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·*Original Article*·

Efficacy and safety of on demand tadalafil in the treatment of East and Southeast Asian men with erectile dysfunction: a randomized double-blind, parallel, placebo-controlled clinical study

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Abstract

Aim: To assess the efficacy and safety of tadalafil in comparison to a placebo, when taken on demand for 12 weeks by East/Southeast Asian men with erectile dysfunction (ED). **Methods**: This multicenter, randomized, double-blind, parallel group, placebo-controlled study was conducted at 17 centers across East and Southeast Asia between August 2002 and February 2003. Men more than 18 years of age with mild to severe ED of various etiologies were randomized to receive a placebo or 20 mg of tadalafil taken as needed (maximum once daily). Efficacy assessments included the International Index of Erectile Function, the Sexual Encounter Profile diary and Global Assessment Questions. **Results**: Tadalafil significantly improved erectile function as compared to the placebo ($P < 0.001$). At the endpoint, the patients receiving 20 mg of tadalafil reported a greater mean per patient percentage of successful intercourse attempts (Sexual Encounter Profile question 3: 70.9% compared to 33.5% in the placebo) and a greater proportion of improved erections (Global Assessment Question: 86.2% compared to 30.1%). Most ($\geqslant$ 3%) treatment emergent adverse events were mild or moderate. The most common treatment emergent adverse events were headache, back pain, dizziness and dyspepsia. **Conclusion**: Tadalafil was an effective and well-tolerated treatment for ED in East and Southeast Asian men. *(Asian J Androl 2006 Nov; 8: 685–692)*

Keywords: tadalafil; phosphodiesterase type 5 inhibitor; erectile dysfunction; efficacy; safety; Asian

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1 Introduction

A variety of medical, psychological and lifestyle factors have been implicated in the etiology of erectile dysfunction (ED) [1–3], affecting approximately 150 mil-

lion men worldwide [4] and leading to a negative impact on self-esteem, quality of life and interpersonal relationships [5]. Consistent with increasing life expectancies and the age-related nature of the disease, the number of men with ED is projected more than double in the next 25 years [6].

Phosphodiesterase type 5 (PDE5) inhibitors potentiate the male erectile response to sexual arousal by amplifying the activity of nitric oxide–3'5'-cyclic guanosine monophosphate signaling pathway and potentiate the smooth muscle relaxing effects of nitric oxide within the corpus cavernosum, with consequent penile vasodilation resulting in engorgement of the corpus cavernosum [7, 8]. Tadalafil, an orally administered PDE5 inhibitor, is approved as a therapy for ED in approximately 100 countries and regions, including, Australia, Brazil, Canada, the USA, Taiwan (China), and European countries [9].

Tadalafil is rapidly absorbed with a mean plasma half-life of 17.5 h [10] and its absorption is not affected by food intake [11]. Tadalafil is efficacious up to 36 h after dosing [10]. In clinical trials, tadalafil improves ED of broad spectrum of etiologies and severities and is well tolerated [9, 10, 12].

Because most clinical trials have assessed the efficacy and safety of tadalafil only in Western population of men with ED, we conducted this study to investigate the efficacy and safety of tadalafil in treating men with ED of various etiologies in a large Asian population.

2 Methods

2.1 Study design

This multicenter, randomized, double-blind, placebo-controlled study was conducted at 17 medical centers across Hong Kong (China) (1 site, 40 patients), Indonesia (2 sites, 22 patients), Malaysia (3 sites, 32 patients), the Philippines (4 sites, 43 patients), Singapore (3 sites, 37 patients) and Taiwan (China) (4 sites, 85 patients) between August 2002 and February 2003. The local ethical committees of each medical center reviewed and approved the study protocol. Written informed consent was obtained from each patient prior to randomization.

