

Expert Opinion

1. Introduction
2. Overview of the market
3. Introduction to the compound
4. Chemistry
5. Pharmacodynamics
6. Pharmacokinetics and metabolism
7. Clinical development
8. Safety and tolerability
9. Conclusion
10. Expert opinion

Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction

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Importance of the field: Erectile dysfunction (ED) is a common sexual problem, affecting up to half of men over 50 years of age. Phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil and vardenafil) are currently the first-line treatment option presented to patients with ED. There exists a significant number of men who remain dissatisfied with the available therapies and are either unable to achieve their therapeutic goals or unwilling to tolerate adverse side effects. Therefore, development of novel PDE5 inhibitors with enhanced selectivity, faster onset of action, increased potency and improved tolerability is desirable.

Areas covered in this review: Preclinical and clinical studies of avanafil, a new oral PDE5 inhibitor being investigated for the treatment of ED. Data were obtained by searching for all English peer-reviewed articles on Medline and any related abstracts presented on avanafil at major international congresses.

What the reader will gain: An understanding of the pharmacokinetic and pharmacodynamic characteristics of avanafil and insight into the drug's clinical efficacy and safety profile.

Take home message: We propose that avanafil, which displays enhanced selectivity, faster onset of action, and a favorable side-effect profile relative to currently available PDE5 inhibitors, may offer an alternative first line treatment option for men with ED.

Keywords: avanafil, erectile dysfunction, PDE5, PDE5 inhibitor, phosphodiesterase type 5

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1. Introduction

Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1], is frequently associated with impaired psychological health and reduced self-esteem. The emotional distress of ED can strain marital relations and further compromise the quality of life of both patients and their partners [2-5]. Epidemiologic studies suggest that approximately 5 – 20% of men have moderate to severe ED. According to the Massachusetts Male Aging Study, ED affects an estimated 52% of non-institutionalized men between the ages of 40 and 70 in the Boston area [6]. Currently, 30 million men in the USA and 150 million men worldwide struggle with ED, a number that will inevitably double within the next 20 years as the aged male population increases [7-9]. ED may be a result of either organic or psychogenic causes, and often involves some combination of both [10,11]. Furthermore, researchers are increasingly recognizing that the development of ED can be a harbinger of cardiovascular disease or early indicator of cardiac morbidity and mortality [12-14]. Historically, pharmacological treatment of ED was limited to penile intracavernosal injections or intraurethral insertion of vasoactive agents, such as prostaglandin E1. However,

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Box 1. Drug summary.

Drug name

Avanafil

Phase

Ongoing Phase III studies

Indication

Erectile dysfunction

Pharmacology description/mechanism of action

Phosphodiesterase type 5 (PDE5) inhibitor

Route of administration

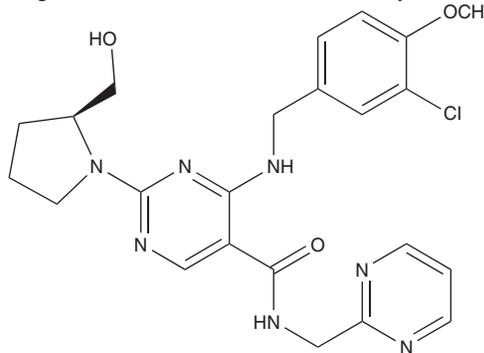
Oral, once daily

Chemical structure

Single enantiomer with S stereochemistry

Pivotal trial(s)

REVIVE (TA-301)
 REVIVE-Diabetes (TA-302)
 TA-303 (ongoing)
 TA-314



these therapies are often associated with penile pain, variable response rates and inconsistent efficacy [15]. With advancements in basic and clinical research in erectile physiology during the last 15 years, the introduction of phosphodiesterase type 5 (PDE5) inhibitors is now widely recognized as first-line therapy for the majority of men with ED [16,17].

Penile erection is determined by vascular pressure changes in the cavernosal sinuses and involves a series of interrelated mechanisms. The nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway is the principal mediator of cavernosal vasodilation and erectile function [18-20]. During sexual arousal or nocturnal tumescence, the release of NO induces smooth muscle relaxation in the trabeculae and arterioles of the penis [21-23]. PDE5 is the major cGMP-hydrolyzing enzyme in the cavernosal tissues and is an important regulator of NO-mediated smooth muscle relaxation. PDE5 inhibitors are structurally similar to cGMP and prevent the breakdown of NO-derived cGMP in vascular smooth muscle cells by competing with cGMP for the catalytic site of PDE5, thus liberating cGMP for continued activation of the NO/cGMP pathway and increasing penile blood flow during sexual stimulation [24]. Acknowledgement of the critical role of PDE5 in erectile physiology, coupled with the synthesis and identification of specific and potent inhibitors of PDE5, has enabled the development of effective oral treatment strategies that have been broadly accepted by healthcare professionals and the lay public alike [24,25]. These medications are considered safe and effective ED treatments, with reported efficacy rates of 60 – 70% [16,25,26].

