A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Avanafil in Subjects with Erectile Dysfunction

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ABSTRACT

Introduction. Phosphodiesterase type 5 (PDE5) inhibitors have become standard treatment for erectile dysfunction (ED).

Aim. To prospectively evaluate the safety and efficacy of avanafil, a novel PDE5 inhibitor, in men with mild to severe ED.

Methods. In this multicenter, double-blind, Phase 3 trial, 646 subjects were randomized to receive avanafil (50 mg, 100 mg, 200 mg) or placebo throughout a 12-week treatment period. Subjects were instructed to take study drug 30 minutes prior to initiation of sexual activity. At least a 12-hour separation time between doses was required; no restrictions were placed on food or alcohol intake.

Main Outcome Measures. Improvement in erectile function (EF) was measured by Sexual Encounter Profile questions 2 and 3 (SEP2 and SEP3) and by the EF domain of the International Index of Erectile Function (IIEF) questionnaire.

Results. Mean change in percentage of successful sexual attempts (SEP2 and SEP3) and IIEF-EF domain score significantly favored all doses of avanafil over placebo ($P \leq 0.001$). Secondary analyses demonstrated achievement of successful intercourse by subjects within 15 minutes of dosing. Of the 300 sexual attempts made during this interval, 64% to 71% were successful in avanafil-treated subjects compared with 27% in placebo-treated subjects. Successful intercourse was also demonstrated >6 hours post dosing, with 59% to 83% of the 80 sexual attempts successful in avanafil-treated subjects compared with 25% of placebo-treated subjects. The most commonly reported adverse events in subjects taking avanafil included headache, flushing, and nasal congestion; there were no drug-related serious adverse events.

Conclusion. Following 12 weeks of avanafil treatment without food or alcohol restrictions, significant improvements in sexual function were observed with all 3 doses of avanafil compared with placebo. Successful intercourse was observed as early as 15 minutes and >6 hours after dosing in some subjects. Avanafil was generally well tolerated for the treatment of ED. **Goldstein I, McCullough AR, Jones LA, Hellstrom WJ, Bowden CH, DiDonato K, Trask B, and Day WW. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med **;**:**–**.**

Key Words. Avanafil; Erectile Dysfunction; Oral Phosphodiesterase Type 5 Inhibitor; Clinical Trial; On-Demand Treatment

Introduction

Erectile dysfunction (ED) is defined as a consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity [1]. ED can have a neurogenic, psychogenic, or endocrinologic basis; however, a common underlying cause is thought to be related to vascular abnormalities of the penile blood supply and erectile tissue. Studies indicate that ED is positively correlated with increased age, cardiovascular disease, diabetes, hypertension, smoking, and depression [2–5].

In 1994, the Massachusetts Male Aging Study reported the combined prevalence of minimal, moderate, and complete impotence to be as high as 52% among men aged 40–70 years [2]. Affecting approximately 18 million men in the United States [4], ED has an estimated incidence of 26 cases per 1,000 man-years, with increased incidence observed with age, lower education level, diabetes, heart disease, and hypertension [3,6]. Oral phosphodiesterase type 5 (PDE5) inhibitors, introduced in 1998 to treat a broad spectrum of ED, are considered standard initial treatment for ED [7]. PDE5 inhibitors increase blood flow to the penis in response to sexual stimuli [8–10]; however, lack of specificity for the PDE5 isoenzyme can lead to unwanted adverse events (AEs) due to activity against other PDE isoenzymes [11–13].

PDE5 inhibitors have relatively similar efficacy profiles, and most are recommended to be administered on demand, approximately 60–120 minutes before anticipated sexual activity. This time range is based on their respective pharmacokinetic profiles; time to maximum concentration (T_{max}) is approximately 60 minutes for sildenafil and vardenafil and 120 minutes for tadalafil [7]. Avanafil is a potent PDE5 inhibitor with a T_{max} of 30–45 minutes, a terminal half-life of 3–5 hours, and dose-related linear increases in maximum concentration and area under the curve [14]. Avanafil is also highly selective for PDE5 [14]. In an in vitro receptor-binding study comparing the inhibitory effects of avanafil on 11 PDE isoenzymes with those of sildenafil, vardenafil, and tadalafil, avanafil potently inhibited PDE5 activity without significant inhibition of other PDE isoenzymes. By contrast, sildenafil, vardenafil, and tadalafil demonstrated inhibitory activity for other PDE isoenzymes (PDE1, PDE6, and PDE11) [14]. No drug accumulation was observed in multiple-dose pharmacokinetic studies evaluating once-daily and twice-daily dosing for up to 2 weeks [14].

In early development studies of avanafil, subjects demonstrated increased ability to complete intercourse and increased satisfaction with their erection and sexual experience compared with patients treated with placebo [14]. In a double-blind, randomized, parallel-design Phase 2 study, the effects of 4 doses of avanafil (50 mg, 100 mg, 200 mg, and 300 mg) were assessed over 12 weeks in men aged 35–70 years with mild to moderate ED. All doses of avanafil were associated with significantly greater rates of successful penetration, intercourse, and subject satisfaction with erection and sexual experience when compared with placebo [14]. In another single-blind, randomized, crossover Phase 2 study, the response to avanafil 50 mg, 100 mg, and 200 mg in conjunction with visual sexual stimulation was clinically assessed using RigiScan (Timm Medical Technologies, Inc.; Eden Prairie, MN, USA), an instrument that measures penile tumescence and rigidity. Responses were measured during 20- to 40-, 60- to 80-, and 100- to 120-minute intervals post dose. Avanafil demonstrated statistical superiority compared with placebo for all RigiScan end points, with the peak effect occurring during the 20- to 40-minute post-dosing assessment period, confirming the rapid onset of effect following avanafil dosing [14–16].

