



Sexual Medicine

Evaluation of the Efficacy and Safety of Once-a-Day Dosing of Tadalafil 5 mg and 10 mg in the Treatment of Erectile Dysfunction: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Hartmut Porst^{a,*}, François Giuliano^b, Sidney Glina^c, David Ralph^d, Adolfo R. Casabé^e, Albert Elion-Mboussa^f, Wei Shen^f, J. Steve Whitaker^g

^a Private Practice of Urology and Andrology, Hamburg, Germany

^b Neuro-Urology Unit, Department of Neurological Rehabilitation, AP-HP, Raymond Poincaré Hospital, Garches, France

^c Hospital Ipiranga, São Paulo, Brazil

^d The Middlesex Hospital, London, UK

^e Instituto Médico Especializado (IME), Buenos Aires, Argentina

^f Lilly Research Laboratories, Indianapolis, Indiana, USA

^g ICOS Corporation, Bothell, Washington, USA

Article info

Article history:

Accepted February 21, 2006

Published online ahead of print on March 20, 2006

Keywords:

Tadalafil

Erectile dysfunction

Once-a-day dosing

EU*ACME

www.eu-acme.org

Please visit

www.eu-acme.org to read and answer the EU-ACME questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Background: Erectile dysfunction (ED) is a chronic disease; however, therapy is currently administered as needed with oral phosphodiesterase 5 (PDE5) inhibitors like tadalafil. Because the 17.5-h half-life of tadalafil enables therapeutic plasma levels to be sustained with daily administration, tadalafil is a good candidate for once daily dosing therapy. **Methods:** This multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week study enrolled 268 men 1:2:2 to placebo, tadalafil 5 mg, and tadalafil 10 mg taken once daily. Primary efficacy measures included changes in the International Index of Erectile Function Erectile Function domain (IIEF EF), Sexual Encounter Profile diary Questions 2 (SEP2: successful penetration), and 3 (SEP3: successful completion of intercourse), and tolerability. Secondary measures included percentage of patients at endpoint who reported improved erectile function (EF), and percentage who reported “no ED” (IIEF EF score 26–30).

Results: For patients who took placebo, tadalafil 5 mg, and tadalafil 10 mg, changes from baseline to endpoint were, respectively, 0.9, 9.7, and 9.4 for IIEF EF; 11.2, 36.5, and 39.4 for SEP2; and 13.2, 45.5, and 50.1 for SEP3. At endpoint, 28.3%, 84.5%, and 84.6% reported improved erections, and 8.3%, 51.5%, and 50.5% reported “no ED,” respectively. All comparisons between tadalafil and placebo were significant ($p < 0.001$). Adverse events that occurred in at least 5% of patients were dyspepsia, headache, back pain, upper abdominal pain, and myalgia; nine patients (3.4%) discontinued because of adverse events.

Conclusions: Once-a-day tadalafil 5 mg or 10 mg was well tolerated and significantly improved EF in men with ED.

© 2006 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Neuer Jungfernstieg 6a, Hamburg, D-20354, Germany.

Tel. +49 40 346 184; Fax: +49 40 351 117.

E-mail address: Porst20354@aol.com (H. Porst).

1. Introduction

Medical management of erectile dysfunction (ED) changed with the observation in 1992 that the nitric oxide-cyclic GMP pathway plays a critical role in erectile function (EF) and defects in this pathway may cause some forms of ED [1]. This observation motivated the development of oral inhibitors of phosphodiesterase 5 for this indication: sildenafil citrate (sildenafil), tadalafil, and vardenafil HCl (vardenafil) [2–4]. Before oral agents were introduced, pharmacological ED treatment was limited to penile injections or intraurethral insertion of vasoactive drugs or prostaglandin E1. Although PDE5 inhibitor pharmacotherapy is less invasive and easier to use, sexual activity remains temporally linked to treatment. For all three PDE5 inhibitors, men must take medication on demand before sexual activity [5–7]. Planning sexual activity around taking a pill is burdensome to some patients and their partners [8].

The mean half-life of sildenafil and vardenafil is about four hours [5,6]; the mean half-life of tadalafil is 17.5 hours [7]. Tadalafil 10 or 20 mg taken on demand is well tolerated and efficacious for up to 36 hours in clinical studies [9,10]. This duration may permit men with ED and their partners to disconnect sexual activity from dosing.

Historically, tadalafil has been taken on demand at doses of 10 or 20 mg. The ability of a drug to reach steady state results from the frequency of administration relative to half-life. The 17.5-hour half-life of tadalafil makes it an ideal candidate for once daily therapy because steady-state plasma concentrations are attained within five days of daily dosing, and exposure is approximately 1.6-fold greater than after a single dose [11]. If 5-mg and 10-mg doses are taken daily, a cumulative tadalafil plasma exposure equivalent to on-demand doses of 8 mg and 16 mg, respectively, could be achieved in a few days.

