ERECTILE DYSFUNCTION

Efficacy and Safety of Avanafil in Chinese Subjects With Erectile Dysfunction: A Multi-Center, Randomized, Double-Blinded, Placebo-Controlled Phase III Clinical Trial

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ABSTRACT

Introduction: The incidence of erectile dysfunction (ED) increases with age in mainland China and phosphodiesterase 5 inhibitors (PDE5i) are the major drugs used for its treatment.

Aim: To determine the efficacy and safety of Chinese developed avanafil as therapy for ED in China.

Methods: This phase III trial was carried out in 7 medical centers in China. Eligible subjects suffering from ED were allocated randomly into 3 groups (ratio 1:1:1) and orally received a placebo, 100 or 200 mg avanafil for a total of 12 weeks.

Main outcome measures: The primary endpoint was changes in erectile function (EF) domain scores according to the International Index of EF (IIEF) questionnaire from baseline to week 12 of therapy. Secondary endpoints assessments were changes in the response rates of SEP, Q2 and Q3; changes in IIEF other domain scores. Safety evaluation monitored treatment-emergent adverse events (TEAEs), serious TEAEs, laboratory test results, vital signs and electrocardiographs.

Results: Of 218 randomized ED subjects, 182 (83.5%) completed the study. After 12-week therapy, alterations from baseline of the mean IIEF-EF domain scores in the 100 mg and 200 mg groups were greater than for the placebo (all $P < .05$) group. The changes in mean SEP Q2 response rates from baseline to week 12 in the placebo, 100 mg and 200 mg groups were 5.4%, 22.3% and 22.1%, and SEP Q3 response rate were 22.7%, 42.6% and 38.1%, respectively. Avanafil treatment (regardless of dose) improved EF vs placebo for most of other secondary efficacy endpoints studied (all $P < .05$). No differences were detected in efficacy endpoints between the 100 and 200 mg dosage groups (all $P > .05$) or in the incidence of TEAEs and drug-related TEAEs among the 3 groups (all $P > .05$).

Conclusion: Avanafil (100 or 200 mg) was effective and generally well tolerated in Chinese subjects with ED.

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Key Words: Avanafil; Erectile Dysfunction; Efficacy; Safety; Phase III Trial

INTRODUCTION

Erectile dysfunction (ED) has been characterized as "a persistent or repeated inability to achieve or maintain an adequate penile erection in order to facilitate a satisfactory sexual performance".[1] The incidence of ED increases with age in mainland China from 20.86% of subjects <30 years old to 93.72% in

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those >70 years old.[2] Systemic diseases, trauma and surgery, as well as medication are closely associated with ED, but it can also be of psychogenic origin. The most common specific physical causes are atherosclerosis, diabetes and complications following prostate surgery.[3-5]

Currently, phosphodiesterase 5 inhibitors (PDE5i) are administered orally as the initial treatment for ED.[6] Oral PDE5i can inhibit the degradation of cGMP, and the elevated cyclic guanosine monophosphate (cGMP) concentration increases the blood volume of the penis and amplifies the neurological signal of erection, thus effectively treating ED.[7] Other treatments include vacuum erection devices,[8] intracavernosal injection of vasoactive substances,[9] low-intensity extracorporeal shock wave therapy,[10] and penile prosthesis surgery.[11]

At present, 3 PDE5i have been approved for sale in China, namely sildenafil, tadalafil and vardenafil. Avanafil (Stendra) was initially approved by the FDA in the US and was shown to be effective and safe for ED therapy.[12,13] Avanafil is rapidly absorbed after oral administration and the maximum plasma concentration (C_{max}) is achieved at a median time to reach C_{max} (t_{max}) of 30−45 minutes with a relative short plasma half-life time (3−5 hours).[14] In addition, avanafil has also been shown to be effective in ED subjects with diabetes[15] and those who underwent prostatectomy.[16] The avanafil used in this phase III trial was developed by Sichuan Haisco Pharmaceutical Co., Ltd, and its main ingredients, route of administration, indications, dosage were completely consistent with the originator avanafil. A previous bioequivalence study demonstrated that generic and avanafil tablets were bioequivalent and exhibited similar safety profiles under fasting and branded fed condition (unpublished work). However, the safety and effectiveness of generic avanafil for ED therapy in a Chinese population has not been unequivocally verified.

Given this background, we carried out a multi-center, randomized, double-blind, placebo-controlled phase III clinical trial of a bioequivalent avanafil tablet (100 mg and 200 mg) in China to evaluate its safety and efficacy for ED therapy after 12-week continuous therapy. We hypothesized that avanafil (100 mg and 200 mg) would be well tolerated and elicit superior improvements of erectile functions over placebo in ED subjects within 12 weeks of the initiation of therapy.

MATERIALS AND METHODS

Design of the Trial

This phase III trial was carried out in 7 hospitals in China between April 23rd 2018 and February 19th 2019. The duration of the trial was divided into 2 time periods: an initial 4-week period without therapy; and 12-weeks continuous therapy. Subjects who were eligible for inclusion were randomized (ratio 1:1:1) and prescribed a placebo, 100 mg or avanafil 200 mg doses, to be taken orally at least 15 minutes before sex − no more than 1 tablet per day. This trial was approved by the Peking University Third Hospital Medical Science Research Ethics Committee (No. 2018-002-01/02) followed by all the Ethics Committee of participating hospitals. Informed written consent was provided by all subjects before they were enrolled in the trial, which was registered at chinadrugtrials.org.cn (number CTR20180189).