Aim

The objective of this study was to compare the safety and efficacy of three dose levels of avanafil (50 mg, 100 mg, and 200 mg) with placebo in men with mild to severe ED.

Methods

This prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial enrolled subjects across 42 study sites in the United States from November 2008 through August 2009 to assess the safety and efficacy of avanafil in the treatment of mild to severe ED in adult heterosexual males (Figure 1). Subjects were screened at Visit 1 and, if qualified, randomized at Visit 2 to receive avanafil 50 mg, avanafil 100 mg, avanafil 200 mg, or placebo using a 1:1:1:1 ratio. The study was conducted in accordance with the revised Declaration of Helsinki. At every site, Institutional Review Board approval and written informed consent from all subjects were obtained prior to enrollment.

Subjects first completed a 4-week, nontreatment, run-in period during which information on

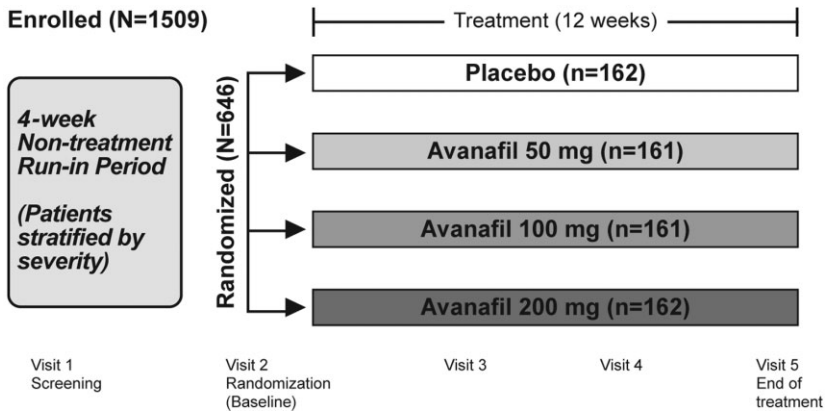

Figure 1 Study design. Randomization was stratified using a centralized, computer-generated randomization system by disease severity as determined by IIEF-EF domain scores (mild = EF domain score of 17–25; moderate = EF domain score of 11–16; severe = EF domain score ≤10) at the randomization visit. IIEF = International Index of Erectile Function; EF = erectile function.

each attempt at sexual intercourse was recorded. Subjects were eligible for randomization to a treatment arm if they had ≥50% failure rate in maintaining erections of sufficient duration to allow for successful intercourse; had an International Index of Erectile Function (IIEF) erectile function (EF) domain score of 5–25, inclusive; and made at least four attempts at sexual intercourse during the run-in period. Randomization was stratified by severity of disease as determined by IIEF-EF domain scores (mild = 17–25; moderate = 11–16; and severe = ≤10).

The run-in period was followed by a 12-week treatment period during which randomized subjects were instructed to administer the study drug approximately 30 minutes prior to initiation of sexual activity. Subjects were allowed to take up to two doses in a 24-hour period, provided that the doses were separated by at least 12 hours. Throughout the run-in and treatment periods, subjects were required to complete a diary with the date/time of medication use (treatment period only), date/time of initiation of sexual activity, and answers to the five Sexual Encounter Profile (SEP) questions.

The full IIEF questionnaire, a validated, self-administered, 15-item (five-domain) instrument designed to assess EF [17] was also administered at each study visit. Subjects returned to the site at 4-week intervals for evaluation and to obtain additional study medication.

Key eligibility criteria for the study included male gender, aged 18 years or older, and a ≥6-month history of mild to severe ED. Each subject was required to be in a monogamous, heterosexual relationship for ≥3 months, to agree to make ≥four attempts at intercourse per month, and to provide informed consent. Key exclusion criteria included allergy or hypersensitivity to avanafil, sildenafil, vardenafil, tadalafil, or any of their components. A history of dose-limiting AEs, consistent treatment failure during previous therapy with a PDE5 inhibitor, or use of any agent known to inhibit cytochrome P_{450} 3A4 activity within 28 days prior to randomization or at any time during the study period was not allowed. Other disqualifiers included current or expected use of organic nitrates during the study, androgen replacement therapy that had not been stable for ≥3 months, ED as a result of spinal cord injury or radical prostatectomy, untreated hypogonadism, a history of or predisposition to priapism, penile implant, prostate-specific antigen level >4 ng/mL or other evidence of prostate cancer, diabetes, uncontrolled hypertension, hypotension, myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization within the past 6 months. It was recommended that subjects not begin alpha-blocker therapy during the study. Subjects who had started treatment with alpha-blockers at least 2 weeks prior to entering the study were permitted to continue, provided the dose remained stable. There were no restrictions regarding food or alcohol use, and previous use of PDE5 inhibitors was permitted.