Once-a-day dosing and every-other-day dosing with tadalafil have been compared with on-demand dosing. In one study, 72% of men preferred once-a-day dosing [12], and in another, 42% preferred every-other-day dosing [13]. Neither study compared the efficacy and safety of scheduled dosing with placebo. Thus, the purpose of the current study was to assess the efficacy and safety of once-a-day dosing of tadalafil 5 and 10 mg versus placebo as a new treatment regimen for ED.

2. Methods

2.1. Patients

Patients ≥ 18 years of age, in a monogamous relationship with a female partner, who reported \geq three-month history of ED

could be enrolled. Patients and partners had to sign informed consent and agree not to use other ED treatments during the study. Written informed consent was obtained in conformity with the Declaration of Helsinki (revised 1989) and applicable local laws. The ethics committees of all participating institutions approved the final protocol. Subjects were excluded from enrollment for any of the following: ED caused by other sexual or endocrine disorders such as premature ejaculation or hypogonadism, history of radical prostatectomy (except bilateral nerve-sparing prostatectomy) or other pelvic surgery with subsequent ED, clinically significant hepatobiliary or renal disease, hemoglobin A1c $>13\%$, unstable cardiovascular disease [14], current nitrate use, congestive heart failure, or recent significant central nervous system injuries. Patients who had previously enrolled in any tadalafil study, and those with prior ineffective treatment with sildenafil were ineligible.

2.2. Study design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of once-a-day dosing of placebo, tadalafil 5 mg, and tadalafil 10 mg, administered for 12 weeks to men with ED from 20 centers from Argentina, Brazil, France, Germany, and the United Kingdom. This study (Lilly ICOS LLC study identifier H6-MC-LVCV) began with a screening period that lasted four to five weeks. Eligible subjects were randomly assigned via central telephone to treatment groups 1:2:2 (placebo:5 mg, tadalafil:10 mg, tadalafil). Randomization was stratified by ED severity as measured by the International Index of Erectile Function Erectile Function domain (IIEF EF) [15]. Three stratifications of severity were used: severe (EF domain score 1–10), moderate (11–16), and mild (17–30). Because patients were enrolled based on a history of ED, some men scored 26–30 (“no ED”) [15] at baseline. The protocol stipulated that these men would be included in the mild category. Treatment lasted 12 to 15 weeks and consisted of three visits four to five weeks apart. Patients were instructed to take one dose of study drug around the same time each day.

2.3. Outcome measures

Three efficacy instruments were used: the IIEF EF domain, the Sexual Encounter Profile (SEP) diary, and a Global Assessment Question (GAQ): “Has the treatment you have been taking during this study improved your erections?”

The co-primary efficacy measures were change from baseline in IIEF EF domain score, and change from baseline in per-patient mean percentage of “yes” responses to SEP Question 2 (SEP2, “Were you able to insert your penis into your partner’s vagina?”) and SEP Question 3 (SEP3, “Did your erection last long enough for you to have successful intercourse?”). Secondary efficacy measures were percentage of “yes” responses to the GAQ; and percentage of men who achieved an EF domain score of at least 26 (“no ED”) at endpoint, who had a baseline EF domain score below 26. A post hoc analysis was also done to determine change from baseline in the EF domain score for each baseline ED severity subgroup.

Safety was assessed by evaluating all reported treatment-emergent adverse events, vital signs measurements, electrocardiograms, and standard safety laboratory assessments for all randomized patients. Treatment-emergent adverse events were defined as any adverse event that first occurred or worsened after randomization, and were mapped with the Medical Dictionary for Regulatory Activities. Subjects voluntarily reported adverse events throughout the study.

2.4. Statistical analysis

A sample size of 250 patients would give approximately 90% power to detect a significant treatment effect between placebo and the least-effective tadalafil dosing group. All analyses were conducted on an intent-to-treat basis.

Efficacy analyses included all randomized patients who had a baseline measurement and at least one post-baseline measurement. The last observation carried forward imputation methodology was used to replace missing IIEF EF domain scores. For each SEP question, baseline and post-baseline scores were the number of "yes" responses relative to the

number of sexual encounters during the run-in and treatment periods, respectively. Proportions of "yes" responses to SEP diary questions were treated as continuous variables. IIEF EF domain, SEP2, and SEP3 were analyzed with an Analysis of Covariance model that included terms of treatment group, pooled site, baseline value for each primary efficacy variable, and baseline-by-treatment interaction (if $p < 0.10$). To protect against type 1 error caused by comparing two tadalafil doses with placebo, the pairwise p -values that compared treatment groups were adjusted by the method of Dunnett [16].

A logistic regression model that included terms of pooled site, treatment group, EF at baseline, and baseline-by-treatment interaction was used to perform secondary analysis to evaluate GAQ at endpoint by treatment group. Only patients who responded to GAQ were included in the analysis. The percentage of patients who attained an IIEF EF score of 26–30 at endpoint was analyzed with a logistic model that included terms of pooled site, treatment group, EF at baseline, and baseline-by-treatment interaction (if $p < 0.10$). Data analyses were performed by the Eli Lilly Global Statistical Science Group.