Participants in the Trial

Males aged from 22 (inclusive) to 65 years old, who had suffered from ED for ≥3 months, with a score ≤21 in question 5 of the International Index of Erectile Function (IIEF-5) at visit 1, who had stable marital relationships or adult female sexual partners during the previous 3 months and who, during the course of the trial, agreed to have attempts at sexual intercourse ≥4 times a month were included. In addition, subjects agreed not to take other approved or experimental drugs to treat ED for the duration of the trial, including PDE5i, specific herbal preparations, traditional Chinese medicines, or use other treatment devices. Subjects who had a history of ED due to endocrine disorders including hypothyroidism, hypopituitarism and/or hypogonadism or because of premature ejaculation, or those with clinically significant penile malformations, a history of penile prosthesis implantation or CNS injury, including spinal cord injury or a stroke, during the 6 months prior to the trial were excluded. For further details of inclusion and exclusion criteria, see **Appendix 1**.

Randomization and Masking

According to the protocol, SAS software (SAS Institute Inc, Cary, NC) was used to generate a random table for eligible participants (blinded). Once a subject was given a random number, the random number could not be assigned to another individual for re-use, regardless of whether the subject received the trial drug or terminated the trial for any reason. The trial used a double-blinded, double-simulation technique in which neither the researchers nor the subjects knew which drug they were receiving. After researchers entered the randomization inventory management of embedded configurable operating system (eCOS), the random number and the corresponding drug numbers for subjects were obtained.

Outcome Assessments

Primary efficacy endpoint: Changes in the EF domain scores of the IIEF (IIEF-EF) questionnaire[17] from baseline to the 12th week of therapy. The IIEF-EF domain score was calculated as the sum of the scores for questions 1 to 5 and 15.

Secondary efficacy endpoints: (i) alterations in the percentage of subjects who could insert their penis into their partner's vagina from baseline to the 12th week of therapy (SEP Q2, %); (ii) a change in the percentage of subjects who had an erection sufficiently long to complete successful intercourse from baseline to the 12th week of therapy (SEP Q3, %); (iii) alterations in the

orgasmic function score of IIEF (IIEF-OF) questionnaire from baseline to week 12, which was calculated as the sum of questions 9 and 10 scores from the IIEF questionnaire; (iv) changes in sexual desire score of IIEF (IIEF-SD) questionnaire from baseline to week 12, which was calculated as the sum of questions 11 and 12 scores from the IIEF questionnaire; (v) changes in the intercourse satisfaction score of the IIEF (IIEF-IS) questionnaire from baseline to week 12, which was evaluated as the sum of questions 6 to 8 scores obtained from the IIEF questionnaire; (vi) changes in the overall satisfaction score of IIEF (IIEF-OS) questionnaire from baseline to week 12, which was calculated as the total scores of questions 13 and 14; (vii) percentage of subjects who answered yes to questions 1 and 2 for the global assessment questions (GAQ) at week 12; (viii) the percentage of subjects whose IIEF-EF domain scores returned to normal (≥26) by week 12 of therapy.

Evaluation of safety: Safety evaluations included an assessment of treatment-emergent AEs (TEAEs), serious TEAEs, laboratory test results, vital signs and electrocardiograph assessments. TEAEs were characterized according to System Organ Class (SOC) and Preferred Term (PT) and the degree of severity was graded using NCI CTCAE 4.03.

Sample Size

The cohort numbers in the trial were estimated based on changes in the mean IIEF-EF domain scores from baseline to week 12 of treatment. According to previous studies,[12,13,18] assuming that the standard deviation (SD) of changes in IIEF-EF domain scores from baseline to the 12th week of therapy was 7 in the avanafil and placebo groups, approximately 58 subjects in each group would need to be enrolled to provide the trial with 80% power to show a difference of 3.7 between the groups. In addition, taking into account a potential dropout rate of 20%, 216 subjects (72 in each group) were needed for randomization in this trial.

Statistical Analysis

All analyses were carried out using SAS ver. 9.4 (SAS Institute Inc, Cary, NC) in which the continuous variables were represented as means ± SDs and categorical variables by numbers of subjects and percentages. Statistical significance was deemed to be a P value < 0.05 with a confidence interval of 95%.

The full analysis set (FAS) was all subjects who received 1 or more doses of avanafil and provided ≥ 1 primary efficacy indicator (IIEF-EF domain questionnaire score measurement after baseline, which was mainly used for analysis as an efficacy indicator. For the analysis of primary efficacy indicators, taken the baseline IIEF-EF domain questionnaire score as the concomitant variable, and taken the dose group and the ED severity at baseline as the fixed effect, covariance analysis was employed to compare potential differences between each group. Predicted values generated from a covariance model based on the last observation carried forward (LOCF), were employed to fill in any missing data of the primary efficacy indicators at week 12. Stratification factors of subgroup analysis for primary endpoint included age (< 40 and ≥ 40 years old), severity of ED at baseline (either mild, moderate or severe), previously used PDE5i or PDE5i naïve, previously treated for ED or not and diabetes status. Among the secondary efficacy endpoints, the Cochran-Mantel-Haensel (CMH) method based on the adjustment of the ED severity at baseline was employed to compare GAQ and the percentage of subjects with IIEF-EF domain scores that had returned to normal at week 12 of therapy in the 3 groups. The analysis methods of the remaining secondary efficacy indicators were consistent with the primary efficacy indicator. The method to fill in the missing data of secondary endpoints was the same as for the primary endpoint, except for SEP Q2 and SEP Q3 response rates.

