

Tadalafil: a novel treatment for erectile dysfunction

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Tadalafil, a potent, selective and reversible inhibitor of phosphodiesterase type 5 that is under review as an oral therapy for erectile dysfunction, has a time to maximum concentration of 2 h and a half-life of 17.5 h. Systemic tadalafil exposure was not clinically significantly altered by age or diabetes. Food did not alter the rate and extent of absorption of tadalafil, and no restrictions regarding food or alcohol intake were imposed on patients in tadalafil clinical trials. Furthermore, the time of dosing had no significant effect on the systemic distribution of tadalafil. Integrated analyses of data from five phase III trials demonstrated that tadalafil at doses from 5 mg to 20 mg significantly improved erectile function (vs placebo) by all

efficacy measures. Tadalafil was safe and well tolerated in the phase III studies, with headache and dyspepsia being the most frequent adverse events. Additionally, in a separate study of patients with erectile dysfunction and diabetes, tadalafil 10 mg and 20 mg significantly improved all efficacy measures as compared with placebo.

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Introduction

The role of the nitric oxide–guanylate cyclase–cyclic guanosine monophosphate system in the physiology of penile erection is well characterized^[1–4]. Additional evidence suggests that inhibition of the enzyme phosphodiesterase (PDE) type 5 is effective in maintaining nitric oxide mediated smooth muscle relaxation in the corpus cavernosum and thus erection^[2–5]. Indeed, sildenafil citrate (Viagra[®], Pfizer Inc.), a selective inhibitor of PDE5, has demonstrated this on the basis of its mechanism of action and its efficacy in the treatment of erectile dysfunction (ED)^[5–9].

Although the vast majority of the data concerning PDE5 inhibitors and ED comes from studies involving sildenafil, two new PDE5 inhibitors, namely tadalafil (Cialis[™]; Lilly ICOS LLC, Indianapolis, IN, U.S.A.)^[10,11] and vardenafil (Bayer AG, Bothell, WA, U.S.A.)^[11,12], are currently pending approval for the treatment of ED in Europe and in the U.S.A. Additionally, several other PDE5 inhibitors are at various earlier stages of development^[13–16]. Some of these new PDE5 inhibitors could potentially offer patients a

treatment for ED with an improved safety profile, better efficacy and greater convenience, which may translate into better treatment continuation.

The data presented herein describe the novel pharmacokinetic and pharmacodynamic characteristics of tadalafil; characterize the efficacy and safety of tadalafil, based on integrated analyses from five phase III clinical trials in patients with ED; describe the period of responsiveness to tadalafil in patients with ED; and describe the efficacy and safety of tadalafil in diabetic patients with ED.

Pharmacological profile

Integrated analyses of 13 clinical pharmacology studies in healthy persons were performed in order to describe the distribution characteristics of the primary pharmacokinetic parameters for tadalafil 20 mg^[17]. Results from that integrated analyses (Table 1) demonstrated that tadalafil is rapidly absorbed following oral administration, with a mean maximum observed concentration of 378 µg/l in plasma, and the median time to maximum concentration was 2 h. The half-life for tadalafil is 17.5 h. It is widely distributed in the tissues, as indicated by an apparent volume of distribution of 62.6 l.

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Table 1 Pharmacokinetics of tadalafil

Parameter	Geometric mean (CV%)
$t_{1/2}$ (h)	17.5 (32.3)
CL/F (l/h)	2.48 (39.3)
V_z/F (l)	62.6 (25.4)
AUC ($\mu\text{g}\cdot\text{h/l}$)	8066 (39.3)
T_{max}^* (h)	2.0 (0.5–12.0)
C_{max} ($\mu\text{g/l}$)	378 (27.6)

A total of 237 patients were assessed. *Median and range are given; all other variables are geometric mean (CV%). AUC=area under the plasma concentration curve from zero to infinity; CL/F=apparent oral clearance; C_{max} = maximum observed concentration; $t_{1/2}$ =half-life; T_{max} =time to C_{max} ; V_z/F =apparent volume of distribution. (Data from Patterson *et al.*[17].)