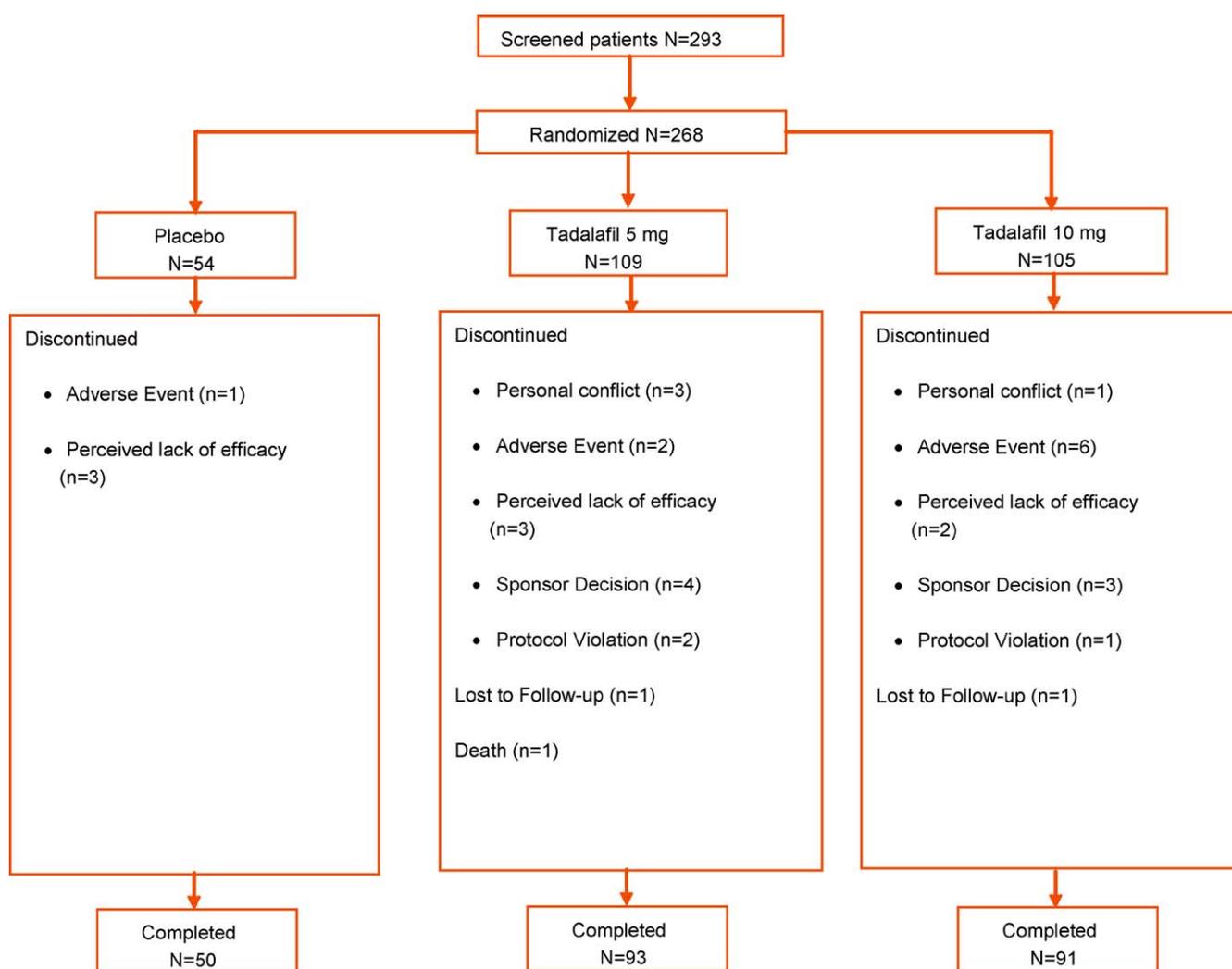


Fig. 1 – Progress of patients through the study. One patient in the tadalafil 5 mg group diagnosed with renal cell carcinoma died during the treatment phase of the study. In the opinion of the investigator, the death was not related to the study drug.

3. Results

3.1. Patients

The first subject was randomized October 2001 and the last completed treatment in March 2002. Of 293 patients screened, 268 were enrolled and 234 completed the study (Fig. 1). Treatment compliance was defined as taking at least 70% of doses between visits; 96.2% (placebo), 94.2% (tadalafil 5 mg), and 93.0% (tadalafil 10 mg) of patients were compliant. Treatment group demographics were similar at baseline (Table 1).

