safety profile in the different age subgroups has been characterized. However, further assessment of the safety in the older population was requested. The small number in certain age subgroups (such as subjects older than 75 years) do not allow for making a specific recommendation. The wording of the SPC reflects the limited number of very elderly subjects included in the clinical studies. Furthermore, elderly males of >70 years of age have been included as missing information and will be specifically monitored.

In the race-based subgroup analysis, incidence of TEAE seemed to be higher in non-black subjects, while the incidence of targeted medical events was similar for both race subgroups.

Furthermore a higher incidence reporting of AEs was found in the diabetic subgroup (at baseline) compared to the non-diabetics for all treatment groups (including placebo). A similar trend was observed based on hypertension status at baseline.

An increased amount of subjects with coronary artery disease history (at baseline) and treated with avanafil 200 mg reported an SAE compared with those without a history of coronary disease. In that same subpopulation, more subjects with coronary artery disease at baseline treated with avanafil 200 mg experienced AE resulting in study drug discontinuation compared with subjects without coronary artery disease at baseline treated with avanafil 200 mg. This concludes that the 200mg avanafil dose is not well tolerated by this subgroup of patients and caution should be exercised when avanafil doses

over 100mg are used. In addition, information on the interaction with medicinal products reducing systemic blood pressure has been included in the SmPC.

Among subjects with concomitant alpha-blocker use, the subjects assigned to avanafil 200mg reported a higher incidence of TEAEs, drug-related TEAEs and SAEs, as it would be expected due to the additive hypotensive effects of both drugs. The number of subjects with concomitant alpha-blocker and avanafil use was low (n=22) to reach a robust conclusion. The SmPC indicates that concomitant use of alpha-blockers treatment with avanafil should be started at the lowest dose.

With regards to laboratory values and vital signs abnormalities, no new or unexpected signals have been identified. A specific assessment of avanafil effect on vital signs was done in the clinical pharmacology trials.

Mild-moderate renal or hepatic impairments were not exclusion criteria for the pivotal studies, Further safety (as well as efficacy) data from patients with impaired hepatic/renal function included in the pivotal studies or the open label extension study TA-314 was requested. Additionally provided data on renally impaired subjects did not show any new safety signals. However, no additional clinical data are available from subjects with mild-moderate hepatic impairment.

Concomitant use of avanafil and potent CYP3A4 inhibitors produces a marked increase in the plasma levels of avanfil. That drug-drug interaction was also observed with moderate CYP3A4, with a less pronounced increase in the plasma levels of avanafil. A significant interaction between avanafil and nitrates has been reported. When compared to the interaction seen between nitrates and sildenafil, the magnitude of the effect seems to be slightly smaller, although the clinical relevance of this difference is uncertain. The SmPC contraindicates avanafil administration to patients who are under chronic nitrate treatment.

The Applicant has also assessed the concomitant use of avanafil with alpha-blockers and avanafil with antihypertensives. As it would be expected, those combinations present additive effects in blood pressure.

Since avanafil can be used on a daily basis, induction of the metabolism of concomitantly administered drugs may be of relevance, the CHMP recommends the Applicant to post-authorisation conduct *In vitro* studies evaluating the potential of avanafil as an inducer of drug-metabolizing enzymes and submit the report. Furthermore, the CHMP recommends the Applicant to post-authorisation conduct a study evaluating the potential of avanafil as inhibitor of drug transporters and submit the report as well.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The overall safety profile for avanafil seems to be in line with that known for other PDE5 inhibitors already authorised and no new safety signals have been observed.

The CHMP considered that the safety profile acceptable and the SmPC has been adequately worded and appropriate measures are described in the risk management plan.

2.7. *Pharmacovigilance*

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant (DDPS, version1.0 dated on 03-October-2012) fulfils the legislative requirements.

The Applicant has not provided the summary of their Pharmacovigilance System Master File during the course of the evaluation of this procedure. Therefore, the CHMP considered that the applicant should provide it according to the rules established by the new legislation on pharmacovigilance after the marketing authorization has been granted.

Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3, the PRAC considered by consensus that the risk management system for avanafil (Spedra) in the treatment of erectile dysfunction (ED) in adult men could be acceptable provided an updated risk management plan and satisfactory responses to the questions detailed in below were submitted:

• The MAA is requested to complete table 4.2. (Summary of safety concerns from the non-clinical part of the safety specification) classifying the safety concerns into the following categories: important identified risks, important potential risks, important missing information.

• The MAA is required to consider that patients above 70 years of age have not been adequately studied in the clinical trial programme instead of patients above 75 years and modify it in the different corresponding sections of the RMP.