2. Overview of the market

As recommended in the guidelines of both the American Urological Association (AUA) and the European Association of Urology (EAU), three drugs, sildenafil, tadalafil and vardenafil, are licensed for use in the treatment of ED around the world [25,27]. These orally active agents are self-administered on an as needed basis prior to intercourse. The major clinical differences among these drugs are related to variation of onset and duration of action (Table 1). Sildenafil (Viagra, Pfizer Inc., New York, NY) was the first commercially available PDE5 inhibitor and is generally effective within 30 to 60 min of administration. Sildenafil has a plasma $t_{1/2}$ of about 4 h and a duration of action of up to 12 h [28]. However, maximal plasma sildenafil concentration and time-to-peak are reduced when administration occurs after a high-fat meal [29]. Tadalafil (Cialis, Eli Lilly, Indianapolis, IN) is effective 60 – 120 min after administration, with peak plasma concentration occurring at approximately 2 h and a $t_{1/2}$ of 17.5 h. Efficacy is maintained for up to 36 h and is not affected by food intake. Vardenafil (Levitra, Bayer, Leverkusen, Germany) has a $t_{1/2}$ of about 3.94 h and is also effective 30 – 60 min after administration; however, like sildenafil, a fatty meal (> 57% in fat) may reduce its erectogenic effect [30].

There are a number of different PDE enzymes distributed throughout the various tissues of the body, primarily located in vascular, visceral and pulmonary smooth muscle, with especially high concentrations of PDE5 in the smooth muscle of the corpora cavernosa of the penis. Therefore, the biochemical

Table 1. Summary pharmacokinetics of avanafil relative to commercially available PDE5 inhibitors.

Parameter	Sildenafil 100 mg	Vardenafil 20 mg	Tadalafil 20 mg	Avanafil		
				50 mg	100 mg	20 mg
T _{max} (h)	1.16 ± 0.99	0.660	2.0	0.686	0.555	0.593
t _{1/2} (h)	3.82 ± 0.84	3.94 ± 1.31	17.5	1.07	1.23	1.19
C _{max} (ng/ml)	327 ± 236	20.9 ± 1.83	378	366	871	2153
AUC (ng·h/ml)	1963 ± 859	745 ± 1.82	8066	511	1498	3908

selectivity of an inhibitor of PDE5 is a key factor in determining its side-effect profile [31-33]. Sildenafil and, to less of an extent, vardenafil cross-react slightly with PDE6, the isozyme that predominates in the retina, and has been associated with visual disturbances in up to 6% of patients. Tadalafil, on the other hand, is more than 9000 times more selective for PDE5 over the other PDE isozymes; however, there remains some cross-reactivity with PDE11, an isozyme found in the testes and prostate [34]. This crossreactivity appears to have no effect on either spermatogenesis or testicular function; however, up to 6% of patients using tadalafil complain of back pain and myalgia [35]. Other common adverse side-effects of all PDE5 inhibitors include headache (10–16%), flushing (5–12%), dyspepsia (4–12%), nasal congestion (1–10%), and dizziness (2–3%) [34]. Notably, all three currently available PDE5 inhibitors are contraindicated for coadministration with nitrates because of the risk of developing recalcitrant hypotension [36]. In addition, the concomitant use of PDE5 inhibitors with α -blockers, commonly prescribed to treat symptoms of benign prostatic hypertrophy (BPH), may cause symptomatic orthostatic hypotension under some conditions [37]. Though initially labeled as contraindicated for use with α -blockers, all three PDE5 inhibitors are now labeled for parallel use with caution. As PDE5 inhibitors are mild vasodilators, the additive effect with α -blockers has been shown to decrease blood pressures, thus current recommendations are to begin a PDE5 therapy only once a patient is stable at a particular α -blocker dose, and to begin their PDE5 treatment at the lowest available dose [36,37].

Although the success rates of the three PDE-5 inhibitors range from approximately 60 to 70% [16,25,26], there are still a number of patients who fail to respond clinically. These are usually patients with severe ED involving diabetes mellitus, severe vascular insufficiency, or post-prostatectomy complications [38]. Due to the increased interest in the pharmacological treatment of ED, a number of newer agents (udenafil, mirodenafil) with higher efficacy and lower side-effect profiles are now available in a few countries while others (avanafil, lodenafil, SLx-2101, mirodenafil) are currently under development [27,39].