3.2. Primary efficacy endpoints

Tadalafil 5 and 10 mg taken daily significantly improved EF as measured by all primary efficacy variables (Table 2). As stipulated in the protocol, the primary analysis did not exclude patients with an IIEF EF domain score ≥ 26 at baseline. A

post hoc analysis that excluded 14 patients with “no ED” at baseline resulted in slightly lower baseline and endpoint scores without change in statistical interpretation (Table 2). A post hoc analysis of efficacy by ED severity group (excluding the 14 patients with “no ED”) showed EF improvement regardless of baseline ED severity (Figs. 2–4).

3.3. Secondary efficacy endpoints

Tadalafil 5 and 10 mg taken once daily significantly improved EF as measured by all secondary efficacy variables. Based on “yes” responses to GAQ, 84.5% (tadalafil 5 mg) and 84.6% (tadalafil 10 mg) of men thought treatment improved their erections (28.3% of men who took placebo, $p < 0.001$). Of the men who had an IIEF EF domain score < 26 at baseline, 51.5% (tadalafil 5 mg) and 50.5% (tadalafil 10 mg) achieved an EF domain score 26–30 (“no ED”) at endpoint (8.3% of men who took placebo, $p < 0.001$).

Table 1 – Patient demographics

Variable	Placebo (N = 54)	Tadalafil 5 mg (N = 109)	Tadalafil 10 mg (N = 105)	Total (N = 268)
Age, mean (range)	56 (21–73)	56 (24–78)	57 (21–78)	56 (21–78)
Age >65, n (%)	13 (24%)	23 (21%)	24 (23%)	60 (22%)
Ethnicity, n (%)				
African descent	2 (4%)	2 (2%)	4 (4%)	8 (3%)
Western Asian	0	0	1 (1%)	1 (0.4%)
Caucasian	47 (87%)	95 (87%)	89 (85%)	231 (86%)
Hispanic	0	0	1 (1%)	1 (0.4%)
Other	5 (9%)	12 (11%)	10 (10%)	27 (10%)
Previous Sildenafil Users	34 (63%)	88 (81%)	70 (67%)	192 (72%)
Naïve Patients	20 (37%)	21 (19%)	35 (33%)	76 (28%)
ED Duration, n (%)				
≥ 1 year	48 (89%)	105 (96%)	97 (92%)	250 (93%)
IIEF EF Severity, n (%)				
Mild (17–30) ^a	18 (33%)	35 (32%)	36 (34%)	89 (33%)
Moderate (11–16)	15 (28%)	29 (27%)	28 (27%)	72 (27%)
Severe (1–10)	21 (39%)	45 (41%)	41 (39%)	107 (40%)
IIEF EF Domain, mean (range)	14.1 (1–29)	13.1 (3–29)	13.4 (4–29)	13.4 (1–29)
ED Etiology, n (%)				
Psychogenic	11 (20%)	33 (30%)	20 (19%)	64 (24%)
Organic	25 (46%)	41 (38%)	48 (46%)	114 (43%)
Mixed	18 (33%)	35 (32%)	37 (35%)	90 (34%)
Comorbid conditions				
Coronary Artery Disease	5 (9%)	3 (3%)	5 (5%)	13 (5%)
Depression	2 (4%)	2 (2%)	4 (4%)	8 (3%)
Diabetes mellitus	7 (13%)	19 (17%)	13 (12%)	39 (15%)
Hyperlipidaemia	8 (15%)	12 (11%)	7 (7%)	27 (10%)
Hypertension	15 (28%)	28 (26%)	36 (34%)	79 (29%)
Prostatic Disease	10 (19%)	20 (18%)	19 (18%)	49 (18%)

^a Patients were included based on a history of erectile dysfunction. Subsequent assessment of erectile function by the International Index of Erectile Function (IIEF) at baseline revealed that 14 (5.2%) patients had an IIEF EF domain score in the normal range (26 to 30). For efficacy analyses, these patients were included in the mild subgroup.

Table 2 – Improvement in erectile function: primary efficacy outcomes

Efficacy Outcome ^a	Placebo	Tadalafil 5 mg	Tadalafil 10 mg	p-value 5 mg vs. placebo	p-value 10 mg vs. placebo
Mean IIEF EF at Endpoint					
All Patients (N = 268)	15.0	22.8	22.8	<0.001	<0.001
IIEF EF ≥26 excluded (N = 254)	13.5	22.7	22.5	<0.001	<0.001
Mean Per-Patient Percent SEP2 “Yes” Responses					
All Patients (N = 268)	51.7	79.4	81.2	<0.001	<0.001
IIEF EF ≥26 excluded (N = 254)	46.5	79.3	80.5	<0.001	<0.001
Mean Per-Patient Percent SEP3 “Yes” Responses					
All Patients (N = 268)	36.7	67.2	72.8	<0.001	<0.001
IIEF EF ≥26 excluded (N = 254)	31.3	67.0	71.8	<0.001	<0.001

^a The primary efficacy analysis included all patients, regardless of IIEF EF domain score at baseline.