• Regarding the lack of information in elderly patients the MAA should include in each PSUR a description of the use of the drug according to the age of patients (elderly versus non-elderly) and a comparison of the pattern and severity of reported ADRs between elderly and non-elderly patients including a discussion on whether there is a need of additional pharmacovigilance activities (i.e. a PASS) in order to characterize the risks in this population.

• Considering that risk minimization on the safety concerns in the RMP will be addressed through labelling in the SmPC and PIL, it should be ensured that the final SmPC and PIL contain appropriate wordings.

a. In particular, the MAA is requested to change the following paragraphs in the SPC of Spedra as follows (wording underlined), as a risk minimisation measure for the important missing information in elderly males > 70 years of age:

o 4.2 Special populations. Elderly men (≥ 65 years old)

Dose adjustments are not required in elderly patients. Data on men ≥ 70 years old are limited.

o 5.2 subparagraph “Special populations. Geriatric”

Healthy elderly volunteers (65 years or over) had comparable exposure to that seen in healthy younger volunteers (18-45 years). However, data on subjects older than 70 years are limited.

b. Regarding the important potential risk of Hypotension/increased hypotensive effect the MAA should to add a sentence at the end of section 4.8.of the SmPC, in order to reflect that as a class effect, hypotension has been reported in clinical trials and post-marketing with other PDE5 inhibitors.

- The identified risk "Pre-existing cardiovascular disease (in men for who sexual activity is inadvisable)" should be formulated as "pre-existing cardiovascular disease" also in section 1.6.3 of the RMP.
- The MAA is requested to provide in the RMP detailed milestones for the on-going studies (Human study TA-401 and Human study TA-402) included in the Pharmacovigilance Plan.
- The Summary of the RMP should be updated including the requirements contained in this assessment report.

This advice is based on the following content of the Risk Management Plan:

- Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Pre-existing cardiovascular disease
	Prolonged erection (priapism)
Important potential risks	Hypotension/increased hypotensive effect
	Non-artertitic anterior ischaemic optic neuropathy
	Sudden hearing loss
Important missing information	Very elderly males >75 years of age
	Adult males with ED due to spinal cord injury
	Adult males with significant pre-existing cardiovascular disease
	Adult males with severe renal or hepatic impairment
	Patients with retinitis pigmentosa
	Effect of avanafil in 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

- Pharmacovigilance plans

Table 2.2: Ongoing and planned studies in the PhV development plan

Activity/Study title	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Human study 1899-1, category 3	To characterize the effect of avanafil on spermatogenesis	Missing information: E effects of avanafil on spermatogenesis in healthy adult males and adult males with mild ED	Started	February 2014
Human study 1899-2, category 3	To characterize the effect of avanafil on vision	Missing information: Effects of avanafil on multiple parameters of vision	Started	August 2013

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

- Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Pre-existing cardiovascular disease	The SPC and PL contain appropriate contraindications and warnings regarding the use of avanafil by men with pre-existing cardio-vascular disease and in whom sexual activity is inadvisable. This approach to labelling is consistent with other marketed PDE5 inhibitors and will reinforce what is already well-known by healthcare professionals.	N/A
Prolonged erection (priapism)	The SPC and PL contain appropriate warnings about the need to seek medical attention in case of prolonged erection>4 hours. The SPC and PL also warn about using avanafil with caution in patients with penile deformity and in the presence of co-morbid conditions that may predispose to priapism.	N/A
Important potential risks		
Hypotension/increased hypotensive effect	The SPC and PL contain appropriate warnings that the use of avanafil with nitrates may augment the hypotensive effect and regarding the additive	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	vasodilatory effect when used with α-blockers and alcohol.	
Non-artertitic anterior ischaemic optic neuropathy	The SPC and PL contain appropriate contra-indications and warnings to prevent the use of avanafil in people with a history of NAION and to require immediate cessation of use and medical attention if the patient develops visual symptoms.	N/A
Sudden hearing loss	The SPC and PL contain appropriate warnings that the use of avanafil must be dis-continued and medical attention sought if there is any hearing loss or auditory symptoms such as tinnitus develop.	N/A
Important missing information		
Very elderly males >75 years of age	The SPC states that dose adjustment is not required in elderly men.	N/A
Adult males with significant pre-existing cardiovascular disease	The SPC describes the patient populations studied, which do not include men with significant pre-existing cardiovascular disease	N/A
Adult males with severe renal or hepatic impairment	The SPC states that avanafil has not been investigated in men with severe renal or hepatic impairment	N/A
Adult males with ED due to spinal cord injury	There is no reference to patients with spinal cord injury, though there is no reason to suspect any difference in safety in this sub-group. Together, the missing information is adequately described as such in the SPC and also reflected in the PL.	N/A
Patients with retinitis pigmentosa	The SPC includes a contra-indication as per other drugs in the same class as avanafil.	N/A
Effect of avanafil in patients with bleeding disorders or active peptic ulceration	The SPC includes a special warning and precaution for use as per other drugs in the same class as avanafil.	N/A
Effect of avanafil on spermatogenesis in healthy adult males and adult males with mild ED	Specific study in each population to generate further data.	N/A
Effects of avanafil on multiple parameters of	Specific study to generate further data.	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
vision		

The CHMP endorsed this advice without changes.