3. Introduction to the compound

There is currently considerable interest in developing safer and more effective therapies for the treatment of ED based

upon the PDE5 inhibition model. This article focuses on avanafil, a new PDE5 inhibitor that is being developed by Vivus (Mountain View, CA, USA). Avanafil, now in Phase III clinical trials, is a second-generation, highly selective, oral PDE5 inhibitor being investigated for the treatment of ED. Studies to date have demonstrated that avanafil has a T_{max} of 35 min and a t_{1/2} of less than 1.5 h, with 67 – 72% of patients successfully completing intercourse within 15 min of administration. This unique drug profile suggests that avanafil may have a quicker onset of action and may be more selective than other PDE5 inhibitors, which may result in a lower incidence of side effects commonly associated with the currently available PDE5 inhibitors [40].

4. Chemistry

Avanafil (4-[(3-chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide;(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-pyrimidinylmethyl) carbamoyl]pyrimidine) is a pyrimidine derivative that exists as a single enantiomer with S stereochemistry and has a molecular weight of 483.95 Da (Box 1). In its pure form it appears as a white crystalline powder that is minimally soluble in water and moderately soluble in organic solvent. Provisional data on aqueous solubility at a range of pH values indicate that avanafil is more soluble in acidic buffers (~ pH 4) and is much less soluble in neutral and alkaline buffers [41].

5. Pharmacodynamics

The enzymatic inhibition of various PDE isozymes by avanafil was tested relative to that of sildenafil. Avanafil and sildenafil both inhibited PDE5 isolated from canine lung in a concentration-dependent manner; however, avanafil exhibited less inhibition of PDE6 and PDE1 relative to PDE5 when compared with sildenafil [42]. Inhibition of the PDE6 isozyme, which controls levels of cGMP in the retina, may cause the perception of a bluish haze in some patients, an adverse side effect often reported by patients taking sildenafil [43-45]. Research completed using anesthetized dogs has shown that avanafil, when given within a pharmacologically appropriate dose range, is less likely to affect retinal function, supporting evidence of reduced non-specific inhibition of PDE6. In

contrast, sildenafil produced a dose-dependent time delay to peak of the electroretinogram (ERG) positive wave, indicating decreased activation of retinal cone cells secondary to increased inhibition of PDE6. These effects were also demonstrated in male and female conscious dogs, further supporting the conclusion that avanafil, at pharmacologically relevant doses, does not affect retinal function, as assessed by ERG [46].

In a study of isolated rabbit corpora, avanafil, similar to sildenafil, was shown to cause a potentiation of electrical field stimulation-induced relaxation in a concentration-dependent manner (range: 0.01 – 0.3 μM). In anesthetized dogs, pelvic nerve stimulation 5 min after drug injection of both avanafil and sildenafil produced a dose-dependent potentiation of penile tumescence, as well as a dose-dependent linear increase in plasma concentration. The 200% effective doses (ED_{200}) of avanafil and sildenafil on tumescence after intravenous injection were 37.5 $\mu\text{g}/\text{kg}$ and 34.6 $\mu\text{g}/\text{kg}$, respectively.

At intravenous doses of 1 – 300 $\mu\text{g}/\text{kg}/\text{min}$, both avanafil and sildenafil produced a decrease in mean arterial pressure (MAP); however, the hypotensive effect of sildenafil was notably greater than that of avanafil. Avanafil had little or no effect on MAP or vascular resistance of vertebral artery (VRVA) at plasma concentrations of 24.7 – 272.3 $\mu\text{g}/\text{ml}$, whereas sildenafil had greater effects on both MAP and VRVA relative to avanafil at plasma concentrations of 6.6 – 126.4 $\mu\text{g}/\text{ml}$. In intraduodenal tests with anesthetized dogs, avanafil showed a more rapid onset and shorter duration of effect than sildenafil, with maximum effects on penile tumescence of avanafil occurring at 10 min after dosing and that of sildenafil at 30 min after dosing. The effective concentrations 200, 300 and 400% of avanafil were 24.7, 82.0 and 272.3 ng/ml, respectively, while those of sildenafil were 6.6, 28.9 and 126.4 ng/ml, respectively [47].