In vitro metabolic data suggested that tadalafil is metabolized primarily via cytochrome P450 3A4 (CYP3A4) pathway in the liver (Lilly ICOS LLC, data on file). These in vitro findings warranted clinical investigation of the effect of tadalafil on CYP3A4 activity. This was assessed by examining how tadalafil affects the metabolism of lovastatin, which is a substrate for CYP3A4. In healthy volunteers, tadalafil, at therapeutic concentrations, had no effect on the metabolism of lovastatin (Lilly ICOS LLC, data on file), indicating that tadalafil neither inhibits nor induces the CYP3A4 pathway. In addition, the effects of a potent CYP3A4 inhibitor (ketoconazole) and a potent CYP3A4 inducer (rifampicin) on the pharmacokinetics of tadalafil were examined in a phase I clinical pharmacology study (Lilly ICOS LLC; data on file). In healthy volunteers, the area under the curve for the concentration of tadalafil versus time was increased 107% when tadalafil was co-administered with ketoconazole. Alternatively, coadministration of rifampicin and tadalafil reduced the area under the curve for tadalafil by 88%. These results suggest that tadalafil neither inhibits nor induces CYP3A4, and corroborate the in vitro findings that tadalafil is metabolized primarily through the CYP3A4 pathway in the liver in humans.

Several conventional pharmacokinetic studies were conducted to investigate the effect of intrinsic (age and diabetes) and extrinsic (time of dose, alcohol and food) factors on the pharmacokinetics of tadalafil[18]. Systemic exposure to tadalafil 10 mg was 25% greater in elderly persons than in young subjects, indicating a slight reduction in clearance with age. However, the increase in exposure with age was not considered to be clinically significant. Likewise, systemic exposure to tadalafil based on area under the curve was decreased by 19% in subjects with diabetes; this change was not statistically or clinically significant and does not warrant a dosage adjustment.

Based on studies used to examine the effects of extrinsic factors on the pharmacodynamics of tadalafil, consumption of food before tadalafil administration did not alter the rate and extent of absorption of tadalafil. In addition, the administration of tadalafil 2 h before the consumption of alcohol had no effect on systemic exposure to alcohol, and no pharmacodynamic interaction was demonstrated between tadalafil and alcohol. Finally, the time of

administration of tadalafil (morning vs evening) had no effect on systemic distribution to tadalafil[18].

Efficacy and safety profiles

Assessments

Efficacy

In randomized controlled studies involving tadalafil, the effects of treatments on erectile function were assessed using the International Index of Erectile Function (IIEF) questionnaire, Sexual Encounter Profile (SEP) diaries, and a Global Assessment Question (GAQ). The IIEF[19] is a self-administered, 15-item recall questionnaire that addresses five domains of sexual functioning (over a designated interval): erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. For a question, response options range from 0 ('no sexual activity/did not attempt intercourse') to 5 ('almost always/always' or 'not difficult'), with better sexual functioning being indicated by higher scores.

The IIEF erectile function domain comprises six similarly worded questions concerning attaining and maintaining an erection, frequency of penetration, maintaining erection after penetration, maintaining erection to completion of intercourse, and confidence in attaining and maintaining an erection. The maximum attainable score in this domain is 30.

In addition, patients kept SEP diaries, which enabled one or both sexual partners to rate aspects of sexual activity via responses to 'yes'/'no' questions. Finally, a GAQ was also used to evaluate treatment efficacy over a specified study interval; the GAQ reads 'Has the treatment you have been taking improved your erections?' and requires a simple 'yes'/'no' response.

Safety

At each visit, adverse events were monitored, vital signs were obtained and clinical laboratory tests (serum chemistry, haematology, urinalysis) were performed. Twelve-lead electrocardiography, medical history and physical examination were performed at screening and/or study end-point or premature discontinuation.