The study was comprised of a 4-week, treatment-free, run-in period and a 12-week treatment period. After the 4-week treatment-free run-in period, patients completed the International Index of Erectile Function (IIEF) questionnaire to determine their baseline ED severity (mild, moderate or severe). Within each severity group, patients were randomly allocated in a 2:1 ratio to treatment with either 20 mg of tadalafil or a placebo for 12 weeks. During the treatment phase patients returned for a study visit every 4 weeks until they completed or discontinued from the study. Patients were instructed to take one tablet of the study drug as needed before sexual intercourse (maximum of once daily) without regard to food.

2.2 Study population

The patients eligible for inclusion in the study were men at least 18 years of age and who had at least a 3-month history of ED of psychogenic, organic or mixed causes. The study required that the patients have the same female sexual partner during the study for recording responses to efficacy questionnaires. If the qualifying patients had more than one female sexual partner during the study, they were required to respond to the questionnaires based on their sexual interactions with only one of these partners.

ED was defined as an inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance. The etiology of ED was determined according to each investigator's clinical opinion. Exclusion criteria were: ED caused by premature ejaculation or untreated endocrine disease; failure to achieve erection after pelvic surgery including radical prostatectomy (except bilateral nerve-sparing); significant penile deformity or penile implant; clinically significant renal or hepatic insufficiency; poorly controlled diabetes (hemoglobin A1c > 13%); unstable cardiovascular diseases (e.g. unstable angina, recent myocardial infarction or coronary intervention, evidence of congestive heart failure, new significant conduction defect or uncontrolled hypertension); recent history of significant central nervous system injuries; and history of HIV infection. Exclusion of patients with prior ineffective treatment with sildenafil was at the discretion of the investigators. Concomitant use of other therapies for ED was not allowed.

2.3 Efficacy and safety assessments

2.3.1 Efficacy

The efficacy of tadalafil was assessed using the self-administered IIEF [13], a Sexual Encounter Profile (SEP) diary, and Global Assessment Questions (GAQ) [14]. The patients completed the IIEF at the conclusion of the run-

in period (baseline) and after 4, 8 and 12 weeks of double blind treatment. They completed the SEP diary after each sexual encounter at each visit. The patients completed the GAQ at the final visit (end of study or early discontinuation).

The primary efficacy endpoints were the mean changes from baseline to endpoint in the following measures: the IIEF erectile function domain defined as the sum of Questions 1 through 5 and 15 of the IIEF, and the mean per patient percent of "yes" responses to SEP2 (Were you able to insert your penis into your partner's vagina?) and SEP3 (Did your erection last long enough for you to have successful intercourse?). The baseline and endpoint score for each SEP question was the patient's mean percentage of "yes" responses to that question during the run-in period and post-baseline period, respectively.

The secondary efficacy endpoints included the mean changes from baseline in IIEF Intercourse Satisfaction and Overall Satisfaction Domain; IIEF Question 3 (penetration ability) and IIEF Question 4 (maintenance ability); the mean per patient percent of "yes" responses to SEP4 (Were you satisfied with the hardness of your erection?) and SEP5 (Were you satisfied overall with this sexual experience?) and the percentage of "yes" responses to GAQ 1 (Has the treatment you have been taking during this study improved your erections?) and GAQ 2 (If yes, has the treatment improved your ability to engage in sexual activity?).

2.3.2 Safety

A complete medical history, clinical laboratory tests and 12-lead electrocardiograms of the patients were obtained at the first visit. A physical examination was conducted at both the first and the final visits. During the study, adverse events were collected at each visit. The investigator recorded the severity of the adverse events and their relationship to the study drug. Adverse events entered by the investigators were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms Version 5. In addition, concomitant medication use was recorded, and blood pressure and heart rate were measured at each visit.

2.4 Statistical analysis

All efficacy analysis was performed on an intent-to-treat basis and included all patients with baseline and post-baseline observations. Last observation carried forward was used to impute missing data for IIEF. Patient baseline characteristics were summarized for each treatment group. Analysis of covariance (ANCOVA) models for the change from baseline in the IIEF domains and questions and the SEP questions included terms for the baseline value of the efficacy variable, treatment group, pooled investigator site, and baseline-by-treatment group interaction (if significant at $P < 0.10$). Logistic regression models were used to evaluate the GAQ at endpoint and to evaluate the percentage of patients who attained an IIEF erectile function domain score $\geqslant 26$ (defined as normal erectile function) at the endpoint [14]. The logistic regression models included the same covariate terms as in the ANCOVA models, but the baseline IIEF erectile function domain score was used as the baseline efficacy value.