It has been recognized that coadministration of sildenafil with organic nitrates can result in significant and potentially dangerous hypotension [48,49]. In experiments using anesthetized dogs, both avanafil and sildenafil potentiated nitroglycerin (NTG)-induced hypotension; however, the effect of avanafil was significantly less than that of sildenafil. Moreover, avanafil was shown to potentiate the prevention of collagen-induced platelet aggregation by sodium nitropruside (SNP) to a lesser degree than sildenafil. In an *in vitro* study of human platelet-rich plasma from healthy male volunteers, avanafil at a concentration of 10 μM potentiated the inhibition of platelet aggregation by SNP, while sildenafil had a similar effect at concentrations of just 0.1 and 1 μM [50].

Avanafil had no effect on the general activity and behavior of rats at any time during a 24 h observation period after single oral doses of 30 and 180 mg/kg. At doses of up to 1000 mg/kg, avanafil had no effect on body weight of mice under observation. There was a slight decrease in spontaneous activity noted in one out of six rats at 2 h after oral administration of 1000 mg/kg avanafil, but this effect resolved within 4 h after administration. A battery of studies on the effects of avanafil on the CNS of mice and rats showed there was no

effect on sleeping time, spontaneous locomotor activity, acetic acid-induced writhing, or rectal temperature at oral doses of 100 or 300 mg/kg [51].

In the previously discussed study using conscious dogs, systolic blood pressure, mean blood pressure, diastolic blood pressure and heart rate (SBP, MBP, DBP and HR) were all measured and found to be unaffected by avanafil at doses of 3 and 10 mg/kg. However, at doses of 30 mg/kg, SBP, MBP and DBP decreased in two out of four dogs at 1 or 3 h after administration and HR increased (+80%) in one out of four dogs at 1 h post-administration. Neither respiratory rate (RR) nor electrocardiogram (ECG) parameters were affected by doses up to 30 mg/kg. Avanafil also had no effect on cardiac action potential configuration in isolated guinea pig papillary muscle when given at concentrations of 1 and 10 μM . Although both avanafil and sildenafil caused vasodilation at concentrations of 0.1 μM or less, avanafil showed less vasodilator activity than sildenafil at concentrations of 10 μM or more in the isolated rat aorta. Another series of tests on gastrointestinal function indicated that avanafil, at a concentration of 10 μM , produced a mild inhibition of spontaneous movement in isolated rabbit jejunum and agonist-induced contraction of isolated guinea pig ileum, but did not affect gastric emptying or small intestinal transit time in mice at oral doses of 100 and 300 mg/kg. Avanafil also did not significantly affect gastric juice secretion in rats at doses of 100 or 300 mg/kg [52].

In saline-loaded male rats, 10 or 30 mg/kg doses of avanafil had no effect on urine volume or urinary electrolyte excretion over the entire 24-h observation period. In addition, avanafil did not affect hematocrit, prothrombin time, activated partial thromboplastin time, plasma fibrinogen concentration or euglobulin clot lysis time at 1 h after 5 days of successive oral doses of 100 or 300 mg/kg/day in male rats [52].

6. Pharmacokinetics and metabolism

In dogs, after oral administration of ^{14}C -avanafil (1 mg/kg), the absorption of radioactivity across the gastrointestinal tract and the oral bioavailability were 69.4 and 29.6%, respectively. The plasma concentration of unchanged avanafil reached a C_{max} of 120 ng/ml at 0.69 h after dosing (T_{max}), and then decreased with a $t_{1/2}$ of 1.3 h. In rats, after oral administration of ^{14}C -avanafil (3 mg/kg), 78 and 3% of the administered radioactivity was recovered from the bile and urine, respectively, indicating that the absolute gastrointestinal absorption rate was at least 81%. The plasma concentration reached a C_{max} of 7 ng/ml at 0.5 h after dosing in rats and decreased with a $t_{1/2}$ of 0.85 h.

Maximal concentration of radioactivity in all tissues was reached within 0.5 h after dosing. At this time point, the highest concentrations of radioactivity were found in the gastrointestinal contents, liver and kidney, with much lower concentrations in the brain, spinal cord, eyes and testes. Radioactivity levels in most tissues decreased with time and

elimination was almost complete within 24 h, except for in melanin-containing tissues such as hair follicles and uveal tract of the eyes in pigmented rats [53].

The relationship between avanafil dosage and pharmacokinetics in dogs exhibited a linear correlation. The changes in C_{\max} ($r = 1.00$) and AUC ($r = 1.00$) across the 0.3 – 3.0 mg/kg range showed a linear dependence on dose escalation. The T_{\max} and $t_{1/2}$ were between 0.71 – 0.88 h and 1.4 – 2.0 h at all doses, respectively, and were independent of dose. The binding ratios of avanafil to plasma proteins in rats, dogs, and humans *in vitro* were 92, 93 and 99%, respectively, and binding was predominantly with albumin [53].