Main Outcome Measures

Efficacy End Points

The co-primary efficacy end points were: (i) the change in percentage of sexual attempts in which subjects were able to insert the penis into the partner's vagina between the run-in period and the end of the 12-week treatment period (SEP 2); (ii) the change in percentage of sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse between the run-in period and the end of the

12-week treatment period (SEP 3); and (iii) the change from baseline (Visit 2) to end of treatment in IIEF-EF domain score. Each end point was also evaluated in subjects with a history of oral ED treatment and in subjects without a history of oral ED treatment. Key secondary efficacy end points included change in response regarding the other four IIEF domains (orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) between baseline and treatment weeks 4, 8, and 12.

Following completion of the specified primary efficacy analyses, additional analyses were performed to assess successful intercourse reports (SEP 3) over time after dosing and to see if subjects who were stratified as having mild, moderate, or severe impairment at baseline had achieved a normalized IIEF-EF domain score at the end of treatment.

Safety End Points

Safety end points included evaluation of vital signs and AEs at baseline and each study visit during treatment.

Statistical Methods

The primary analysis was based on the intent-to-treat (ITT) population, which included all subjects who were randomized, received ≥1 dose of study drug, and had ≥1 posttreatment efficacy measurement. The safety analysis included all subjects who were randomized, received ≥1 dose of study drug and had ≥1 posttreatment safety measurement. For the IIEF questionnaire end points, last observation carried forward (LOCF) convention was used for subjects who dropped out of the study early or had missing data. No imputations were made for evaluation of co-primary end points 1 and 2.

The comparisons between treatments were based on a 2-way analysis of covariance (ANCOVA) model with factor of treatment and with baseline parameters as the covariate. A step-down multiple comparison procedure was used to compare each dose group with placebo for each end point. If all three avanafil dose groups were significantly better than placebo, then the active dose groups were compared directly. A 95% confidence interval of difference in response rate between treatment groups was derived. With 150 subjects in each treatment group, the current study had more than 90% power to detect a mean difference of 13% using a two-tailed *t*-test with a 5% type-I error for the two diary end points and a mean difference of 3 points in the IIEF-EF domain score.

Results

In total, 1,509 subjects were screened, and 646 were randomized to receive avanafil 50 mg (N = 161), avanafil 100 mg (N = 161), avanafil 200 mg (N = 162), or placebo (N = 162) (Figure 1). Reasons for screening failure included: (i) subject did not meet inclusion/exclusion criteria (N = 772); (ii) subject did not meet randomization criteria (N = 39); or (iii) other reason (N = 52). Baseline demographics in the ITT population were consistent across treatment arms; within each treatment group, approximately one third of subjects presented with mild ED, one third with moderate ED, and one third with severe ED at baseline (Table 1). The overall mean age was 56 years; mean duration of ED was 75 and 79 months for the placebo and avanafil groups, respectively; and mean baseline IIEF-EF scores for the placebo and combined avanafil groups were 12.4 and 12.7, respectively. An analysis of the safety population (N = 644) revealed that 72.2% (N = 465) of all subjects in the study had previously tried another treatment for ED; 71.9% (N = 463) had received an oral ED medication (sildenafil, tadalafil, vardenafil, or over-the-counter herbals), with 7.5% (N = 48) failing on their previous oral ED treatment.

Efficacy

Figure 2A illustrates mean changes from the run-in period to the end of treatment in the percentage of sexual attempts in which subjects were able to insert the penis into their partner's vagina (SEP 2). Compared with placebo, significant improvement was demonstrated with avanafil 50 mg, 100 mg, and 200 mg ($P < 0.001$ for all comparisons vs. placebo; calculated as least-squares [LS] mean). The 50-mg dose of avanafil was inferior to the 100-mg ($P = 0.0064$) and 200-mg ($P = 0.0004$) doses of avanafil; there was no significant difference between the avanafil 100-mg and avanafil 200-mg doses ($P = 0.4221$).

Similarly, mean changes from the run-in period to the end of treatment in the percentage of sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse (SEP 3) demonstrated a significant improvement vs. placebo with avanafil 50 mg ($P = 0.0002$), 100 mg ($P < 0.0001$), and 200 mg ($P < 0.0001$; all *P* values calculated as LS mean; Figure 2B). At the end of treatment, the placebo group experienced a 27% mean change from baseline in successful sexual attempts, whereas the avanafil-treatment groups experienced a 41% mean change in successful sexual attempts with

Table 1 Baseline characteristics (ITT population)