Safety analyses included all randomized patients. Safety was assessed by evaluating all reported adverse events, the change in vital signs and physical examinations. Change in vital signs was evaluated by a ranked analysis of variance model with a term for treatment group. The statistical analyses were done using Statistical Analysis Software version 8.2 (SAS; SAS Institute, Cary, NC, USA). Treatment emergent adverse events are summarized in the present paper. A treatment-emergent adverse event (TEAE) is defined as a condition not present at baseline that appeared post-baseline, or a condition present at baseline that increased in severity post-baseline.

3 Results

Demographic and baseline characteristics were comparable in the treatment groups (Table 1). The mean age (range) of the patients was 54 (28–78) years and 235 of 242 were East/Southeast Asians. The study population also included 7 men of origins other than East/Southeast Asians (Table 1). Approximately 86% of the patients had ED for at least 1 year; the most common etiology was organic. Diabetes mellitus (31%), hypertension (30%) and benign prostatic hyperplasia (19%) were the most common comorbidities. Using an algorithm based on the work by Cappelleri *et al.* [14], the baseline IIEF erectile function domain score determined the patient's baseline ED severity. The majority of patients suffered from mild to moderate ED (i.e. 40.5% and 33.5%, respectively) and 26.0% suffered from severe ED.

Investigators screened 259 patients. Of the 242 ran-

Table 1. Patient demographics and baseline characteristics. *Mean ± SD; †Adapted from Cappelleri [14]. The cause of ED was determined by the investigators based on patient history, physical examination findings and any previous diagnostic testing. ‡The subsequent assessment of erectile function by the IIEF at baseline indicated that 1.7% (4/242) of patients had an erectile function domain score in the normal range (26–30). ED, erectile dysfunction; *N*, number of randomized patients per treatment group; *n*, number of patients; IIEF, International Index of Erectile Function.

Variable	Placebo (*N* = 83)	Tadalafil (20 mg) (*N* = 159)
Age (years)*	55.0 ± 9.5	53 ± 9.4
Weight (kg)*	68.6 ± 9.5	70.3 ± 10.6
Height (cm)*	166.8 ± 6.1	166.8 ± 6.1
Duration of ED ⩾ 12 months		
n (%)	76 (91.6)	131(82.4)
Ethinicity, *n* (%)		
East/Southeast Asian	81 (97.6)	154 (96.9)
Western Asian	2 (2.4)	3 (1.9)
Caucasian	0	1 (0.6)
Other	0	1 (0.4)
ED Etiology, *n* (%)		
Psychogenic	19 (22.9)	22 (13.8)
Organic	54 (65.1)	94 (59.1)
Mixed	10 (12.0)	43 (27.0)
IIEF erectile function severity†, *n* (%)‡		
Mild (17–30)	35 (42.2)	63 (39.6)
Moderate (11–16)	26 (31.3)	55 (34.6)
Severe (1–10)	22 (26.5)	41 (25.8)
Medical history, *n* (%)		
Diabetes mellitus	26 (31.3)	49 (30.8)
Hypertension	25 (30.1)	48 (30.2)
Benign prostatic hyperplasia	19 (22.9)	28 (17.6)
Hypercholesterolemia	9 (10.8)	9 (5.7)