Avanafil underwent extensive biotransformation in human liver microsomes with at least 11 metabolites formed mainly by breakdown via cytochrome P450 (CYP3A4), with minor contributions by CYP2C. The inhibitory effects of avanafil metabolites on PDE5 activity were significantly decreased relative to those of the parent compound [53]. Bile served as the main route of excretion of avanafil and its metabolites after both oral and intravenous administration, while at least 34% was reabsorbed via enterohepatic circulation. The excretion of avanafil and its metabolites was nearly complete after 96 h post-intravenous administration in both in dogs and rats (99.2 and 98.6%, respectively). The main route of excretion was in the feces (more than 92% of the dose) via bile after both oral and intravenous dosing [53].

7. Clinical development

7.1 Phase I studies

The safety, tolerability, and pharmacokinetic profile of avanafil was assessed in healthy male volunteers with single doses ranging from 12.5 to 800 mg. Avanafil was shown to be rapidly absorbed and quickly eliminated following oral administration, with a T_{\max} ranging from 0.55 to 1.2 h and an alpha half-life ranging from 0.65 to 1.28 h. C_{\max} and AUC measurements increased in a linear manner over a dose range of 12.5 – 600 mg. Concomitant food intake decreased the C_{\max} by 24% and increased the AUC by 14% compared with fasting conditions [54]. In another study of 48 healthy volunteers between ages 30 and 54, participants were treated with 50, 100 and 200 mg of avanafil or placebo. The results show that calculated values of T_{\max} and $t_{1/2}$ were similar across each of the three dose levels, with T_{\max} ranging from 0.555 to 0.686 h and $t_{1/2}$ ranging from 1.07 to 1.23 h. C_{\max} increased from 0.366 µg/ml for the 50 mg dose to 2.153 µg/ml for the 200 mg dose. Calculated values of pharmacokinetic parameters following 14 days of daily dosing were similar to values obtained following single doses of the drug. One study on the effects of a single 200 mg dose showed the accumulation index to be 1.04 (90% CI 0.88 – 1.20), while another study designed to evaluate the effect of dosing with avanafil every 12 h for 7 days showed it to be 1.07 (90% CI 0.89 – 1.18), indicating that there is no significant drug accumulation with either once- or twice-daily dosing [55].

7.2 Phase II studies

The first double-blind, randomized at-home Phase II trial was completed in June 2003. The erectile response to avanafil after in-clinic administration of 50, 100 and 200 mg doses, in conjunction with visual sexual stimulation, showed that patients had significantly greater penile rigidity, as assessed by RigiScan, than placebo at all doses. Responses to avanafil were similar to or greater than responses to 50 mg sildenafil. With both products, subjects produced erections sufficient to achieve vaginal penetration on approximately 80% of attempts within an average of 20 min of dosing. However, the peak response to avanafil occurred earlier (20 – 40 min post-dose) than the peak response to sildenafil (60 – 120 min post-dose) [56]. The results of this double-blind, randomized, crossover, at-home trial continues to support the rapid absorption and onset of action seen in the earlier in-clinic trial [57].

The hemodynamic effects of coadministration of avanafil with glyceryl trinitrate (GTN) were also assessed by a double blind crossover-design study. The results show that both avanafil and sildenafil are associated with significant reductions in SBP and increases in HR, relative to placebo, when administered with GTN. However, SBP decreases and HR increases following avanafil were consistently less than similar changes following sildenafil, and these differences were statistically significant at multiple time points. The erectogenic effect of avanafil diminished between 4 and 8 h after administration, whereas that of sildenafil remained evident after 12 h. The maximum effect of avanafil was observed at 0.5 h after treatment, which coincided with maximum, or near maximum, plasma concentrations [58].

A double-blind, randomized, parallel-design Phase II study began in March 2004 and assessed the safety and efficacy of avanafil at doses ranging from 50 to 300 mg in the home setting of subjects with mild to moderate ED. Results showed avanafil was able to significantly increase the positive responses for all efficacy parameters (percentage of erections enabling vaginal penetration, percentage of erections lasting long enough for successful intercourse, and erectile function score) at all doses, except for the erectile function score response at the low dose of 50 mg. Avanafil produced erections sufficient for vaginal penetration on 76, 79, 80 and 84% of sexual attempts for the 50, 100, 200 and 300 mg doses, respectively ($p < 0.05$). Erections lasting long enough for successful intercourse were achieved on 54, 59, 62 and 64% of attempts, respectively ($p < 0.0001$) [59].