3.4. Safety

The safety evaluation included all 268 enrolled subjects. The mean number of doses per week was calculated as the number of doses taken divided by the number of weeks on therapy until the last scheduled visit. Subjects on tadalafil took an average of 6.5 doses per week; subjects on placebo took an average of 6.6 doses per week.

The majority (87.3%) of subjects completed the study. Nine (3.4%) discontinued because of adverse events (Fig. 1): one for headache (placebo); one each for headache and dizziness (tadalafil 5 mg); one each for myalgia, headache, dyspnea, and dyspepsia; and two for upper abdominal pain (tadalafil 10 mg). One patient in the tadalafil 5 mg group with renal cell carcinoma died during the treatment period. The

study investigator determined that his death was unrelated to the drug.

Treatment-emergent adverse events were generally mild to moderate in severity: 53.8% reported as mild and 32.8% reported as moderate. The most common treatment-emergent adverse events reported were dyspepsia, headache, back pain, upper abdominal pain, and myalgia (Table 3). One patient who took tadalafil 5 mg reported an incident of “gritty feeling in the eyes.” There were no incidents of myocardial infarction (MI).

4. Discussion

ED is a chronic disease associated with underlying cardiovascular, neurological, endocrine, and psy-

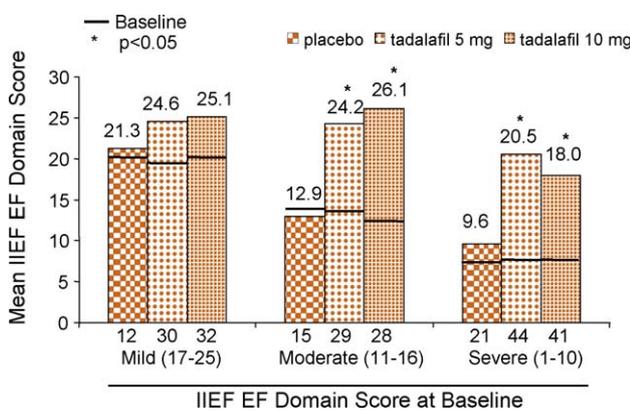


Fig. 2 – Treatment with tadalafil 5 mg and 10 mg taken once a day improved EF. The graph shows change from baseline to endpoint in IIEF EF domain score and endpoint scores by treatment group, by severity. Solid lines indicate baseline IIEF EF domain scores. Numbers below the bars indicate the number of evaluable men (those with a baseline and at least one post-baseline attempt) in each treatment group who had a baseline IIEF EF domain score <26.

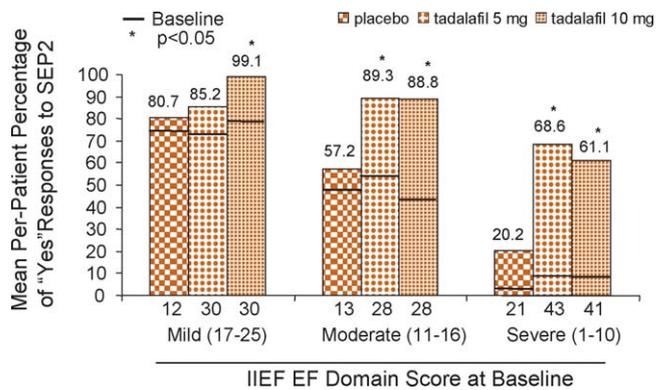


Fig. 3 – Treatment with tadalafil 5 mg and 10 mg taken once a day improved vaginal penetration (SEP2). The graph shows the mean per-patient percentage of successful penetration attempts over the 12-week treatment period by treatment group, by severity. Solid lines indicate SEP2 per-patient means at baseline. Numbers below the bars indicate the number of evaluable men (those with a baseline and at least one post-baseline attempt) in each treatment group who had a baseline IIEF EF domain score <26.

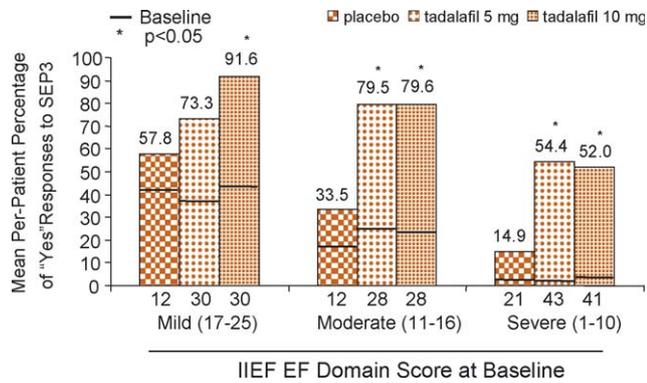


Fig. 4 – Treatment with tadalafil 5 mg and 10 mg taken once a day improved the ability to successfully complete intercourse (SEP3). The graph shows the mean per-patient percentage of successful intercourse attempts over the 12-week treatment period by treatment group, by severity. Solid lines indicate SEP3 per-patient means at baseline. Numbers below the bars indicate the number of evaluable men (those with a baseline and at least one post-baseline attempt) in each treatment group who had a baseline IIEF EF domain score <26.

chological diseases and factors [17]. Historically, pharmacologic ED treatment has been linked to anticipated sexual activity. This required men to inject vasoactive drugs into the penis or apply mechanical devices such as a vacuum device just before sexual activity. Oral PDE5 inhibitors alleviate many of these inconveniences and complications, but, treatment requires that dosing and sexual activity occur within a restricted time window.