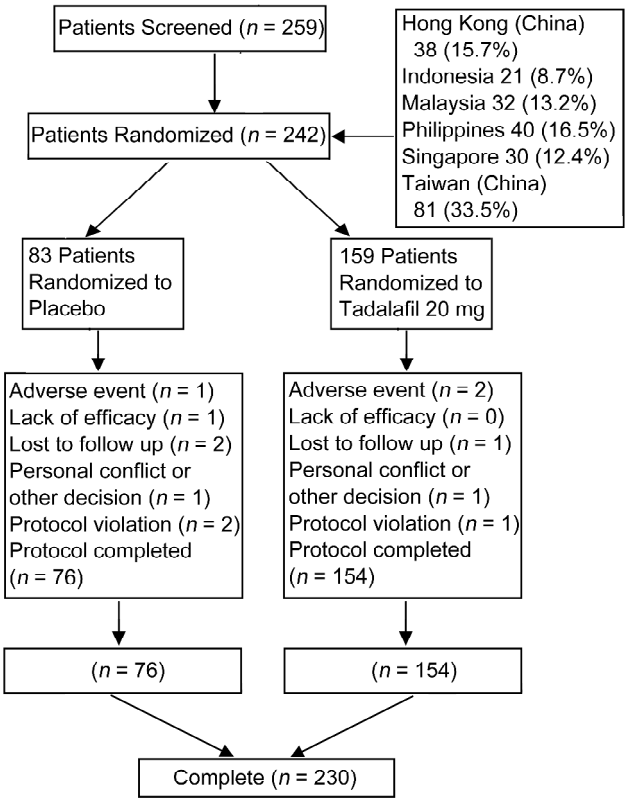

Figure 1. Patient disposition.

domized to treatment (placebo: *n* = 83; 20 mg tadalafil: *n* = 159), the majority of patients (230, 95.0%) completed the study. The reasons for study discontinuations are outlined in a patient flow diagram in Figure 1.

3.1 Efficacy results

Tadalafil therapy significantly improved erectile function compared with the placebo as assessed by each of the three primary endpoints (Table 2). The mean change from baseline to endpoint in the IIEF erectile function domain score for the tadalafil group was 8.5 as compared to 2.1 for the placebo group ($P < 0.001$). Similarly, the improvement from 53.2% at the baseline to 83.3% in the mean per patient percent of "yes" responses to SEP2 (successful penetration) and the improvement from 24.2% at the baseline to 70.9% at the endpoint in the mean per patient percent of "yes" responses to SEP3 (successful intercourse) for the tadalafil group were significantly greater compared with –1.2% and 8.9%, respectively, for the placebo group ($P < 0.001$).

Patients with mild, moderate or severe ED at the baseline demonstrated significantly greater mean changes from the baseline to the endpoint in the IIEF erectile function domain score in the 20 mg of tadalafil group compared with the placebo (Figure 2).

The secondary endpoint efficacy variables are also summarized in Table 2. Tadalafil therapy significantly improved erectile function and patient satisfaction compared with the placebo on all secondary efficacy variables ($P < 0.001$). Responses to questions assessing penetration ability, erection maintenance, hardness and overall satisfaction indicated that tadalafil was significantly superior to the placebo. Tadalafil treatment sig-

Table 2. Summary of major efficacy variables at endpoint. IIEF-Q3, "Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?"; IIEF-Q4, "Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?". The maximum scores for each question and domain: The erectile function domain: the sum of Questions 1 through 5 and 15 of the IIEF (possible total score 1 through 30), IIEF intercourse satisfaction: the sum of Questions 6, 7, and 8 (possible total score 0 through 15), IIEF overall satisfaction: the sum of Questions 13 and 14 (possible total score 2 through 10) and for Question 3 (penetration ability) and 4 (erection maintenance) of the IIEF questionnaire scores graded on scale of 1 to 5. IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile; GAQ, Global Assessment Question; *N*, number of patients randomized per treatment group. *P*-value for mean change from baseline to endpoint, tadalafil *vs.* placebo.