7.3 Phase III studies

Two Phase III studies (TA-301/302) were recently completed, while two others (TA-303/314) are currently underway (Table 2). TA-301 was a randomized, double-blind, placebo-controlled efficacy and safety study that evaluated three doses of avanafil (50-, 100- and 200-mg) in 646 men with a history of ED. Participants in the study had an average age of 56, with an average duration of ED of 79.3 months and average

Table 2. Phase III clinical studies overview.

Phase-III	ED population	Patient number	Treatment duration	Doses (mg)	Results				
					IIEF*	SEP2(%) [†]	SEP3(%) [‡]	Discontinuation (%)	Adverse events (%)
REVIVE (TA-301)	General	646	12 weeks	Placebo	12.4→15.3	47→54	13→27	3.1	9.1
				50	12.7→18.1	45→64	13→41	1.9	22.8
				100	12.6→20.9	46→74	14→57	3.7	
				200	12.7→22.4	48→77	12→57	2.5	
REVIVE-D (TA-302)	Diabetes	390	12 weeks	Placebo	11.3→13.2	36→42	10→20	15.4	6.9
				100	11.2→15.8	32→54	8→34	15.5	19.0
				200	11.9→17.3	42→63	8→40	13.0	
REVIVE-RP (TA-303)	Post-radical prostatectomy	375	12 weeks	Placebo/100/200	Expected to be available by late 2010				
REVIVE-S (TA-314)	Open-label	300	6 months	NA	Expected to be available by late 2010				
		100	12 months						

*IIEF: International Index of Erectile Function.

[†]SEP2(%): Erections sufficient for penetration as measured by the Sexual Encounter Profile (SEP) question 2.

[‡]SEP3(%): Experienced successful intercourse as measured by the SEP question 3.

International Index of Erectile Function (IIEF) scores of 12.7. Improvements in erectile function were determined according to the Sexual Encounter Profile questionnaire, where SEP2 relates to successful vaginal penetration and SEP3 to the ability to successfully complete intercourse, as well as by changes in IIEF scores. Its results were announced on June 1 2010 at the AUA Annual Meeting in San Francisco. The data showed that participants in the treatment group exhibited dose-dependent increases of 45 – 64%, 46 – 74%, and 48 – 77% success rates for vaginal penetration (SEP2) ($p < 0.001$ versus placebo), as well as increases in average IIEF scores of 12.7 – 18.1, 12.6 – 20.9 and 12.7 – 22.2 for the 50-, 100- and 200-mg doses, respectively. The rate of successful intercourse (SEP3) increased to 41 from 13% in the 50-mg avanafil group and to 57% from 14 and 12% in the 100- and 200-mg groups, respectively ($p < 0.001$ versus placebo). Of men who attempted sexual activity within 15 min of dosing, 66 – 72% of patients in the avanafil groups were successful, compared with 29% of those in the placebo group ($p < 0.001$) [40,60].

TA-302 was a 16 week randomized, double-blind, placebo-controlled Phase III study evaluating two doses of avanafil (100 mg, 200 mg) in 390 men with both diabetes and ED. As of June 7, 2010, the data showed that men with both diabetes and ED had positive results similar to men with only ED while taking avanafil and that more than 60% of subjects on the 200 mg dose of avanafil had erections sufficient for vaginal penetration (SEP2). Erections sufficient for penetration (SEP2) increased from 32 to 54% with the 100 mg dose, and from 42 to 63% with the 200 mg dose, versus an increase of just 36 to 42% in the placebo group ($p < 0.001$). Rates of successful intercourse as measured by SEP3 increased from 8 to 34% and from 8 to 40% in the 100 mg and 200 mg groups, respectively, while the placebo group showed an increase of only 10 to 20% ($p < 0.001$). Both TA-301 and

TA-302 reported no serious adverse events related to drug exposure and showed low rates of common PDE5 inhibitor side effects, such as headache, flushing and nasal congestion [61]. Two other Phase III studies are still ongoing and results of these studies are expected to be available by late 2010. In total, the Phase III avanafil clinical program will enroll approximately 1300 patients [61].

8. Safety and tolerability

A total of 669 males enrolled in the eight Phase I and Phase II clinical trials. Adverse events were generally consistent with the known pharmacology of PDE5 inhibitors. The most commonly reported adverse events included headaches, flushing, nausea, back pain, fatigue and muscle cramps. Most of these events were mild in severity and resolved without medical treatment. At higher doses, postural hypotension and vasovagal responses were also observed, although there has been no consistent, dose-related effects of avanafil on seated or standing blood pressure or on heart rate. Avanafil had no effect on visual color discrimination. No abnormal values for blood pressure, ECG results, oral temperature, respiratory rate, or clinical laboratory tests were considered to be clinically significant, although avanafil did increase the rate of cardiovascular events when co-administered with GTN [56-59].