The current study suggests daily administration of tadalafil 5 and 10 mg is efficacious and well tolerated in the treatment of ED. Patients who took tadalafil 5 and 10 mg daily had significant EF improvement compared with placebo as assessed by IIEF, SEP, and GAQ. Although this study did not compare daily to on-demand dosing efficacy results are comparable to those seen in on-demand dosing studies. In the current study, the mean IIEF EF domain score increased by 9.7 (tadalafil 5 mg) and 9.4 points (tadalafil 10 mg). In an analysis of 11 pooled, placebo-controlled studies of tadalafil [9],

the mean IIEF EF domain score increased by 6.5 (10 mg) and 8.6 points (20 mg). The magnitude of change in the mild subgroup in the current study was comparatively small, and frequently did not reach statistical significance. This is expected, since the baseline for mild patients is higher (less “room to improve”). However, the change was 4.5 (5 mg) and 4.8 points (10 mg), which is clinically significant (Raymond C. Rosen, Ph.D., personal communication). Also, the sample size in this study limited the power of the analysis. When subgroups are larger, as in the 11 pooled studies (mild patients, $n = 112$) a 3.7-point change (10 mg on demand) reached statistical significance [9].

Because daily dosing with tadalafil was efficacious, this regimen may provide a novel approach to ED therapy in which sexual activity need not be tied to drug administration. As reported by Hanson-Divers et al., the five measures considered most important to patients in defining success were cure, pleasure, partner satisfaction, reproduction, and naturalness [8]. Thus, taking a long-acting drug once a day may be the best way for some patients to forget their ED and be ready for spontaneous sexual activity.

Two independent studies investigated once daily dosing with tadalafil. The first [18] tested once-a-day tadalafil 10 and 20 mg as salvage therapy for patients who were unresponsive to tadalafil 20 mg on demand. Efficacy endpoints while on once-a-day therapy were all significantly higher than baseline and with endpoints achieved during on-demand dosing. The second [12] directly compared on-demand tadalafil 20 mg with once-a-day tadalafil 10 mg. The mean change from baseline was significantly higher for once-a-day (11.8 points) than for on-demand (8.7 points). Based on these results, once-a-day dosing with tadalafil may provide superior efficacy compared with on-demand tadalafil. Also, 72% of patients preferred taking tadalafil once a day [12]. Because of the broad differences between the McMahon studies and the current study, direct comparisons were not made, but both studies show patients respond well to once-a-day tadalafil.

Table 3 – Treatment-emergent adverse events reported by at least 5% of patients

Adverse event	Placebo (n = 54)		Tadalafil 5 mg (n = 109)		Tadalafil 10 mg (n = 105)	
	n	(%)	n	(%)	n	(%)
Dyspepsia	2	(3.7%)	6	(5.5%)	12	(11.4%)
Headache	4	(7.4%)	7	(6.4%)	11	(10.5%)
Back Pain	2	(3.7%)	4	(3.7%)	10	(9.5%)
Upper Abdominal Pain	0		3	(2.8%)	9	(8.6%)
Myalgia	0		3	(2.8%)	7	(6.7%)

Steady-state tadalafil plasma concentrations are attained within five days of once-a-day dosing, and exposure is approximately 1.6-fold greater than after a single dose [11]. Thus, after five days, a cumulative tadalafil plasma concentration equivalent to on-demand doses of 16 and 8 mg would be achieved for the 10-mg and 5-mg doses, respectively. Tadalafil taken on demand is efficacious 30 minutes to 36 hours after dosing [10]. In most cases, men are able to respond after the first dose, though for some men who need the greatest plasma levels of tadalafil, these would be achieved after the first few days of dosing. Further studies that address this point could be useful for clinicians.

Recently, every-other-day dosing with tadalafil 20 mg has been investigated [13]. The efficacy results for every-other-day dosing are comparable with on-demand and once-a-day dosing, and 42% of men preferred every-other-day dosing. Although McMahon reported 72% of patients preferred daily dosing, once-a-day administration of 10 mg (or 5 mg) is scientifically difficult to compare with every-other-day administration of 20 mg without a cross-over study. However, since every-other-day dosing was efficacious, and nearly half the men preferred this regimen, every-other-day dosing with tadalafil may be another alternative regimen.