Characteristic	Placebo (n = 155)	Avanafil 50 mg (n = 154)	Avanafil 100 mg (n = 157)	Avanafil 200 mg (n = 156)	Total active (N = 467)
Mean age, years	55.8	55.5	56.4	56.1	56.0
Mean weight, kg	90.2	92.2	91.3	91.3	91.6
Mean BMI, kg/m^2	28.3	29.0	28.9	28.7	28.8
Race, n (%)					
Asian	2 (1.3)	1 (0.6)	2 (1.3)	1 (0.6)	4 (0.9)
Black	26 (16.8)	24 (15.6)	21 (13.4)	11 (7.1)	56 (12.0)
White	126 (81.3)	129 (83.8)	133 (84.7)	144 (92.3)	406 (86.9)
Multiple	1 (0.6)	0 (0.0)	1 (0.6)	0 (0)	1 (0.2)
History of smoking, n (%)					
Current	36 (23.2)	30 (19.5)	20 (12.7)	28 (17.9)	78 (16.7)
History	44 (28.4)	44 (28.6)	56 (35.7)	46 (29.5)	146 (31.3)
Never	75 (48.4)	80 (51.9)	81 (51.6)	82 (52.6)	243 (52.0)
ED severity at baseline, n (%)					
Mild	55 (35.5)	55 (35.7)	54 (34.4)	53 (34.0)	162 (34.7)
Moderate	49 (31.6)	48 (31.2)	51 (32.5)	52 (33.3)	151 (32.3)
Severe	51 (32.9)	51 (33.1)	52 (33.1)	51 (32.7)	154 (33.0)
History of ED					
Mean, months	75.4	79.5	88.5	68.4	78.8
<24 months, n (%)	29 (18.7)	23 (14.9)	22 (14.0)	18 (11.5)	63 (13.5)
≥24 and <60 months, n (%)	50 (32.3)	52 (33.8)	59 (37.6)	62 (39.7)	173 (37.0)
≥60 months, n (%)	76 (49.0)	79 (51.3)	76 (48.4)	76 (48.7)	231 (49.5)
Mean erectile function (IIEF-EF score)	12.4	12.6	12.6	12.8	12.7

History of previous ED treatment, n (%)	Placebo (n = 161)	Avanafil 50 mg (n = 160)	Avanafil 100 mg (n = 161)	Avanafil 200 mg (n = 162)	Total active (N = 483)
Any ED treatment	112 (69.6)	110 (68.8)	121 (75.2)	122 (75.3)	353 (73.1)
Any oral ED treatment	111 (68.9)	110 (68.8)	121 (75.2)	121 (74.7)	352 (72.9)
Any failure on previous oral ED treatment	15 (9.3)	11 (6.9)	10 (6.2)	12 (7.4)	33 (6.8)

ITT = intent-to-treat; BMI = body mass index; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function

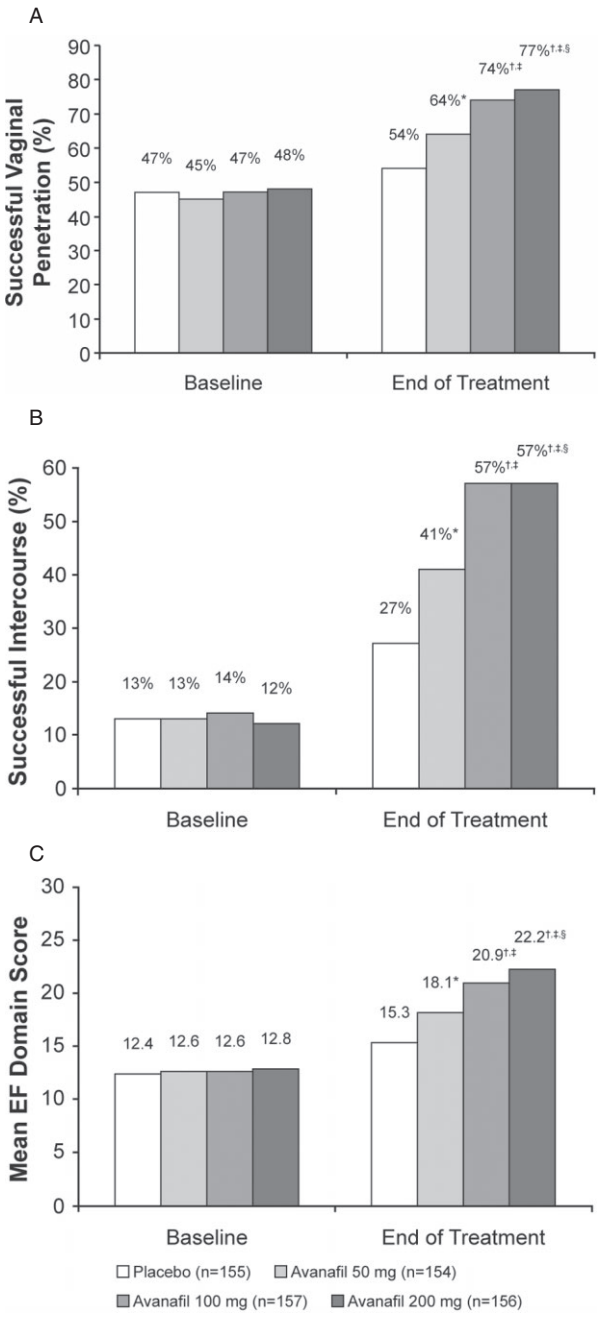

Figure 2 Co-primary end points. (A) Sexual Encounter Profile 2, (B) Sexual Encounter Profile 3, (C) mean change in International Index of Erectile Function-erectile function (IIEF-EF) domain score. (A) Mean percent of sexual attempts in which subjects were able to insert the penis into the partner's vagina at baseline (run-in period) and end of treatment. (B) Mean percent of sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse at baseline (run-in period) and end of treatment. (C) Mean score of the erectile function domain of the IIEF questionnaire at baseline (run-in period) and end of treatment. $^{*}P < 0.005$ vs. placebo; $^{\dagger}P < 0.0001$ vs. placebo; $^{\ddagger}P < 0.01$ vs. avanafil 50 mg; $^{\S}P$ is not significant vs. avanafil 100 mg. *P* values were calculated using least-squares means and intent-to-treat with last observation carried forward analysis.