All the issues raised from the assessment of the RMP were addressed by the Applicant

2.8. *User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Overall the pooled efficacy data showed that the avanafil doses tested in the main efficacy trials (50 mg, 100mg and 200mg), elicited a statistical significant improvement ($p < 0.001$ vs. baseline for the three co-primary efficacy endpoints (percentage of successful vaginal penetrations, percentage of successful intercourses and changes in the IIEF score), although the magnitude of the observed effect for the avanafil 50mg dose was smaller.

In the general population of patients with ED, avanafil, at both the 100 mg and 200 mg doses, resulted in a roughly 30% gain over placebo in the percentage of successful intercourses and 20% increase in vaginal penetration; while the delta in IIEF was greater than 5 points ($p<0.001$ for all comparisons). No statistical difference was observed between the 100 mg and 200 mg doses for any primary endpoint. Similar results were obtained for the secondary endpoints. Roughly 60-70 % of subjects treated with 100 mg or 200 mg gave a positive global assessment questionnaire (GAQ) evaluation of the received treatment compared to 27% of subjects on placebo. Future interest in receiving treatment was expressed in 58-67 % of subjects treated with 100 mg and 200 mg doses, respectively, compared to 27% of subjects who received placebo. Slightly lower percentages of subjects declared themselves interested in future use of avanafil, compared to those who declared to have experienced erection improvement. These findings appear consistent with the indication of the medicinal product in a general population of subjects with ED.

In subjects with ED and diabetes mellitus, avanafil, at 100 mg and 200 mg doses, resulted in a roughly 15% (100 mg) -20% (200 mg) gain over placebo in the percentage of successful intercourses, and in 14-18% increase in vaginal penetration ($p<0.001$ vs. baseline for each endpoint); while the delta in IIEF with placebo was smaller than the previously planned difference of 3 points (2.8; C.I.1.0-4.5). The reduced efficacy of avanafil in the ED subjects with diabetes mellitus was expected and is in line with the generally observed lower efficacy of PDE5 inhibitors in this patient population.

In subjects with ED following a nerve-sparing prostatectomy, a statistically significant improvement over baseline for all three primary efficacy endpoints was observed for Avanafil in subjects. Comparison between the two doses (100 vs. 200 mg) was not performed. The overall rates of achieving an erection

sufficient for penetration were 32% in patients receiving avanafil 100 mg and 41% in those receiving 200 mg, compared to the 20% rate observed with placebo. The overall rate of maintenance of erection to complete a successful intercourse were 23% in patients receiving avanafil 100 mg and 27% in those receiving 200 mg, compared to the 9% achieved with placebo. These findings were statistically significant.

The maintenance of the effect beyond 12 weeks was assessed in an open label extension study with a 52-week treatment period (TA-314). Patients from two of the three double blind pivotal studies were recruited in this study. All patients started with a 100 mg dose regardless of the treatment that they had received on the double blind study. They could escalate to 200 mg or decrease to 50 mg depending on response and tolerance. Overall, the mean percentage of sexual attempts resulting in successful intercourse was 42.1% during the final month of the qualifying study and 66.6% during the 52-week treatment period; the mean change in the percentage of attempts resulting in successful intercourse was 24.5%. There were little differences of results for the avanafil 100mg only group and 100-200mg group. These data seem to suggest that subjects who respond successfully with avanafil treatment are likely to continue responding over time.

Uncertainty in the knowledge about the beneficial effects

Avanafil is the fourth PDE5 inhibitor to be authorised in the EU. The study design of the pivotal trials was performed in line with other available PDE5 inhibitors on the market. Unfortunately, no comparison was made with other PDE5 inhibitors to allow a better understanding of the efficacy results in the context of the current standard of care for treatment of ED.

Although the avanafil clinical development program allowed inclusion of males with no upper age limit, due to the low number of elderly subjects enrolled, it is uncertain whether the efficacy and safety profiles have been well characterized in this subgroup of subjects, especially the very elderly subjects (≥75 years old). This has been adequately addressed in the SmPC and the risk management plan.