In the previously discussed Phase III trials (T-301/302), the most commonly reported side effects (all doses combined) included headache (7.0 – 7.8% versus 1.2 – 1.5% for placebo), flushing (2.7 – 4.6% versus 0% for placebo), nasal congestion (1.9 – 2.3% versus 0.8 – 1.2% for placebo), nasopharyngitis (3.1 versus 4.6% for placebo), sinusitis (1.9 versus 0% for placebo), and dyspepsia (1.6 versus 0% for placebo). There were no reports of 'blue vision', hearing loss, or priapism. No serious drug related adverse events were reported [40,60,61].

9. Conclusion

Avanafil is a potent and highly specific PDE5 inhibitor with an attractive safety and efficacy profile, a rapid onset of action, and a short half-life used for the treatment of ED. Compared with other available PDE5 inhibitors, this agent exhibits higher selectivity for PDE5 than for other PDE isoenzymes, limiting the occurrence of undesirable side effects. Through animal studies it has been shown that avanafil has higher selectivity (120-fold) against PDE6 than both sildenafil (16-fold) and vardenafil (21-fold), significantly reducing the occurrence of visual disturbances. Furthermore, unlike tadalafil, it was not shown to inhibit PDE11 [34,39]. The specific drug-related adverse events of traditional PDE5 inhibitors, including visual disturbances (mainly for sildenafil and vardenafil) and myalgia/back pain (mainly for tadalafil), were rarely reported in the recent clinical trials for avanafil. The most commonly reported side effects in patients taking avanafil included headache, nasopharyngitis, flushing, sinus congestion, sinusitis, and dyspepsia. However, there were no serious drug-related adverse events reported in the literature to date.

Preclinical studies show avanafil absorption after oral administration to be rapid. Its absolute absorption rate was more than 81% and maximal concentration in all tissues was reached within 0.5 h after dosing. Avanafil underwent extensive biotransformation in human liver microsomes with at least 11 metabolites identified and was excreted mainly through the fecal/biliary mechanism. Clinical studies to date have demonstrated that avanafil has a fast onset of action, with activity apparent 15 min or less after administration. Future long-term clinical studies are needed to establish whether the unique characteristics of avanafil, such as time of onset and PDE5 specificity, will offer additional clinical benefits relative to other members of the PDE5 inhibitor class.

10. Expert opinion

With the approval of sildenafil in 1998 as the first PDE5 inhibitor available for treatment of ED, and the subsequent approval of vardenafil (August 2003) and tadalafil (November 2003), the PDE5 inhibitors have rapidly become accepted as the first line treatment for ED. This rise to prominence has been facilitated by their ease of use, rapid onset of action, long duration of erection, high rates of first-dose success, reliable efficacy and tolerability and their apparently benign side-effect profile. The novel PDE5 inhibitor avanafil has undergone a number of preclinical and clinical studies to prove its efficacy in the treatment of ED. Its unique pharmacokinetic profile, with its quick onset and short $t_{1/2}$, has exposed a potential role for it as an alternative to currently available PDE5 inhibitors. Although PDE5 inhibition is the main measure of success for this class of drugs, the selectivity, time of onset, duration of action and patient's perception of drug efficacy remain important factors in determining efficacy

and patient satisfaction. Data is still needed from preference trials, head-to-head clinical trials and selection studies on a large scale to obtain statistically valuable data on potential drug superiority. Additionally, more research is still needed to examine the potential efficacy of avanafil in patients who have previously shown no response to PDE5 inhibitors, as well as to examine the effects and duration of potency after chronic use.

Though the selectivity of the current PDE5 inhibitors for PDE5 over PDE6 is 10-fold for sildenafil, 15-fold for vardenafil, and 700-fold for tadalafil, it has been seen that many of these drugs can also partially inhibit other members of the PDE family [62]. This is particularly relevant with inhibition of the PDE6 enzyme that can result in photoreceptor cell death and retinal degeneration [63]. As a result, this class of drugs has not been recommended for patients with hereditary degenerative retinal disorders, such as retinitis pigmentosa [64]. In this respect, avanafil is an excellent alternative, as it shows significantly less non-specific inhibition of other PDE enzymes, leading to a lower risk of retinal functional disturbances when given within a pharmacologically approved dose range. Though further evaluation of avanafil's effects on visual function is required, it appears that the substitution of avanafil for other PDE5 inhibitors can cause a significantly reduced incidence, if not absence, of the visual disturbances commonly described by PDE5 users.