The safety analysis set (SAS) was defined as all the randomized subjects who had taken ≥ 1 dose of avanafil, which was employed for safety analysis. Fisher's test was used to determine the rate of occurrence of TEAEs among the 3 groups of subjects.

RESULTS

Disposition of Subjects

A total of 270 subjects were screened from 7 research centers, among which 52 subjects failed the screening. Among 218 randomized subjects, 182 (83.5%) completed the trial, and 36 (16.5%) withdrew/discontinued from the trial (**Figure 1**). Finally, 198 subjects were enrolled in the FAS for analysis: 64 received 100 mg avanafil; 69 received 200 mg avanafil; and 65 a placebo. Two hundred and six subjects were enrolled in the SS for analysis, with 68 and 71 subjects in the 100 and 200 mg groups, respectively, with 67 in the placebo group.

Baseline Demographics and Characteristics of Randomized Subjects

The characteristics of the enrolled subjects are summarized in **Table 1**. No differences were detected between the 3 groups (all $P > .05$). Among the 218 randomized subjects, the mean ages of the placebo, 100 mg and 200 mg groups were 40.5, 40.0 and 39.0 years, with a mean ED duration of 33.9, 26.8 and 28.5 months, respectively. A total of 79 subjects had a previous ED treatment history, including 29 cases (40.3%) in the placebo, 22 (30.6%) in the 100 mg and 28 (37.8%) in the 200 mg groups. There were 50, 58 and 56 PDE5i naïve subjects in the placebo, avanafil 100 mg and avanafil 200 mg groups, without significant difference among the 3 groups ($P = .300$).

Primary Efficacy Endpoint

After the 4th week of treatment, alterations in IIEF-EF domain scores from baseline in the 100 mg (6.0 ± 5.9) and 200 mg (6.0 ± 6.6) avanafil groups were considerably improved

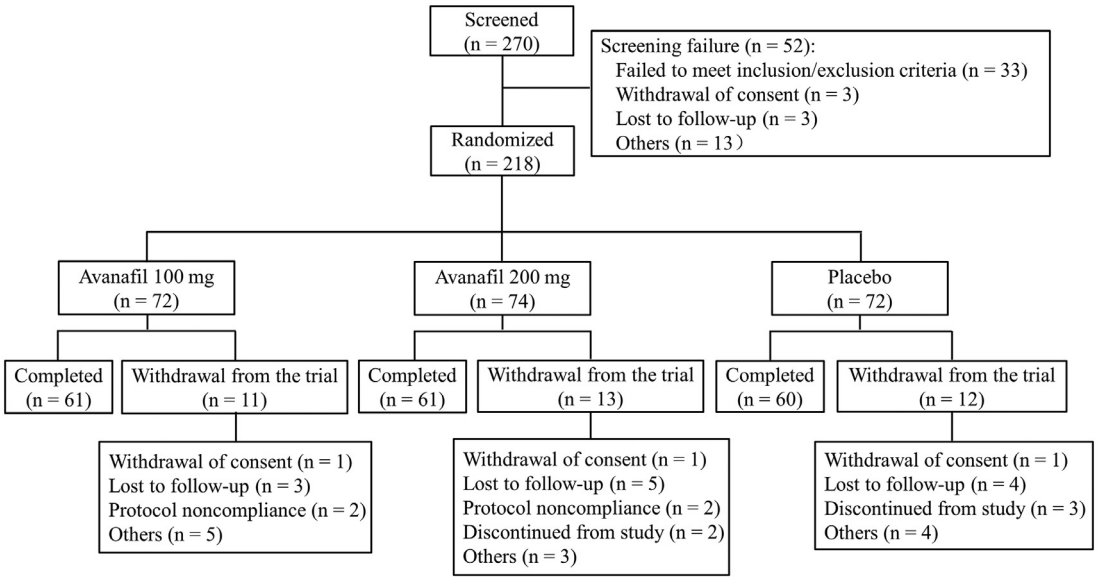


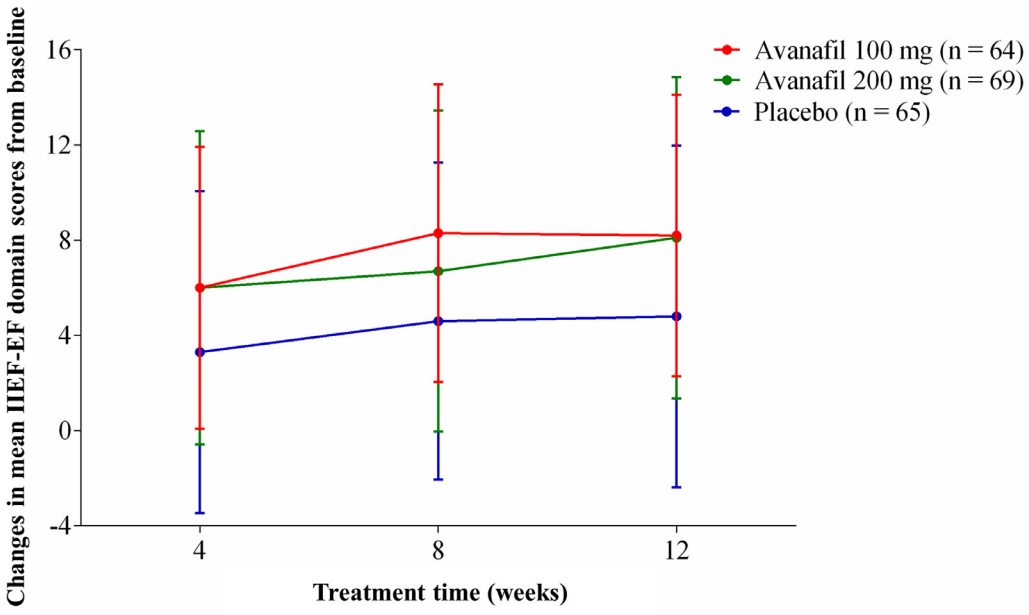
Figure 1. Flow chart of the disposition of subject.