In this study, both doses of tadalafil were well tolerated when taken daily. This is corroborated by both the high rate of treatment compliance and the low frequency of discontinuation caused by adverse events. The discontinuation rate in this study (3.4%) is numerically similar to that seen in on-demand studies (tadalafil 10/20 mg; 1.6%–5.5%) [9,10,19–22] and in a long-term (18–24 months) study (tadalafil 5/10/20 mg 6.3%) [23]. The incidence of adverse events in this study was similar to that seen in the pooled analysis of 11 on-demand studies. The profile of adverse events also was similar, although with a possible reduction in headache (6.4%–10.5% versus 12%–15% in the 11 pooled studies, and 15.8% in the long-term study) [9,23]. However, given the broad differences between the studies, direct comparisons should be interpreted with caution.

The McMahon once-a-day dosing studies reported two [18] and four [12] incidents of MI, all in patients with significant multiple vascular risk factors. All were determined to not be drug related [18]. The MI rates reported by McMahon are inconsistent with incidence rates of MI recorded in 35 clinical trials of tadalafil, which included four studies of daily dosing with tadalafil and 371 patient-years of exposure. The incidence rate of MI for these 35 studies was 0.33 per 100-patient years ($n = 10,460$ patients, 5,088 patient-years exposure to

tadalafil). This rate is no higher than MI rates in placebo-treated patients (0.41 per 100 patient-years; $n = 2,118$; 489 patient-years), or in an age-standardized male population (0.6 per 100 patient-years) [24].

Chronic dosing of PDE5 inhibitors may have medical benefits beyond ED. Chronic administration of PDE5 inhibitor therapy is efficacious in the treatment of pulmonary arterial hypertension [25] and may have cardioprotective effects for ischemia-reperfusion injury [26]. A daily approach also may improve organic ED at the level of vascular endothelial function. Recent data suggest both sildenafil and tadalafil could exert prolonged beneficial effects on vascular endothelial function if taken regularly [27–30]. In this context, the FDA recently approved sildenafil citrate 20 mg (Revatio[®]) at three times per day for the indication of primary pulmonary hypertension. This suggests that daily use of PDE5 inhibitors may have further potential for non-ED and ED indications.

The interpretation of our results is subject to limitations. First, patients with an IIEF EF domain score ≥ 26 were included in the primary analysis, which is consistent with clinical practice; most clinicians do not administer the IIEF. Exclusion of patients with “no ED” increased the magnitude of change from baseline but did not affect the statistical interpretation of the data. Therefore, including these patients may be the more conservative analysis. Whether daily dosing with tadalafil could rescue nonresponders is unknown, because patients with prior experience with tadalafil and patients who were sildenafil nonresponders were not included in this study. Third, because this study did not compare once-a-day dosing with on-demand dosing or every-other-day dosing, we cannot adequately compare the efficacy and tolerability of the regimens or comment on which would be preferred, but the efficacy and tolerability of 5 mg tadalafil taken daily appear to be comparable to the efficacy and tolerability of 20 mg taken on demand or every other day. Further studies that address this comparison could be useful for clinicians.

In conclusion, once-a-day dosing with tadalafil 5 and 10 mg significantly improved EF versus placebo, and patients were highly compliant with this dosing regimen. Adverse events reported by patients tended to be mild or moderate in severity, and the rate of discontinuations caused by adverse events was similar to rates seen in studies that used on-demand dosing. Therefore, once-a-day dosing with tadalafil may be an attractive alternative to on-demand therapy for ED.

Acknowledgments

These data have been reported previously in abstract form:

1. Giuliano F, Porst H, Shen W, Chang S. 2002. Safety and efficacy of Cialis™ (tadalafil) taken daily for the treatment of erectile dysfunction. *Int J Impot Res* 14 (Suppl 4):S16. Abstract PS-4-6.
2. Giuliano F, Glina S, Ralph D, Casabe A, Elion-Mboussa A, Shen W, Stothard D, Whitaker JS, Porst H. The Efficacy and safety of tadalafil taken once a day for up to 1 year for the treatment of erectile dysfunction. *J Sex Med* 2006;3:180.

Funding for this study (study code H6-MC-LVCV) was provided by Lilly ICOS LLC.

The authors wish to acknowledge the other investigators who took part in this study: Dr. Edgardo F Becher, Dr. Jacques Buvat, Dr. Ronaldo Damião, Dr. Wilbert Wallace Dinsmore, Dr. Fernando N. Facio Jr., Dr. Antoine Faix, Dr. Geraldo Faria, Dr. Wolfram Fluehr, Dr. Philip D. Kell, Dr. Olivier Lan, Dr. Miguel A Rivero, Dr. Claudio Teloken, Dr. Luiz O. Torres, Dr. Luiz F. Vieiralves, Dr. Alexander Von Keitz, and Prof. Ulrich Wetterauer. We also acknowledge Dr. Diane R. Stothard (Lilly Research Laboratories, Indianapolis, Indiana, USA) and Dr. William H. Cordell (Lilly Research Laboratories, Indianapolis, Indiana, USA) for writing and editorial support. Support for this study (Study identifier H6-MC-LVCV) was provided by Lilly ICOS LLC.