Efficacy variables	Placebo (N = 83)			Tadalafil (20 mg) (N = 159)			*P*-value
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	
Primary							
IIEF erectile function domain (mean)	14.8	16.9	2.1	14.9	23.3	8.5	< 0.001
Mean per patient "yes" response to SEP questions							
SEP2. Successful penetration (%)	53.9	52.7	–1.2	53.2	83.3	30.1	< 0.001
SEP3. Successful Intercourse (%)	24.6	33.5	8.9	24.2	70.9	46.7	< 0.001
Secondary							
IIEF questions (mean)							
IIEF Q3. Penetration ability	2.8	2.9	0.2	2.8	4.1	1.3	< 0.001
IIEF Q4. Maintenance ability	2.1	2.6	0.5	2.1	3.8	1.7	< 0.001
IIEF domains (mean)							
Intercourse satisfaction	6.5	7.6	1.4	6.5	10.9	4.3	< 0.001
Overall satisfaction	4.4	5.0	0.8	4.4	7.2	2.8	< 0.001
Mean per patient "yes" response to SEP questions							
SEP4. Satisfied with hardness (%)	9.7	20.4	13.9	9.7	59.3	47.8	< 0.001
SEP5. Satisfied overall (%)	8.8	19.3	13.1	8.8	55.6	45.5	< 0.001
GAQ							
GAQ 1 (%)		30.1			86.2		< 0.001
GAQ 2 (%)		28.9			80.5		< 0.001

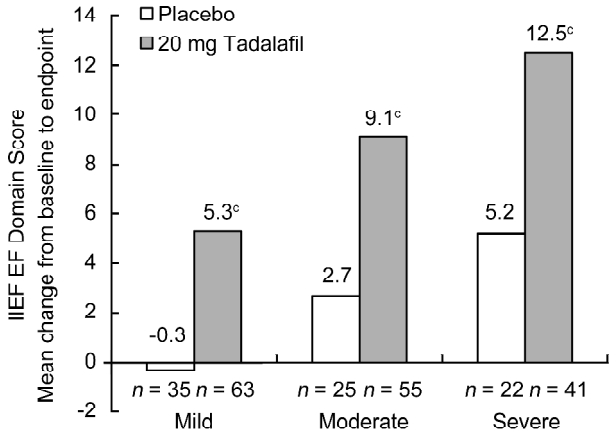

Figure 2. Change from baseline in International Index of Erectile Function (IIEF)-EF domain by ED severity. Population summarized consists of those patients having both baseline and post-baseline data on IIEF-EF domain. *n*, number of patients with IIEF-EF severity; $^{c}P < 0.01$, compared with the placebo.

Table 3. Summary of treatment-emergent adverse events occurring in ⩾ 3% of patients in any treatment group. †Events are ordered by overall decreasing frequency. ‡Frequencies were analyzed using Fisher's Exact test. *N*, number of patients randomized; *n*, number of patients reporting adverse event; %, percent of patients reporting event; Adverse event, Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms Version 5 coding term.

Adverse events†	Placebo (N = 83) *n* (%)	Tadalafil (20 mg) (N = 159) *n* (%)	*P*-value‡
Headache	2 (2.4)	18 (11.3)	0.024
Back pain	3 (3.6)	12 (7.5)	0.274
Dizziness	1 (1.2)	6 (3.8)	0.427
Dyspepsia	0 (0.0)	5 (3.1)	0.168
Myalgia	0 (0.0)	5 (3.1)	0.168

nificantly improved IIEF intercourse satisfaction and overall satisfaction domain scores, compared with the placebo. GAQ indicated that tadalafil significantly improved erections (86.2% tadalafil *vs.* 30.1% placebo) and the ability to engage in sexual activity, compared with the placebo (80.5% tadalafil *vs.* 28.9% placebo).

3.2 Safety results

Incidence of TEAE was generally low, and patients reported the events to be mild or moderate in severity (Table 3). The most frequently reported ($\geqslant$ 3%) TEAE in the tadalafil-treated subjects in the present study were headache (11.3%), back pain (7.5%), dizziness (3.8%), dyspepsia (3.1%) and myalgia (3.1%). Four subjects (3 tadalafil-treated and 1 placebo-treated) experienced serious adverse events (SAE). One SAE (worsening of coronary artery disease) occurred in a tadalafil-treated patient with a history of preexisting coronary artery disease, hypertension, cerebrovascular accident and diabetes mellitus. The SAE relating to worsening of coronary artery disease was considered by the investigator to be possibly related to the study drug. The sponsor's assessment did not concur with that of the investigator. All other SAE were considered unrelated to the study drug (lower limb fracture [n = 1] and dengue fever [n = 1] in the tadalafil group, and 1 patient in the placebo group reported both diabetes mellitus and sepsis).