Table 1. Demographics and the baseline characteristics of enrolled subjects (randomized population)

	Placebo (n = 72)	Avanafil 100 mg (n = 72)	Avanafil 200 mg (n = 74)	*P* value
Age (years)*	40.5 ± 10.9	40.0 ± 11.3	39.0 ± 11.0	.724
Height (cm)*	173.1 ± 6.1	173.3 ± 6.6	173.5 ± 5.1	.928
Weight (kg)*	74.3 ± 10.7	74.6 ± 10.2	73.8 ± 11.4	.910
Smoking status, n (%)				.620
Never	42 (58.3)	43 (59.7)	48 (64.9)	
Current	26 (36.1)	28 (38.9)	23 (31.1)	
History	4 (5.6)	1 (1.4)	3 (4.1)	
Age since first ED diagnosed (years)	37.7± 10.7	37.8 ± 11.1	36.7 ± 10.1	.779
Duration of ED (months)*	33.9 ± 38.3	26.8 ± 32.1	28.5 ± 45.7	.525
No. of subjects by ED duration, n (%)				.344
<24 months	44 (61.1)	52 (72.2)	53 (71.6)	
≥24 and <60 months	18 (25.0)	12 (16.7)	11 (14.9)	
≥60 months	10 (13.9)	8 (11.1)	10 (13.5)	
No. of subjects by ED severity, n (%)				.538
Normal	1 (1.4)	1 (1.4)	1 (1.4)	
Mild	32 (44.4)	38 (52.8)	34 (45.9)	
Moderate	26 (36.1)	23 (31.9)	25 (33.8)	
Severe	13 (18.1)	10 (13.9)	14 (18.9)	
Baseline IIEF-EF domain scores *	15.8 ± 5.4	16.4 ± 5.1	16.1 ± 5.5	.804
Previous ED treatment, n (%)	29 (40.3)	22 (30.6)	28 (37.8)	.450
PDE5i naive, n (%)	50 (69.4)	58 (80.6)	56 (75.7)	.300
Complication, n (%)				
Diabetes mellitus	3 (4.2)	4 (5.6)	4 (5.4)	1.000
Hypertension	10 (13.9)	9 (12.5)	6 (8.1)	.520
Hyperlipidemia	7 (9.7)	14 (19.4)	7 (9.5)	.120
Hypertriglyceridemia	2 (2.8)	0	2 (2.7)	.550
Hypercholesterolemia	1 (1.4)	0	1 (1.4)	1.000

Note.
*Data are presented as the mean ± SD.ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function; PDE5i, phosphodiesterase 5 inhibitors.

A



B

Groups	IIEF-EF domain scores (Mean ± SD)		Changes in IIEF-EF domain scores from baseline to week 12	
	Baseline	Week 12	Mean ± SD	LSM (SE)
Avanafil 100 mg (n = 64)	15.7 ± 4.8	23.9 ± 5.7	8.2 ± 5.9	8.1 (0.7)
Avanafil 200 mg (n = 69)	15.9 ± 5.4	23.8 ± 6.2	8.1 ± 6.8	7.9 (0.7)
Placebo (n = 65)	15.7 ± 5.1	20.6 ± 7.3	4.8 ± 7.2	5.0 (0.7)

Comparison among treatment groups	Analysis of covariance		
	The difference of the LSM	95% CI	*P* value
Avanafil 100 mg vs. Placebo	3.2	(1.1, 5.2)	0.003
Avanafil 200 mg vs. Placebo	2.9	(0.9, 4.9)	0.006
Avanafil 100 mg vs. 200 mg	-0.3	(-2.3, 1.8)	0.795

Note: CI, confidence interval; EF, erectile function; IIEF, international index of erectile function; LSM, least-squares mean; SD, standard deviation; SE, standard error

Figure 2. Changes in IIEF-EF domain questionnaire scores as a result of avanafil therapy from baseline values. (A) Changes of IIEF-EF domain questionnaire scores from baseline to weeks 4, 8 and 12 of therapy; (B) Statistical analysis of IIEF-EF domain questionnaire scores from baseline to week 12 of therapy.

compared to the placebo (3.3 ± 6.8) group (**Figure 2A**). By the 12th week of therapy, the change in the mean IIEF-EF domain scores from baseline in the placebo, 100 and 200 mg groups were 4.80, 8.20 and 8.10, respectively. Compared to the placebo, these differences were significant for the 100 mg (P = .003) and 200 mg (P = .006) avanafil dosage groups. However, no alteration in the mean IIEF-EF domain scores in the 100 mg and 200 mg dosage groups was detected (P = .795) (**Figure 2B**).