Studies complied with the Declaration of Helsinki. Study protocols and informed consent documents were reviewed and approved by ethical review boards, and both patients and their partners provided written informed consent.

Integrated safety and efficacy

A total of 1112 patients were enrolled in five randomized, double-blind, placebo-controlled, parallel-group trials conducted at 74 study centres worldwide[20]. During a screening visit, medical history, physical examination and laboratory safety tests, including an electrocardiogram, were assessed. Patients who made at least four attempts at sexual intercourse during a treatment-free run-in period

were randomly assigned to receive placebo (n = 308) or tadalafil at fixed doses of 2.5 mg (n = 74), 5 mg (n = 151), 10 mg (n = 321) or 20 mg (n = 258). Not all doses were included in all studies. Patients were instructed to self-administer treatment as needed before sexual activity, with no restriction on timing of sexual activity after dosing and no restriction on timing of food or alcohol intake relative to dosing. Patients were allowed a maximum of one dose per day. Patients were seen at 4-week intervals until they completed the study or discontinued early for any reason.

Men aged 18 years or older who had at least a 3-month history of mild to severe ED of organic, psychogenic or mixed aetiology (as determined by the investigator), and who were in a monogamous relationship with a female partner were eligible to participate in the studies. Patients were excluded if they failed to achieve erection following radical prostatectomy or pelvic surgery, or had clinically significant penile deformities or implants. Other reasons for exclusion included a recent history of stroke or spinal cord trauma, cardiovascular disease (unstable angina, myocardial infarction or myocardial revascularization within the prior 90 days, or poorly controlled hypertension), and/or significant renal or hepatic insufficiency. Men treated with nitrates, chemotherapy or antiandrogens were also excluded.

The effects of tadalafil on erectile function were evaluated using the IIEF^[19], SEP diaries and the GAQ. The IIEF was administered at baseline and at 4-week intervals following initiation of treatment. Patients completed the SEP diary questions after each sexual attempt throughout the study, and the GAQ was assessed at the end of the study or at the discontinuation visit.

The three coprimary end-points for the studies were the mean change from baseline to end-point on the erectile function domain and the mean change from baseline to end-point in proportions of 'yes' responses to SEP question 2 ('Were you able to insert your penis into your partner's vagina?') and SEP question 3 ('Did your erection last long enough for you to have successful intercourse?'). Several other efficacy variables were also evaluated, including the absolute proportion of affirmative responses to the GAQ; the proportion of patients achieving a final IIEF erectile function domain score of at least 26 (normal erectile function domain score, according to work by Cappelleri *et al.*^[21]); the mean change from baseline to end-point on the IIEF intercourse satisfaction domain; and the mean change from baseline to end-point on the IIEF overall satisfaction domain.

All analyses were conducted on an intent-to-treat basis. Patients who had a baseline measurement and at least one post-baseline measurement were included in the analysis of efficacy. The analysis of safety included all randomized patients. The study design and patient population were consistent across all five studies, and therefore efficacy and safety data from all five studies were pooled for all analyses. Each of the five studies was adequately powered to demonstrate statistically significant differences between placebo and tadalafil for each efficacy variable.

Patient demographics were well balanced across all treatment groups (Table 2). The mean patient age was 59 years. Most (90%) of the patients had had ED for more than 1 year, and the aetiology of ED was primarily organic

Table 2 Patient demographic characteristics

Parameter	Value
Mean age (years)	59
ED duration >1 year (%)	90
ED aetiology (%)	
Psychogenic	8.7
Organic	60.5
Mixed	30.8
Diabetes (%)	21
Hypertension (%)	30
Coronary disease (%)	8
Baseline IIEF erectile function domain score	14.6

ED=erectile dysfunction; IIEF=International Index of Erectile Function. (Data from Brock *et al.*^[20])

(60.5%), with mixed and psychogenic causes accounting the remainder of the patients (30.8% and 8.7%, respectively). Of the patients enrolled in these studies, 21% had diabetes, 30% had hypertension and 8% had coronary disease. The mean baseline IIEF erectile function domain score was 14.6, which indicates moderate ED severity^[20].