50 mg and a 57% mean change in successful sexual attempts with the 100-mg and 200-mg doses. Significant differences were also found between avanafil 100 mg and avanafil 50 mg ($P < 0.0001$) and between avanafil 200 mg and avanafil 50 mg ($P < 0.0001$); the difference between avanafil 100 mg and avanafil 200 mg was not significant ($P = 0.8198$).

The change in IIEF-EF domain score from baseline (Visit 2) to end of treatment (Visit 5 or LOCF) demonstrated a significant improvement with avanafil 50 mg vs. placebo ($P = 0.0014$), avanafil 100 mg vs. placebo ($P < 0.0001$), and avanafil 200 mg vs. placebo ($P < 0.0001$; all *P* values calculated as LS mean; Figure 2C). As before, avanafil 100 mg and 200 mg produced significant differences compared with 50 mg ($P < 0.0005$), but there was no significant difference between the avanafil 100-mg and 200-mg doses ($P = 0.1366$). The change in individual domains of the IIEF, including orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, also significantly favored avanafil over placebo (Table 2). When stratified by ED severity at baseline, SEP 2, SEP 3, and IIEF-EF domain score were each improved compared with placebo (Figure 3).

Among subjects with a history of previous oral ED treatment, LS mean change was significant vs. baseline for all doses of avanafil for all three end points ($P < 0.0001$ vs. baseline). Similarly, subjects receiving avanafil with no previous history of oral ED treatment use had significant LS mean change for all three co-primary end points vs. baseline ($P < 0.0001$ vs. baseline for all three doses of avanafil).

After the primary IIEF outcome was obtained, an additional analysis was conducted to determine the proportion of subjects who achieved a normalized IIEF-EF domain score (≥26) at the end of the treatment period, as stratified by baseline ED severity. The percentage of subjects with normalized IIEF-EF domain score was greater with all doses of avanafil compared with placebo regardless of baseline ED severity (Figure 4).

In addition, an analysis of the number of successful attempts at intercourse at various times post dosing was performed (based on response to SEP 3). In total, 300 sexual attempts were made

Table 2 Secondary end points: changes in individual IIEF domains, baseline to end of treatment (ITT)

	Placebo		Avanafil 50 mg			Avanafil 100 mg			Avanafil 200 mg		
IIEF domain score, mean	Baseline	End of treatment	Baseline	End of treatment	*P* value vs. placebo	Baseline	End of treatment	*P* value vs. placebo	Baseline	End of treatment	*P* value vs. placebo
Orgasmic function	4.8	5.2	4.8	6.3	0.0002	4.8	7.4	<0.0001	4.7	7.5	<0.0001
Sexual desire	6.4	6.6	6.2	6.9	0.0325	6.8	7.4	0.0006	6.7	7.6	<0.0001
Intercourse satisfaction	6.5	7.6	6.5	8.7	0.0005	6.6	10.0	<0.0001	6.3	9.9	<0.0001
Overall satisfaction	4.0	5.1	3.9	5.7	0.0186	4.2	6.8	<0.0001	3.9	6.9	<0.0001

IIEF = international index of erectile function; ITT = intent-to-treat

within 15 minutes of dosing, and between 64% and 71% attempts were successful with avanafil compared with 27% with placebo treatment. The percentages of successful attempts occurring at 15–30 minutes, 30–45 minutes, 2–4 hours, and 4–6 hours post avanafil dose were superior to placebo and mostly dose dependent. The same analysis also showed that of the 80 attempts occurring >6 hours after dosing with avanafil, 59% to 83% were successful vs. 25% of attempts with placebo (Figure 5).

Safety

Treatment with avanafil was generally well tolerated. In total, 183 (37.9%) subjects who received avanafil treatment and 42 (26.1%) subjects who received placebo experienced a treatment-emergent adverse event (TEAE; Table 3). The most frequently reported TEAEs, occurring in >2% of subjects in any treatment group, included headache, flushing, nasal congestion, back pain, nasopharyngitis, and bronchitis (Table 4). Dyspepsia was reported in two avanafil-treated subjects (one in the avanafil 50-mg group and one in the avanafil 100-mg group), and hemodynamic AEs (dizziness or syncope) were reported in <2% of subjects treated with avanafil. A total of 96 (14.9%) subjects discontinued from the study. The majority of subjects who discontinued did so due to lack of compliance with the protocol (8.2%) or were lost to follow up (3.4%). Rates of discontinuation due to AEs from the avanafil 50 mg, avanafil 100 mg, avanafil 200 mg, and placebo arms were 1.9%, 3.1%, 2.5%, and 3.1%, respectively. There were no drug-related serious AEs in the study. One death, unrelated to study drug, due to a gunshot wound was reported during the study.