A subgroup analysis of changes in the mean IIEF-EF domain score from baseline to week 12 of therapy, stratified by age (<40 and ≥40 years old) was performed. Regardless of the avanafil dose, alterations in the IIEF-EF domain scores from baseline until the 12th week of therapy revealed a significant improvement compared with placebo for subjects aged ≥40 years who were treated with 100 mg (P = .004) or 200 mg (P = .008) avanafil, with mean changes of 7.7, 8.5 and 2.8 in the avanafil 100 mg and 200 mg groups and the placebo group, respectively (**Table 2**).

Subgroup analysis designed to detect any alterations in mean IIEF-EF domain scores from baseline to week 12 of therapy, having been stratified according to the severity of ED at baseline (mild, moderate or severe), was performed. The IIEF-EF domain scores from baseline to the 12th week of therapy were improved in comparison with placebo, but this improvement was significant only in the mild (P = .022, avanafil 200 mg) and moderate (P = .006, avanafil 100 mg and P = .045 for the 200 mg avanafil) ED subjects (**Table 2**).

Table 2. Changes in IIEF-EF domain scores from baseline to week 12 of therapy stratified according to age and the severity of ED at baseline, previous ED treatment history and whether subjects had diabetes (FAS)

Stratification factor	Placebo (n = 65)	Avanafil 100 mg (n = 64)	Avanafil 200 mg (n = 69)	*P* value: Avanafil 100 mg vs placebo	*P* value: Avanafil 200 mg vs placebo	*P* value: Avanafil 100 mg vs 200 mg
Age range						
<40 years	6.7 ± 6.8 (n = 36)	8.7 ± 6.0 (n = 32)	7.7 ± 5.9 (n = 42)	.250	.520	.530
≥40 years	2.8 ± 7.1 (n = 29)	7.7 ± 5.9 (n = 32)	8.5 ± 7.9 (n = 27)	.004	.008	.670
ED severity at baseline						
Mild	3.2 ± 6.1 (n = 29)	5.9 ± 4.4 (n = 32)	5.5 ± 4.2 (n = 32)	.058	.022	.690
Moderate	4.7 ± 7.0 (n = 25)	9.9 ± 6.2 (n = 22)	8.2 ± 6.8 (n = 23)	.006	.045	.413
Severe	9.7 ± 8.5 (n = 11)	11.6 ± 7.2 (n = 10)	13.6 ± 8.3 (n = 14)	.852	.724	.883
Previously used PDE5i status						
PDE5i naïve	5.2 ± 6.0 (n = 44)	8.4 ± 5.8 (n = 51)	7.3 ± 6.3 (n = 52)	.010	.120	.380
Previously used PDE5i	4.0 ± 9.4 (n = 21)	7.2 ± 6.3 (n = 13)	10.3 ± 7.8 (n = 17)	.290	.048	.270
Previous treatment for ED						
Yes	4.8 ± 8.6 (n = 27)	8.3 ± 6.5 (n = 20)	8.8 ± 7.2 (n = 26)	.390	.239	.801
No	4.9 ± 6.2 (n = 38)	8.1 ± 5.7 (n = 44)	7.5 ± 6.5 (n = 43)	.004	.018	.555
Complicated with diabetes						
Yes	4.7 ± 4.9 (n = 3)	7.7 ± 13.1 (n = 3)	8.0 ± 9.9 (n = 4)	.480	.790	.586
No	4.9 ± 7.3 (n = 62)	8.2 ± 5.6 (n = 61)	8.1 ± 6.7 (n = 65)	.004	.004	.975

Note. All data are presented as means ± SD followed by the numbers of subjects in each subgroup.
FAS, full analysis set; ED, erectile dysfunction; PDE5i, phosphodiesterase 5 inhibitors.

As shown in Table 2, a subgroup analysis of changes in the mean IIEF-EF domain scores from baseline to week 12 of therapy, stratified by subjects who previously received PDE5i or were PDE5i naïve, was performed. The changes in mean IIEF-EF domain scores in the avanafil groups were both improved compared to the placebo group, regardless of subjects being PDE5i naïve or had previous used PDE5i. However, statistically significant difference was only reached in PDE5i naive cases who received avanafil 100 mg (P = .010) doses and in cases with previous PDE5i usage who received avanafil 200 mg (P = .048) doses. In the avanafil 200 mg group, subjects with previous PDE5i usage appeared to show superior improvement in erectile function compared to the avanafil 200 mg PDE5i naïve cases (10.3 ± 7.8 vs 7.3 ± 6.3), but statistically significance was not reached (P = .140).

Subgroup analysis that looked for changes in the mean IIEF-EF domain scores from baseline to week 12 of therapy for subjects with or without a previous ED treatment history was performed. Regardless of whether the subjects had been treated for ED or not, changes in mean IIEF-EF domain scores in the avanafil groups were both improved compared to the placebo group, but were only statistically significant in subjects who did not have a previous history of treatment for ED (P = .004 for the 100 mg avanafil group and P = .018 for the 200 mg avanafil group) (Table 2).

A subgroup analysis to look for alterations in the mean IIEF-EF domain scores from baseline to week 12 was conducted on subjects diagnosed with (n = 10) or without (n = 188) diabetes. Regardless of whether the subjects had diabetes or not, changes in IIEF-EF domain scores in the avanafil groups were improved compared with the placebo group, but this improvement was statistically significant only in ED subjects who were not diabetics (P = .004 for both 100 mg and 200 mg).