Therapy with tadalafil at doses of 2.5 mg to 20 mg significantly improved erectile function as assessed by all three coprimary efficacy measures. When compared with placebo treatment, the mean IIEF erectile function domain score at end-point increased significantly for all doses of tadalafil (Fig. 1, Table 3). As demonstrated in Fig. 2, patients with more severe ED tended to experience greater improvement in erectile function following treatment. Within each baseline severity category, tadalafil treatment at doses of 5 mg or higher significantly improved IIEF erectile function domain scores as compared with placebo^[20].

Mean changes from baseline to end-point in the proportions of sexual attempts marked by successful penetration (SEP question 2; 'Were you able to insert your penis into your partner's vagina?') and erection lasting long enough to have successful intercourse (SEP question 3; 'Did your erection last long enough for you to have successful intercourse?') were significantly increased in each group receiving tadalafil as compared with placebo (Table 3). In addition, 61% of intercourse attempts in patients receiving tadalafil 10 mg and 75% of those in patients receiving tadalafil 20 mg were successful, as assessed by SEP question 3 (Fig. 3)^[20].

When compared with placebo, all doses of tadalafil resulted in a significantly greater proportion of patients with normal erectile function (IIEF erectile function domain score of ≥ 26) following treatment (Fig. 4)^[21]. Of those who received tadalafil 10 mg and 20 mg, 40% and 59%, respectively, had returned to having normal erectile function at end-point as compared with 11% of placebo treated patients^[20].

With respect to the secondary efficacy measures, namely the proportion of patients with improved erections, as assessed using the GAQ, was significantly greater for all tadalafil treatment groups when compared with placebo (Table 3). In addition, tadalafil at doses of 5 mg to 20 mg significantly improved sexual satisfaction as assessed using

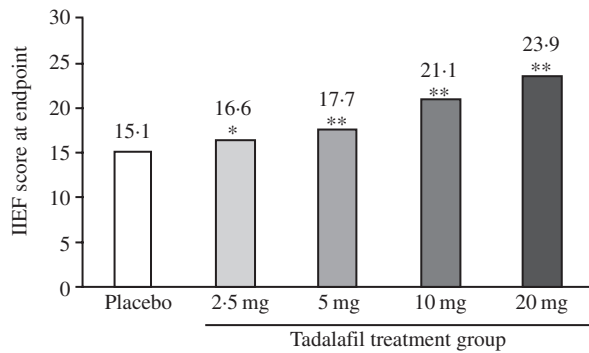


Figure 1 International Index of Erectile Function (IIEF) erectile function domain scores at endpoint. Shown are the mean IIEF erectile function domain scores (LOCF) at endpoint, including all randomized patients (based on five phase III studies); not all doses were included in all studies. * $P < 0.05$, ** $P < 0.001$ vs placebo. (Data from Brock et al.^[20])

the IIEF intercourse satisfaction and overall satisfaction domains (Table 3)^[20].

The period of responsiveness to tadalafil was also examined using pooled data from the phase III studies. These results demonstrated that, following treatment with tadalafil 20 mg, 59% of intercourse attempts within 30 min of dosing were successful. Additionally, 71–80% of attempts made between 30 min and 24 h were successful (Fig. 5)^[20]. These findings were consistent with the results of studies specifically designed to examine the period of responsiveness to tadalafil (presented below).

Taken together, results from the five phase III randomized, placebo-controlled, parallel-group studies indicate that tadalafil significantly improved erectile function, as assessed using all primary and secondary efficacy measures. These results were consistent and particularly evident at tadalafil doses of 5 mg to 20 mg.