References

- [1] Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. *N Engl J Med* 1992;326:90-4.
- [2] Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998;338:1397-404.
- [3] Padma-Nathan H, McMurray JG, Pullman WE, et al. On-demand IC351 (Cialis(trademark)) enhances erectile function in patients with erectile dysfunction. *Int J Impot Res* 2001;13:2-9.
- [4] Porst H, Rosen R, Padma-Nathan H, Goldstein I, Guiliano F, Vardenafil. a new highly selective PDE5 inhibitor, improves erectile function irrespective of the baseline severity and aetiology of ED or age of patient. *Eur Urol* 2001;39:17.
- [5] Viagra (sildenafil citrate) label. <http://www.fda.gov/cder/foi/label/2002/20895s11s15s18lbl.pdf> 2002. New York, Pfizer Inc. 6-22-0004. Last Accessed January 9, 2006.
- [6] Levitra (vardenafil HCl) label. <http://www.fda.gov/cder/foi/label/2005/021400s004lbl.pdf> 2003. Last Accessed January 9, 2006.
- [7] Cialis (tadalafil) label. <http://www.fda.gov/cder/foi/label/2005/021368s006lbl.pdf> 2003. Last Accessed January 9, 2006.
- [8] Hanson-Divers C, Jackson SE, Lue TF, Crawford SY, Rosen RC. Health outcomes variables important to patients in the treatment of erectile dysfunction. *J Urol* 1998;159:1541-7.
- [9] Carson CC, Rajfer J, Eardley I, et al. The efficacy and safety of tadalafil: an update. *BJU Int* 2004;93:1276-81.
- [10] Young JM, Feldman RA, Auerbach SM, et al. Tadalafil improved erectile function at twenty-four and thirty-six hours after dosing in men with erectile dysfunction: US trial. *J Androl* 2005;26:310-8.
- [11] Forgue ST, Patterson BE, Bedding AW, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006;61:280-8.
- [12] McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med* 2005;2:415-24.
- [13] Mirone V, Costa P, Damber J-E, et al. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. *Eur Urol* 2005;47:846-54.
- [14] Debusk R, Drory Y, Goldstein I, et al. Management of sexual dysfunction in patients with cardiovascular disease: Recommendations of the Princeton consensus panel. *Am J Cardiol* 2000;86:175-81.
- [15] Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology* 1999;54:346-51.
- [16] Dunnett C. A multiple comparison procedure for comparing several treatments with a control. *J Amer Statist Assoc* 1955;50:1096-121.
- [17] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54-61.
- [18] McMahon C. Efficacy and safety daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med* 2004;1:292-300.
- [19] Montorsi F, Nathan HP, McCullough A, et al. Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: A randomized, double-blind, placebo controlled trial. *J Urol* 2004;172:1036-41.
- [20] Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: Results of integrated analyses. *J Urol* 2002;168:1332-6.
- [21] Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care* 2002;25:2159-64.
- [22] Skoumal R, Chen J, Kula K, et al. Efficacy and treatment satisfaction with on-demand tadalafil (Cialis) in men with erectile dysfunction. *Eur Urol* 2004;46:362-9.

- [23] Montorsi F, Verheyden B, Meuleman E, et al. Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004;45:339-45.
- [24] Jackson G, Kloner RA, Costigan TM, Warner MR, Emmick JT. Update on clinical trials of tadalafil demonstrates no increased risk of cardiovascular adverse events. *J Sex Med* 2004;1:161-7.
- [25] Chockalingam A, Gnanavelu G, Venkatesan S, et al. Efficacy and optimal dose of sildenafil in primary pulmonary hypertension. *Int J Cardiol* 2005;99:91-5.
- [26] Kukreja RC, Ockaili R, Salloum F, et al. Cardioprotection with phosphodiesterase-5 inhibition - A novel preconditioning strategy. *J Mol Cell Cardiol* 2004;36:165-73.
- [27] Behr-Roussel D, Gorny D, Mevel K, et al. Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: Lack of tachyphylaxis. *Eur Urol* 2005;47:87-91.
- [28] Caretta N, Palego P, Ferlin A, et al. Resumption of spontaneous erections in selected patients affected by erectile dysfunction and various degrees of carotid wall alteration: Role of tadalafil. *Eur Urol* 2005;48:326-32.
- [29] Desouza C, Parulkar A, Lumpkin D, Akers D, Fonseca VA. Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes. *Diabetes Care* 2002;25:1336-9.
- [30] Rosano GMC, Aversa A, Vitale C, Fabbri A, Fini M, Spera G. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. *Eur Urol* 2005;47:214-22.