Discussion

In this study of avanafil in heterosexual men with mild to severe ED, all three doses of avanafil (50 mg, 100 mg, and 200 mg) were effective when compared with placebo for all primary and secondary end points. After 12 weeks of treatment, subjects taking 100 mg and 200 mg of avanafil experienced an erection sufficient for vaginal penetration (SEP 2) nearly 8 out of 10 times and an erection of sufficient duration for intercourse (SEP 3) nearly 6 out of 10 times. The treatment effect of avanafil generally increased with dose for all primary (SEP 2, SEP 3, IIEF-EF domain scores) and secondary efficacy outcomes regardless of baseline severity. Both avanafil 100 mg and

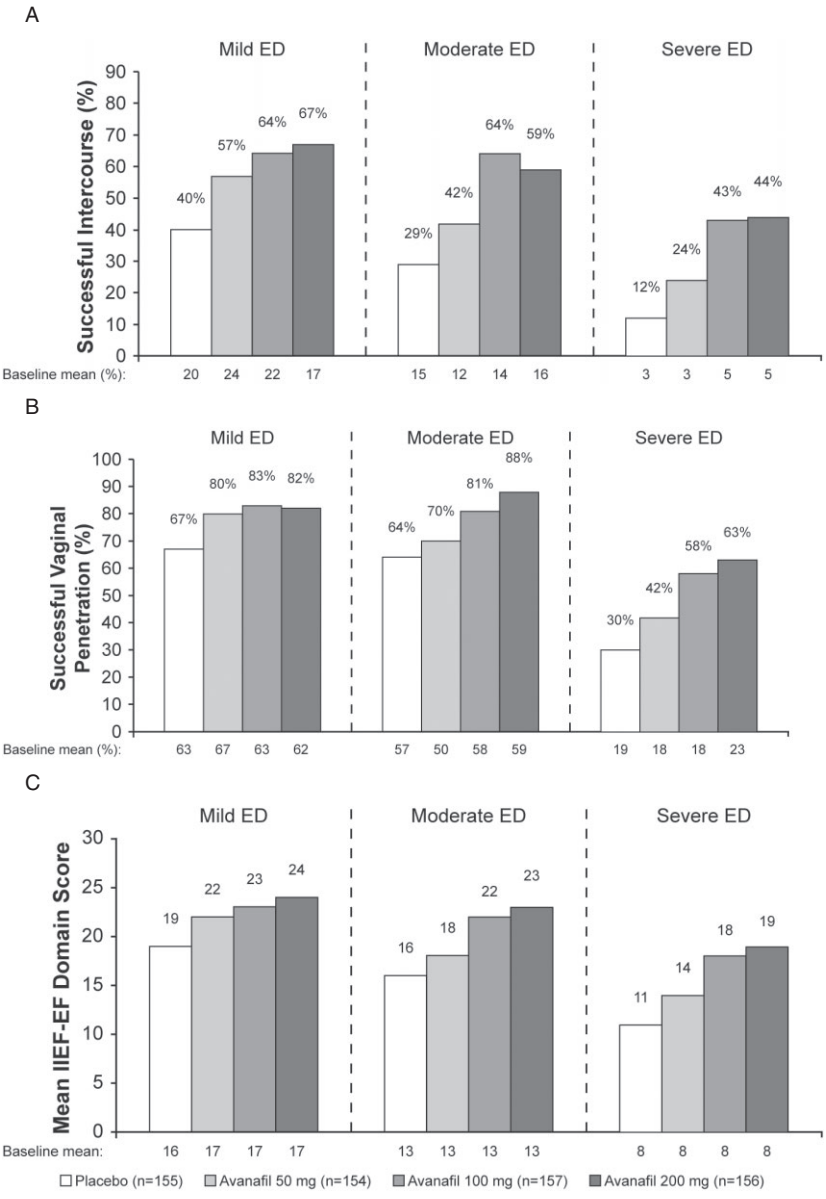

Figure 3 Co-primary end point at end of treatment by baseline severity of erectile dysfunction (ED; intent-to-treat): (A) Sexual Encounter Profile 2, (B) Sexual Encounter Profile 3, (C) mean change in International Index of Erectile Function (IIEF)-erectile function domain score. (A) Mean percent of sexual attempts in which subjects were able to insert the penis into the partner's vagina at baseline (run-in period) and end of treatment. (B) Mean percent of sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse at baseline (run-in period) and end of treatment. (C) Mean score of the erectile function domain of the IIEF questionnaire at baseline (run-in period) and end of treatment.