In many patients, ED is just one component of a wider systemic disease, such as diabetes or cardiovascular disease. For those with cardiovascular disease requiring treatment with nitrates, the use of all currently approved PDE5 inhibitors is contraindicated because of the potential for a dramatic fall in blood pressure [65,66]. Phase II clinical studies of avanafil, however, have revealed that, compared with sildenafil, avanafil treatment resulted in smaller changes in SBP and HR when administered in conjunction with NTG. Moreover, the duration of the hemodynamic interaction with NTG was shorter for avanafil than sildenafil, with fewer subjects experiencing clinically significant drops in blood pressure. These data suggest that avanafil, possibly secondary to its significantly shorter $t_{1/2}$, may have the significant secondary benefit as a potentially safe treatment for ED in patients who require nitrates for heart disease, though further clinical studies are still required. Furthermore, as both sildenafil and tadalafil are currently approved for the treatment of pulmonary arterial hypertension, due to a clinically significant increase in pulmonary vasodilation and vascular remodeling, the use of avanafil in this regard also needs to be further investigated [67-69].

Phase I clinical studies have revealed that avanafil has a favorable pharmacokinetic profile (T_{max} of 0.55 – 1.2 h and a $t_{1/2}$ of 1.05 – 1.46 h) that provides rapid onset of action and a potential for twice-daily dosing as needed [55]. Avanafil's rapid absorption justifies dosing the product as little as 30 min prior to sexual activity, and its short plasma $t_{1/2}$ minimizes the risks of drug-drug interactions and adverse side effects. These pharmacokinetic properties are well suited for a drug used as on-demand treatment for ED.

The pivotal Phase III Research Evaluating an Investigational Medication for Erectile Dysfunction (REVIVE; TA-301) study demonstrated avanafil's impressive efficacy and rapid onset of action. Nearly 80% of all patients on the 200 mg dose of avanafil were able to attain erections sufficient for intercourse (SEP2). Moreover, successful intercourse was reported in as little as 15 min and as long as six hours after dosing in subjects who attempted intercourse at those time points. Current data show that prior intake of both food and alcohol before dosing have no deleterious effects on the potency of avanafil, while research has also shown that the efficacy of both sildenafil and vardenafil is improved when taken on an empty stomach. This fact, in association with the rapid onset of action, supports a role for avanafil as a superior treatment for individuals who require on-demand results without prior modifications in lifestyle.

ED is a frequent and distressing complication of common medical conditions with a prevalence among diabetics ranging 35 – 90% [70-72]. Diabetic ED is multifactorial in etiology and is more severe and more resistant to medical treatment compared with nondiabetic ED [73]. The latest TA-302 study on diabetic ED showed that avanafil produced highly significant improvement in erectile function after 16 weeks of drug therapy at 100 – 200 mg doses, with 43 – 54% of men successfully achieving vaginal penetration and 34 – 40% of men successfully completing intercourse, compared with 20% in the placebo group for the latter. These results are similar to those obtained in previous studies performed with sildenafil (56%) [74], vardenafil (57 – 72%) [75] and tadalafil (56 – 64%) [76].

In summary, the mechanism of action of all the PDE5 inhibitors is similar and it seems likely that members of this class can only be differentiated from each other by features other than their efficacy. Factors related to individual chemistries or compound-related toxicities may give rise to differences in safety or tolerability. The available preclinical and clinical results suggest that avanafil is likely to be another effective commercially available PDE5 inhibitor. It has provided high satisfaction rates, rapid onset of action, relatively high selectivity for PDE5, and mild side effects, while the pharmacokinetic and pharmacodynamic profiles are more or less similar to other PDE5 inhibitors. Most notably, however, the relatively short $t_{1/2}$ may provide a significant advantage in terms of ED treatment options for patients on other medications, particularly those taking nitrates for moderate to severe heart disease. In the near future, avanafil may provide a welcome addition to the current therapies for ED, as many patients wish to try a variety of the available drugs before deciding which one is most suitable for their continuous use.

Declaration of interest

M Limin and N Johnson declare no conflicts of interest. WJG Hellstrom has served as a consultant/investigator/advisor for: American Medical Systems, Auxilium, Boehringer Ingelheim, Coloplast, Endo, GlaxoSmithKline, Schering Plough, Bayer, Johnson & Johnson, Medtronic, sanofi-aventis, Shionogi, Slate, Solvay, Theralogix and Vivus. He has also served as a board member, officer and trustee for the NIH.

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