No differences were detected in IIEF-EF domain scores in subjects who took 100 mg or 200 mg tablets when stratified according to age, the severity of ED at baseline, previously used PDE5i or PDE5i naïve, their previous ED treatment history, or whether subjects had associated diabetes (all $P > .05$) (Table 2).

Table 3. Summary of secondary efficacy endpoints among the 3 groups (FAS)

	Placebo (n = 65)	Avanafil 100 mg (n = 64)	Avanafil 200 mg (n = 69)	*P* value		
				Avanafil 100 mg vs placebo	Avanafil 200 mg vs placebo	Avanafil 100 mg vs 200 mg
Changes from baseline to week 12						
SEP Q2 (%)*	5.4 ± 43.7	22.3 ± 37.4	22.1 ± 36.9	.005	.025	.499
SEP Q3 (%)*	22.7 ± 37.3	42.6 ± 41.1	38.1 ± 43.4	.005	.020	.566
IIEF-OF score*	0.5 ± 2.6	2.5 ± 2. 5	2.6 ± 2.9	< .001	< .001	.626
IIEF-SD score*	0.7 ± 2.1	2.0 ± 1.9	1.7 ± 2.3	.014	.081	.434
IIEF-IF score*	2.2 ± 2.7	4.0 ± 2.9	3.8 ± 3.2	.001	.006	.577
IIEF-OS score*	1.4 ± 2.0	2.6 ± 2.3	2.4 ± 2.6	.001	.021	.331
Percentage of subjects at week 12, n (%)						
Answered "Yes" to GAQ	26 (40.0)	44 (68.8)	41 (59.4)	.005	.023	.222
IIEF-EF domain score returned to normal (≥ 26)	17 (26.2)	31 (48.4)	32 (46.4)	.009	.016	.813

Note.
*Data are presented as the mean ± SD.ED, erectile dysfunction; EF, erectile function; FAS, full analysis set; GAQ, global assessment questions; IIEF, International Index of Erectile Function; IS, intercourse satisfaction; OF, orgasmic function; OS, overall satisfaction; PDE5i, phosphodiesterase 5 inhibitors; SD, sexual desire; SEP Q2, percentage of subjects who could insert their penis into their partner's vagina; SEP Q3, percentage of subjects who had an erection sufficiently long to complete successful intercourse.

Secondary Efficacy Endpoints

The changes in mean SEP Q2 response rates from baseline to week 12 in the placebo, 100 mg and 200 mg groups were 5.4%, 22.3% and 22.1%, and SEP Q3 response rate were 22.7%, 42.6% and 38.1%, respectively (**Table 3**). Treatment with avanafil (regardless of dose) improved EF compared to placebo after 12 weeks of therapy for all secondary efficacy endpoints (all $P <$ .05), except the IIEF-SD scores for 200 mg avanafil therapy (P = .081). In addition, no differences were found between the 100 mg and 200 mg dosage groups for all secondary efficacy endpoints investigated (all $P >$ .05).

Safety

Among 206 subjects in the SS group, 94 (45.6%) had at least one TEAE, and the incidences of TEAEs in the placebo, 100 and 200 mg avanafil groups were 41.8% (28/67), 51.5% (35/68) and 43.7% (31/71), respectively. The severity of the majority of TEAEs was grade 1 and 2, and only 1 case of grade 3 TEAEs occurred in the 100 mg group. All subjects who experienced TEAEs were referred to recovery/remission without requiring appropriate treatment. There were 11 (16.4%), 16 (23.5%) and 13 (18.3%) subjects with drug-related TEAEs in the placebo, 100 and 200 mg avanafil groups, respectively. All drug-related TEAEs had a severity of grade 1, among which the most commonly occurring TEAEs were headaches, dizziness, nasal congestion and a feverish feeling (**Table 4**), and only 1 subject in the avanafil 100 mg group experienced back pain. There were 2, 1 and 1 subjects in the placebo, 100 and 200 mg avanafil groups, respectively who discontinued the trial due to TEAEs and 2 subjects in the placebo group and 1 subject in the avanafil group who withdrew from the trial because of TEAEs. No serious TEAEs or deaths were recorded in the avanafil groups or the placebo group. There was no difference in the occurrence rate of TEAEs or TEAEs related to avanafil among the 3 groups ($P >$ .05). No notable differences were found in laboratory test results, the electrocardiogram or blood pressure measurements in the 3 groups ($P >$ .05).

During the 12th week of treatment, the mean number of times for intercourse in the 100 and 200 mg avanafil and placebo groups were 23.9, 23.8 and 21.7, respectively and the mean number of times for medication were 23.8, 23.7 and 21.4, respectively, all without significant difference ($P >$ .05). However, the mean times of intercourse and medication in subjects treated with avanafil 100 mg (8.2 vs 8.2) and 200 mg (8.7 vs 8.7) were statistically significant compared to the placebo group (6.6 vs 6.6) (both P = .038) during the treatment period 9 to 12 weeks. The mean compliance of medication was 98.3%, 99.4% and 99.8% in the placebo and avanafil groups throughout the treatment period, and were without significant difference (P = .806).

DISCUSSION

This multicenter phase III clinical trial confirmed that the effectiveness and safety profile of the Chinese developed avanafil at doses of 100 or 200 mg was better than a placebo in improving ED and showed an acceptable tolerability in the Chinese subjects.