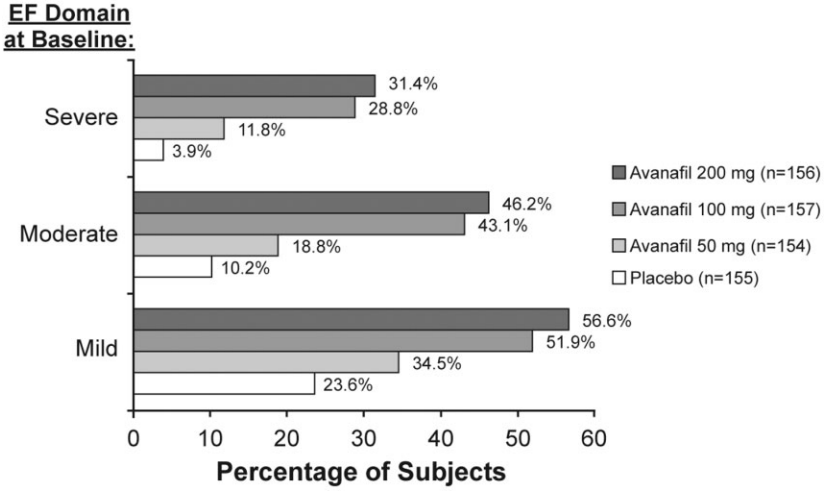

Figure 4 Normalization of International Index of Erectile Function erectile function (IIEF-EF) domain score (≥26) at study end.

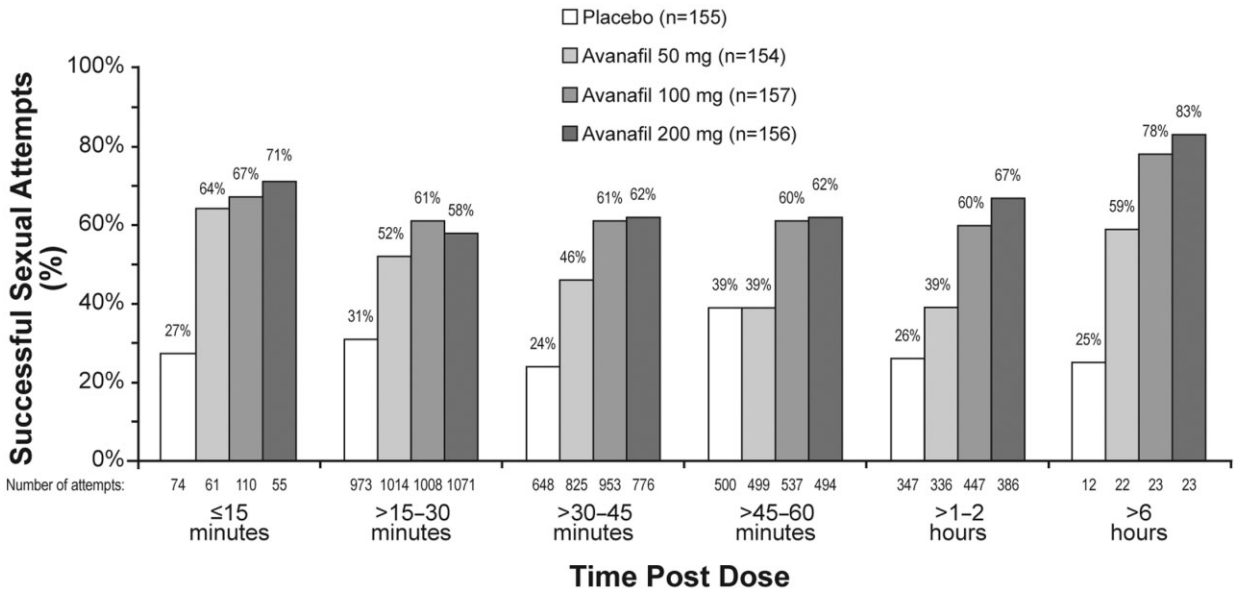

Figure 5 Successful intercourse by time interval from dose to attempt. Sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse by post-dose time interval; Sexual Encounter Profile 3.

200 mg were superior to avanafil 50 mg, although there was no significant difference between the two higher doses. Based on outcomes from this study, a starting dose of 100 mg is recommended.

To further evaluate the functional utility of avanafil, we performed an analysis to assess efficacy over time after drug administration. This analysis, which evaluated the timing of successful intercourse attempts following dosing, using SEP 3, indicated an onset of action beginning with the earliest interval measured (≤15 minutes). These data are consistent with the observed pharmacokinetic profile of avanafil, which shows relatively rapid absorption, with the maximum observed plasma concentrations being reached within 30–45 minutes after oral dosing in the fasted state [14]. Interestingly, a pharmacodynamic effect also persisted at 6 hours post dose, albeit based on a

Table 3 Summary of adverse events (safety population)

Adverse events, n (%)	Placebo (n = 161)	Avanafil 50 mg (n = 160)	Avanafil 100 mg (n = 161)	Avanafil 200 mg (n = 162)
Any TEAE	42 (26.1)	52 (32.5)	68 (42.2)	63 (38.9)
Any severe TEAE	1 (0.6)	2 (1.3)	5 (3.1)	2 (1.2)
Interrupted or discontinued study drug due to an AE	5 (3.1)	3 (1.9)	6 (3.7)	4 (2.5)
SAE	2 (1.2)	1 (0.6)	3 (1.9)	3 (1.9)
Death	0 (0)	0 (0)	1 (0.6)	0 (0)

TEAE = treatment-emergent adverse event; AE = adverse event; SAE = serious adverse event

Table 4 Summary of all treatment-emergent adverse events (TEAEs) reported in >2% of subjects