Of patients, two (1.3%) discontinued from the tadalafil group (because of back pain and lower limb fracture) and one (1.2%) from the placebo group (because of headache). The mean change from baseline to endpoint in the heart rate for the tadalafil group was 1.0 as compared to 0.6 for the placebo group (P = 0.743). Similarly, the mean changes in the systolic blood pressure of –2.9 mmHg and in diastolic blood pressure of –0.8 mmHg in the tadalafil treated group were not significantly different from changes in the placebo group of –1.1 mmHg (P = 0.215) and –0.4 mmHg (P = 0.547), respectively.

4 Discussion

Tadalafil treatment significantly improved erectile function in Asian men with ED of varying causes (organic, psychogenic or mixed) and severity. Cultural beliefs, embarrassment and misinformation about ED might prevent some Asian men from seeking treatment [15, 16]. Therefore, effective and well-tolerated oral therapy might encourage more Asian men to seek treatment for their ED. The efficacy measures used to assess erectile function in the present study included the IIEF, the SEP diary and the GAQ. The IIEF has been shown to be valid cross-culturally [14] and its adaptation to Asian languages has not been associated with problems of comprehension [17].

Tadalafil 20 mg provided statistically significant improvements ($P < 0.001$) in each of the three co-primary efficacy endpoints in this as in previously reported similar studies [9, 12, 18]. Men randomized to the tadalafil group experienced a statistically superior increase in IIEF erectile function domain score and improvement from the baseline in proportion of affirmative responses to SEP2 (successful penetration) and SEP3 (successful intercourse) when compared with the placebo group.

This improvement on tadalafil was evident regardless of baseline ED severity, as demonstrated by the significant difference compared with the placebo in the IIEF erectile function domain score in men with mild, moderate and severe ED.

Patients treated with tadalafil further demonstrated improvement in secondary efficacy measures, including improved erections, erection hardness, ability to penetrate their partner's vagina and maintenance of erection. Additionally, tadalafil also provided significant enhancement on measures of satisfaction. Significant improvements were noted in satisfaction with hardness of erection and overall satisfaction as reported by patients through answers to SEP diary questions 4 and 5. Intercourse satisfaction and overall satisfaction domains of the IIEF exhibited a similarly strong improvement. Of patients treated with tadalafil in the present study, 86.2% reported improved erections. This pattern of significantly improved erection, satisfaction with erection hardness, and satisfaction with erectile function overall is consistent with other studies of PDE5 inhibitors' and with studies involving Asian men and men from Western geographies [16, 19]. As an example, the endpoint success rate for SEP3, one of the most important measures of treatment success, was 70.9% for the treated arm *vs.* 33.5% for placebo, which compares to 70% and 31% in the largely Western population database of five tadalafil studies [9].

Tadalafil (20 mg) was well tolerated and the most frequent treatment emergent adverse events in the tadalafil treated group included headache, back pain, dizziness and dyspepsia. No clinically relevant changes occurred in vital signs. These reported events are consistent with

the known safety profile of PDE5 inhibition and are reported previously in studies with PDE5 inhibitors [9, 12, 16, 18–20].

One limitation of the present study may be that according to the study protocol patients who, in the opinion of the investigator, had prior ineffective treatment with sildenafil might have been excluded from the study and, therefore, efficacy results could be overestimated compared to a PDE5 inhibitor naive population.

In conclusion, tadalafil (20 mg) taken on demand enabled Asian men with mild to severe ED with a broad spectrum of etiology to significantly improve their sexual functioning, satisfaction with the hardness of their erections, and satisfaction with their overall sexual experience. Tadalafil was well tolerated in Asian men with ED in this clinical trial.

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