Risks

Unfavourable effects

The overall safety profile for avanafil seems to be in line with that known for other PDE5 inhibitors already authorised and no new safety signals have been observed. In the largest safety cohort, approximately a third of the subjects reported a TEAE, with a higher incidence in the avanafil treatment groups compared to placebo, although a clear dose-related trend could not be identified. With regards to severity, the majority of the events were mild-moderate in severity, including the drug-related TEAEs. The incidences of the following TEAEs were higher in the avanafil groups than in the placebo group: upper respiratory tract infection (placebo, 0.3%; avanafil 1.1-1.8%) influenza (placebo, 0.0%; avanafil 0.3-1.7%), headache (placebo, 1.7%; avanafil 5.1-10.5%), nasal congestion (placebo, 1.1%; avanafil 1.8-2.9%), sinus congestion (placebo, 0.3%; avanafil 50 mg, 0.5-1.7%), flushing (placebo, 0.0%; avanafil 3.2-4.3%), and dyspepsia (placebo, 0.0%; avanafil 0.5-1.4%).

The most frequent drug-related TEAEs were headaches, with an incidence ranging between 4.1% (for placebo) and 4.6%-9.1% (for the avanafil groups), and an increasing trend, as the avanafil dose increases. Other frequent drug-related TEAEs were: flushing (placebo, 0.0%; avanafil 2.8-4.3%) and nasal congestion (placebo, 0.9%; avanafil 50 mg, 1.7-2.0%).

Regarding targeted medical events (symptomatic events related to hemodynamic changes, special sensory effects (vision or hearing), major cardiac events, upper respiratory events and priapism), the

reporting of events was low, and similar across avanafil treatment groups. The rate of events was not higher than the rate of events observed in similar trials with PDE5 inhibitors for ED.

Uncertainty in the knowledge about the unfavourable effects

Due to the low number of elderly subjects enrolled, it is uncertain whether the efficacy and safety profiles have been well characterized in this subgroup of subjects, especially the elderly subjects (≥70 years old). The limited data in elderly subjects precludes from making a recommendation in this subpopulation at this time and hence section 4.4 and 5.2 of the SmPC has been amended to reflect this. In addition this has been addressed as missing information in the RMP.

A study evaluating the avanafil effects (therapeutic and supratherapeutic dosing) on QTc prolongation in healthy male subjects did not highlight clinical relevant effects on cardiac repolarisation, although the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval exceeded 10 msec (10.2 msec) thus raising the potential issue that the mean effect of avanafil on QT/QTc interval may be greater than the threshold of 5 msec. To rule out any effect of Avanafil on QTc, the Applicant has been recommended at post-authorisation to present data from the study evaluating the QTc prolongation of avanafil by quartiles of QTc duration for each of the four different algorithms (QTcb, QTcf, QTcI, QTbb).

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment with all three doses of avanafil showed superiority over placebo in the intended indication. The lack of a pre-planned definition of responders and clinically significant change from baseline for all three co-primary endpoints hampers the interpretation of the magnitude of the effect. Also, the absence of a direct comparison with other PDE5 inhibitors poses a limitation to understand the efficacy results in the current clinical setting of ED treatment.

The reported safety profile for avanafil seems to be in line with that known for other PDE5 inhibitors already authorised and no new safety signals or concerns have been observed. TEAEs were generally mild or moderate in severity and resulted in infrequent discontinuations. Based on available safety data a maximum dosing frequency of once a day has been recommended, based on the current available evidence.

Benefit-risk balance

Erectile dysfunction (ED) is becoming more prominent as a result of the aging of EU population and prolonged exposure to some therapies negatively impacting erectile function. Successful treatment of ED is aimed at improving sexual activity, as well as sexual aspects of quality of life, and may indirectly relieve symptoms of depression. The authorization of PDE5 inhibitors in the last decade has significantly improved the medical management of ED. Currently marketed PDE-5 inhibitors share similar beneficial effects and similar safety profile and they have been authorised on the basis of the results from clinical trials with similar designs and endpoints.

Avanafil's clinical developmental program is similar to the other PDE5 inhibitors both in terms of efficacy endpoints, as well as in terms of the baseline characteristics of the target patient population. Clinical efficacy of avanafil in males with ED is supported by three phase III pivotal studies and an open-label extension study. In the general population of patients with ED, avanafil, at both the 100 mg and 200 mg

doses, resulted in a roughly 30% gain over placebo in the percentage of successful intercourses and 20% increase in vaginal penetration; the change in the assessment score for erectile function (delta in International Index of Erectile Function (IIEF) questionnaire) was greater than 5 points ($p<0.001$ for all comparisons). A comparison between the 100-mg and 200-mg doses showed no statistically significant difference.

Overall, the efficacy of avanafil over placebo has been demonstrated. The AE profile of avanafil is within the expected with those known for other PDE5 inhibitors already authorised and no new safety signals have been observed with avanafil.

The benefit/risk balance of avanafil in the treatment of erectile dysfunction in adult males is positive, for the intended indication “treatment of ED in adult males”.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Spedra in the treatment of erectile dysfunction in adult males is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

• Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that avanafil is qualified as a new active substance.