With regard to the safety of tadalafil in these studies, all doses of tadalafil were well tolerated. Headache and dyspepsia were the most commonly reported treatment-emergent adverse events, followed by back pain, rhinitis, myalgia and vasodilatation (flushing; Table 4). These events were mostly mild or moderate in severity and decreased in frequency with continued treatment in most patients. The rate of discontinuation due to adverse events was low and not statistically different between placebo (1.3%) and all tadalafil treatment groups (2.1%).

Period of responsiveness

The period of responsiveness to tadalafil (including time to offset and time to onset) was examined in two at-home, randomized, placebo-controlled, parallel studies in men with various severities and aetiologies of ED^[22,23]. The purpose of the first study was to determine the time to offset following administration of tadalafil 20 mg. That study consisted of a 4-week, treatment-free run-in period followed by two 4-week treatment periods. During one 4-week treatment period, patients were to attempt sexual intercourse twice in conjunction with medication (tadalafil 20 mg or placebo), each time approximately 24 h after dosing, with an 8- to 10-day washout period between

Table 3 Summary of major efficacy variables at endpoint

Efficacy variables	Tadalafil treatment group										Overall <i>P</i> value
	Placebo (n = 308)		2.5 mg (n = 74)		5 mg (n = 151)		10 mg (n = 321)		20 mg (n = 258)		
	EP	Change	EP	Change	EP	Change	EP	Change	EP	Change	
Primary											
IIEF erectile function domain (mean score)	15.1	0.6	16.6	3.2*	17.7	4.6**	21.1	6.5**	23.9	7.9**	<0.001
SEP question 2 (achieving erections [mean % of success])	48	2	56	15**	57	16**	73	24**	80	27**	<0.001
SEP question 3 (maintaining erections [mean % of success])	31	6	37	20*	40	22**	58	34**	70	39**	<0.001
Secondary											
GAQ ¹ (improved erection [%])	35	–	42%*	–	50**	–	67%**	–	81%**	–	<0.001
IIEF intercourse satisfaction domain (mean score)	7.4	0.8	7.8	1.6	8.5	1.6**	9.3	2.6**	10.5	3.4**	<0.001
IIEF overall satisfaction domain (mean score)	5.2	0.5	5.8	0.8	6.1	1.3**	6.7	1.8**	7.4	2.4**	<0.001

Pair-wise comparisons between placebo and each treatment were adjusted using the method of Bonferroni: * $P < 0.05$; ** $P < 0.001$.

¹GAQ results for four 12-week studies: placebo (n = 261), tadalafil 2.5 mg (n = 74), tadalafil 5 mg (n = 151), tadalafil 10 mg (n = 321) and tadalafil 20 mg (n = 165). EP=end-point; GAQ=Global Assessment Question; IIEF=International Index of Erectile Function; SEP=Sexual Encounter Profile. (Data from Brock et al.^[20])