Table 4. Incidence of TEAEs reported in the 3 groups (safety population)

				P value		
	Placebo (n = 67)	Avanafil 100 mg (n = 68)	Avanafil 200 mg (n = 71)	Avanafil 100 mg vs placebo	Avanafil 200mg vs placebo	Avanafil 100mg vs 200mg
Any TEAEs	28 (41.8)	35 (51.5)	31 (43.7)	.412	.779	.687
Severity grade = 1	24 (35.8)	32 (47.1)	26 (36.6)			
Severity grade = 2	6 (9.0)	9 (13.2)	8 (11.3)			
Severity grade ≥ 3	0	1 (1.5)	0			
Drug-related TEAEs	11 (16.4)	16 (23.5)	13 (18.3)	.426	.834	.701
Severity grade = 1	11 (16.4)	16 (23.5)	13 (18.3)			
Serious TEAEs	0	0	0			
Discontinued from the trial	2 (3.0)	1 (1.5)	1 (1.4)	1.000	1.000	1.000
Withdrawal from the trial	2 (3.0)	1 (1.5)	0	1.000	.499	1.000
Death	0	0	0			
Most commonly occurring drug-related TEAEs (>2%)						
Headache	0	3 (4.4)	4 (5.6)			
Dizziness	1 (1.5)	3 (4.4)	4 (5.6)			
Feverish feeling	1 (1.5)	3 (4.4)	0			
Nasal congestion	1 (1.5)	1 (1.5)	2 (2.8)			
Nausea	1 (1.5)	2 (2.9)	0			
Palpitation	1 (1.5)	2 (2.9)	0			
Elevated serum uric acid	2 (3.0)	0	1 (1.4)			
Flushing	1 (1.5)	2 (2.9)	0			

Note. All data are presented as the number of subjects and percentages. TEAEs, treatment emergent adverse event

After 12 weeks of therapy, alterations in the mean IIEF-EF domain scores from baseline (primary efficacy endpoint) in the 100 and 200 mg avanafil dose groups were 8.2 and 8.10, respectively and greater than for the placebo group (4.8) ($P < .05$), a finding confirming earlier studies of branded avanafil.[12,18-20] Similarly, for either the primary or all the secondary efficacy endpoints investigated, no differences were found between the 100 and 200 mg doses, nor a significant difference in the subgroup analysis.[16,19]

All secondary efficacy endpoints were significantly improved after avanafil treatment (regardless of dose) compared to the placebo (all $P < .05$), except for IIEF-SD scores in the 200 mg avanafil group ($P = .081$). Changes in the IIEF-SD scores in subjects treated with avanafil 200 mg were significant higher compared to placebo in the analysis of the per protocol set (PPS) ($P = .035$), indicating that subjects who completed the trial exhibited significant improvement after treatment with 200 mg avanafil over the placebo. This difference of analysis results in FAS and PPS may be related to the filling in of the missing data.

For both doses of avanafil (100 mg, 200 mg), an improvement in the primary efficacy endpoint was found in all subgroups, including for age, ED severity at baseline, previously used PDE5i or PDE5i naive, previous ED treatment history and diabetes status. Notably, avanafil treatment in subjects aged ≥ 40 years and subjects with mild and moderate ED, who were ED treatment-naive and did not have diabetes, exhibited improvements in changes of IIEF-EF domain scores in comparison with subjects who received the placebo ($P < .05$).

In the present trial, due to an insufficient sample size (a total of 10 subjects in each of 3 groups), there was no significant benefits in avanafil therapy compared with placebo for ED subjects with diabetes. But in a multicenter, double-blind, placebo-controlled trial specially conducted in ED subjects with diabetes, regardless of the form of diabetes (type I or type II), avanafil (100 or 200 mg) was an effective therapy and was comparable to other PDE5i.[15,21]

Similar to a previous study, the avanafil therapy was most effective in subjects aged ≥40 years compared with placebo.[16] Subjects aged <40 years showed a similar improvement in the IIEF-EF domain scores from baseline until the 12th week of avanafil therapy but due to the high improvement scores in the placebo group, changes did not reach statistical significance. Commonly, psychogenic factors are important in the pathogenesis of ED in young subjects,[22,23] and the placebo was associated with an improvement in psychogenic ED.[24]

The changes in mean IIEF-EF domain scores in the avanafil groups were significantly improved in PDE5i naive cases who received the avanafil 100 mg ($P = .010$) and subjects who

previously received PDE5i and were distributed to the avanafil 200 mg (P = .048) group. In the avanafil 200 mg group, improvements in erectile function were higher in previously PDE5i medicated cases than for PDE5i naïve cases (10.3 ± 7.8 vs 7.3 ± 6.3, P = .140), which may indicate that avanafil may be used as a PDE5i salvage therapy at a dose of 200 mg. However, this assumption needs confirmation with a larger cohort of subjects in a future trial, since the difference was not significant.

Due to the pharmacokinetic characteristics and high selectivity of PDE5i, avanafil was generally well tolerated and no vision abnormalities were reported, as found for other PDE5i.[25] Similar findings were found in our trial in that the most frequent TEAEs related to avanafil were headache, dizziness, feverish feeling and nasal congestion, also with a low incidence of back pain.[16,18,26] The compliance of avanafil was excellent, with a low discontinuations rate of <3%, which was not related to avanafil. All subjects who experienced TEAEs were referred to recovery/remission without appropriate treatment, and the incidence of TEAEs in the avanafil (100 or 200 mg) groups was not significantly different from the placebo (all $P > .05$). Generally, significant changes in blood pressure did not occur after avanafil treatment compared with placebo.[27] In previous studies, it was reported that the initial recommended dose of avanafil in clinical practice should be 100 mg, but based on efficacy and safety data the dose can be increased to 200 mg.[12,28] Therefore, based on efficacy and safety outcomes, the initial dosage of avanafil used in the present trial is also recommended to be 100 mg.