Subjects with any TEAE, n (%)	Placebo (n = 161)	Avanafil 50 mg (n = 160)	Avanafil 100 mg (n = 161)	Avanafil 200 mg (n = 162)	Total active (N = 483)
Headache	2 (1.2)	7 (4.4)	12 (7.5)	15 (9.3)	34 (7.0)
Flushing	0 (0.0)	6 (3.8)	10 (6.2)	6 (3.7)	22 (4.6)
Back pain	1 (0.6)	4 (2.5)	4 (2.5)	3 (1.9)	11 (2.3)
Nasal congestion	2 (1.2)	1 (0.6)	7 (4.3)	3 (1.9)	11 (2.3)
Nasopharyngitis	2 (1.2)	1 (0.6)	2 (1.2)	6 (3.7)	9 (1.9)
Bronchitis	1 (0.6)	3 (1.9)	1 (0.6)	4 (2.5)	8 (1.7)

smaller number of attempts than in the earlier time points. Since these treatments are taken on demand, an effective ED treatment with a rapid onset of action and sustained effect, such as avanafil, has the potential to provide an additional option for the treatment of ED.

The most commonly reported AEs seen in the avanafil-treatment groups were generally consistent with those observed with other PDE5 inhibitors [7,18]. However, rates of headache, flushing, and nasopharyngitis were low overall. In addition, dyspepsia, an AE commonly reported with PDE5 treatment [7,18], was reported by only 0.4% of subjects receiving avanafil. Currently approved PDE5 inhibitors have been associated with inhibition of PDE6, which may lead to visual disturbances, as well as inhibition of PDE11, which can result in peripheral vasodilation [13]. Because this was not a head-to-head study, comparisons between PDE5 inhibitors should not be made based on this data set. However, in vitro studies of avanafil have demonstrated higher selectivity against PDE6 compared with sildenafil and vardenafil, as well as higher selectivity against PDE11 compared with tadalafil [14]. Therefore, one might hypothesize that avanafil treatment would be associated with fewer effects mediated by inhibition of these PDE isoenzymes. In the current study, there were no reports of visual disturbances, such as cyanopsia, hearing loss, or priapism. Although these events are infrequently observed with other PDE5 inhibitors, the absence of cyanopsia is consistent with the significant selectivity of avanafil to PDE5 as compared with PDE6. In addition, alcohol restrictions exist for some of the currently available PDE5 inhibitors due to their vasodilatory properties, which may have a synergistic effect, decreasing blood pressure and increasing heart rate when taken with alcohol [19]. In this study, the incidence of adverse hemodynamic effects associated with avanafil was <2%.

This study differs from previous trials with PDE5 inhibitors in that subjects were permitted to have had previous exposure to ED treatment. As a result, more than 70% of subjects in this study reported such a history. Although this may be perceived as a limitation, it in fact may bias against the efficacy of avanafil because there was no exclusion to previous PDE5-inhibitor use unless there had been dose-limiting AEs or consistent failure of efficacy, making it likely that some of the enrollees had failed at least one previous PDE5 inhibitor (Supplementary Table S1). The efficacy observed in this population indicates that avanafil is effective in subjects with previous exposure to other PDE5 inhibitors (Supplementary Tables S2, S3, S4). A previous study with tadalafil showed similar efficacy and tolerability responses between treatment-naïve subjects and sildenafil previous responders [20]. Another study limitation is the exclusion of subjects with type 1 or type 2 diabetes or those with previous nerve-sparing prostatectomy. Per U.S. Food and Drug Administration requirements, separate trials were performed to assess the efficacy and safety of avanafil for the treatment of ED in men with type 1 or type 2 diabetes mellitus and in men with ED following radical prostatectomy. Both studies, as well as previously performed Phase 2 studies, demonstrated a similar efficacy and tolerability profile to the present study, including the rapid onset of action and persistence of effect [14,21,22].

Conclusion

Avanafil is a novel, fast-acting oral PDE5 inhibitor that was shown to be well tolerated and effective for the treatment of ED in men with mild to severe ED. Following 12 weeks of treatment without restrictions to food or alcohol, all three doses of avanafil (50 mg, 100 mg, and 200 mg) were significantly superior to placebo for all primary end points ($P \leq 0.001$). A post hoc analysis using SEP 3 to evaluate the number of successful intercourse attempts at various times post dosing revealed that avanafil was associated with a significant treatment response as early as 15 minutes after dosing in some subjects, with effects seen beyond 6 hours post dose in some subjects. The improvement in sexual function, tolerability, lack of restrictions relating to alcohol, food, or previous PDE5-inhibitor therapy, coupled with the rapid onset of action and durability of effect, make avanafil a viable candidate for on-demand treatment of ED.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Ad hoc summary of erectile dysfunction previous treatment safety population
Table S2 Subgroup analysis—Summary and analysis of primary end points by previous use of oral erectile dysfunction treatment, change in percent of successful intercourse intent-to-treat population
Table S3 Subgroup analysis—Summary and analysis of primary end points by previous use of oral erectile dysfunction treatment, change in percent of successful insertions intent-to-treat population
Table S4 Subgroup analysis—Summary and analysis of primary end points by previous use of oral erectile dysfunction treatment, change in erectile function domain score intent-to-treat population

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