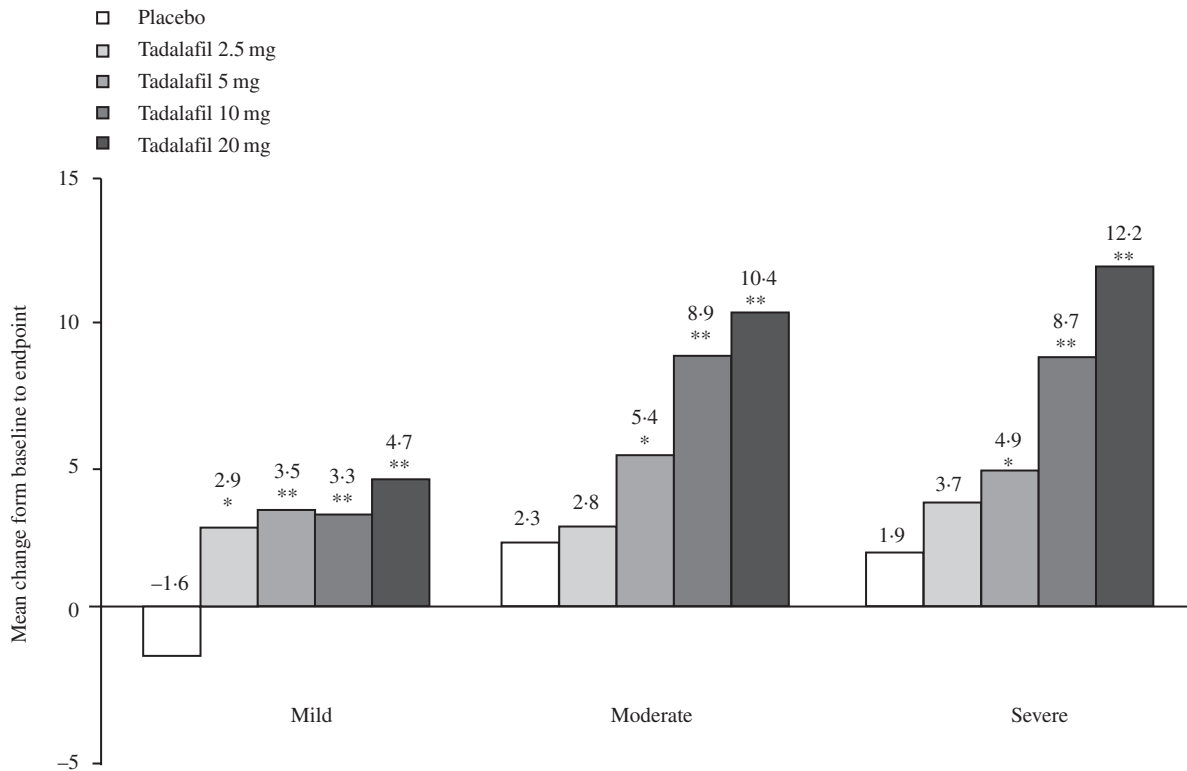


Figure 2 Change from baseline in International Index of Erectile Function (IIEF) erectile function domain scores at end-point by baseline severity. Shown are the mean IIEF erectile function domain scores (LOCF) at endpoint, including all randomized patients (based on five phase III studies); not all doses were included in all studies. Representative values for baseline severity were 7 (severe), 14 (moderate) and 21 (mild – data on file; Lilly ICOS LLC). * $P < 0.05$, ** $P \leq 0.001$ vs placebo. (Data from Brock et al.^[20])

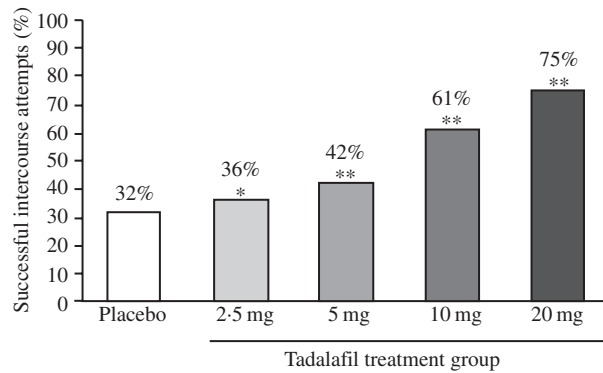


Figure 3 Mean percentage of successful intercourse attempts during study. Shown are the mean percentages of positive responses to Sexual Encounter Profile (SEP) question 3 – ‘Did your erection last long enough for you to have successful intercourse?’, including all randomized patients (based on five phase III studies); not all doses were included in all studies. * $P < 0.05$, ** $P < 0.001$ vs placebo.

Of the 348 men who were enrolled in the study, 327 completed treatment. The mean patient age was 57 years for both treatment groups. All other baseline characteristics were well balanced between the tadalafil 20 mg and placebo treatment groups^[23].