A meta-analysis that assessed the results of 7 randomized clinical trials that examined the efficacy and safety of avanafil therapy indicated that a 200 mg dose of avanafil produced a clinically significant improvement in the changes of IIEF-EF domain scores and SEP Q3, compared to a 100 mg dose.[29] An efficacy difference between the 2 doses in a total population or subgroups was not found in the present trial, which may require confirmation with a larger cohort of subjects and a longer treatment period in a future trial. The limitations of the present trial was the relative short treatment duration of 12 weeks, which did not permit us to assess long term efficacy and a lack of ED type differentiation data during the screening period.

CONCLUSIONS

In conclusion, subject compliance to avanafil was excellent. Chinese developed avanafil exhibited superior efficacy over placebo with good tolerance and can therefore be used to treat Chinese subjects with ED. The results of this phase III clinical trial indicate that avanafil 100 mg should be recommended as the initial dose and up to 200 mg, with an appropriate prescription, if required.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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APPENDIX 1. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

Patients had to meet all the following criteria to be included in the trial:

1. Male, aged 22 (inclusive) to 65 years;
2. Had a history of ED for at least 3 months, with a score ≤21 in question 5 of the IIEF International Index of Erectile Function (IIEF-5) at visit 1;
3. Had stable marital relationships or adult female sexual partners in the last 3 months and during the trial;
4. Agreed to attempt sexual intercourse at least 4 times a month;
5. Agreed not to use any other approved or experimental ED drugs during the study period, including other phosphodiesterase 5 (PDE5) inhibitors, or specific herbal preparations, traditional Chinese medicines, or other treatment devices;
6. Voluntarily participate in the clinical trial, understand the study procedures and had signed informed consent;
7. Patients who were considered reliable and agreed to complete all appointments during clinical visits, as well as to complete all examinations and procedures required by the attending physician during routine clinical practice.

Exclusion criteria

Patients meeting any of the following criteria were not enrolled in the trial:

1. Had a history of ED due to other primary sexual dysfunction (eg, premature ejaculation) or untreated endocrine disorder (eg, hypopituitarism, hypothyroidism or hypogonadism);
2. Patients with penile deformity considered clinically significant by researchers;
3. Had a history of penile prosthesis implantation;
4. Had a history of significant central nervous system injury (including stroke or spinal cord injury) during the past 6 months;
5. Had a history of any of the following heart diseases:
   a) Myocardial infarction or stroke during the past 6 months;
   b) Had a combination of unstable angina or angina during sexual intercourse;
   c) Had heart failure with New York Heart Association (NYHA) grade 2 during the past 6 months;
   d) Also uncontrolled arrhythmias;
   e) Had uncontrolled hypertension (≥160/90 mm Hg) or hypotension (<90/60 mm Hg); or postural hypotension;
6. Patients with complications of significant hepatic and renal dysfunction, defined as AST or ALT exceeding the normal upper limit by a factor of 3; or creatinine exceeding the normal upper limit by a factor of 2;
7. Diabetic patients who had unstable blood glucose control, with a fasting blood glucose ≥120% of the normal upper limit, or had diabetic complications (eg, diabetic nephropathy, peripheral neuropathy or diabetic retinopathy);
8. Patients who were treated with vacuum erection devices, intracavernosal injection (ICI) of vasoactive substances, and other medications for erectile dysfunction and were unable to discontinue these potential treatments during the trial period;
9. Patients who were not able to discontinue any nitrate drugs or potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir) in current use during the trial period;
10. Patients with known or suspected hypersensitivity to PDE5 inhibitors (including, but not limited to avanafil, sildenafil, vardenafil, tadalafil and their excipients, or patients with a history of intolerance to PDE5 inhibitors or failure to respond to PDE5 inhibitor treatment;
11. Had been or are receiving anti-androgen therapy or had a stable history of androgen replacement therapy for <3 months;
12. Had a history of prostate cancer or radical prostatectomy;
13. Had an incremental or changed dose level of an α-adrenoceptor antagonist within 14 days before enrollment;
14. Patients with a known history of retinitis pigmentosa or blindness due to nonarterioinflammatory anterior ischemic optic neuropathy (NAION), regardless of whether the event was associated with previous exposure to PDE5 inhibitors;
15. Patients who presented with urinary tract and/or bladder infections;
16. Patients with a psychiatric disorder who the researchers determined were not eligible to participate in the study;
17. Had a history of malignant tumors;
18. Had an alcohol dependence or a history of substance abuse during the past 6 months (Alcohol dependence was defined as men drinking more than 28 units of alcohol per week; a standard unit contains 14 g of alcohol, such as 360 mL beer or 45 mL spirits with 40% alcohol or 150 mL wine);
19. Had participated in clinical trials for other drugs during the past 1 month;
20. Patients with an IIEF-EF domain score ≥26 at visit 2;
21. Patients who were currently having sexual relations with a fertile woman but did not take appropriate contraceptive measures during the trial period or within 2 weeks after the end of the trial;
22. Patients whose partner was in a lactation/pregnancy/pregnancy preparation period, suffers from gynecological diseases or restricted activities during the treatment period;
23. Had a history of sudden hearing loss or deafness;
24. Patients considered to be excluded from the trial due to other medical conditions.

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