The proportion of successful intercourse attempts at 24 h following dosing, as assessed by positive responses to SEP question 3 (‘Did your erection last long enough for you to have successful intercourse?’), was significantly greater following administration of tadalafil 20 mg (57%, 153 out of 267 attempts) than following placebo (31%, 90 out of 288 attempts; $P < 0.001$). At 36 h, 60% (166 out of 275 attempts) of intercourse attempts were successful in patients randomized to the tadalafil 20 mg dose as compared with 30% (79 out of 264 attempts) in those receiving placebo ($P < 0.001$). Tadalafil 20 mg was well tolerated in the study, with headache, flushing and dyspepsia being the most commonly reported adverse events^[23].

A separate clinical trial was designed to determine the earliest time to onset of action and the period of responsiveness to tadalafil 10 mg and 20 mg in men with ED^[22]. Patients in each arm of the study received a total of four doses of study drug for four sexual attempts. Each dose was separated from the previous dose by 8–10 days. Patients were given no instruction regarding food or alcohol consumption relative to dosing. After ingesting each dose,

attempts. During the other 4-week treatment period, the two sexual intercourse attempts were to occur approximately 36 h after dosing with either tadalafil 20 mg or placebo.

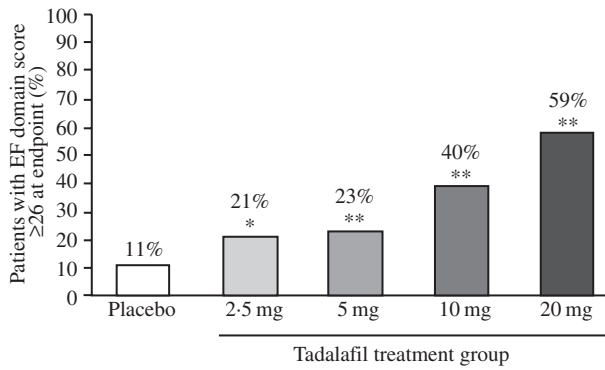


Figure 4 Percentage of patients with normal erectile function at end-point. Shown are the mean percentages of patients with International Index of Erectile Function (IIEF) erectile function domain scores (LOCF) ≥ 26 at endpoint, including all randomized patients (based on five phase III studies); not all doses were included in all studies. 'Normal' is defined as an IIEF erectile function domain score ≥ 26 . * $P < 0.05$, ** $P < 0.001$ vs placebo. (Data from Brock *et al.*^[20].)

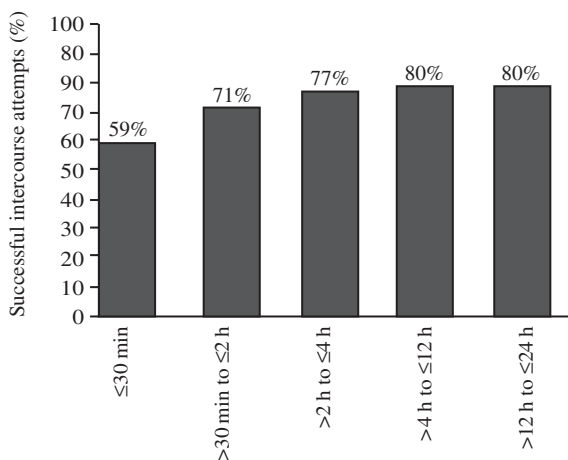


Figure 5 Intercourse success rate with tadalafil 20 mg as a function of time. Shown are the mean percentages of positive responses to Sexual Encounter Profile (SEP) question 3 – 'Did your erection last long enough for you to have successful intercourse?', including all randomized patients (based on three as-needed phase III studies). (Data on file, Lilly ICOS LLC.)

patients used a stopwatch to measure the earliest time to achievement of an erection sufficient for vaginal penetration that resulted in successful intercourse.

A total of 223 patients completed this study. Demographic and other baseline characteristics were similar among the three treatment groups. The mean age was 58.8 years in the placebo group, 57.6 years in the tadalafil 10 mg group, and 59.1 years in the tadalafil 20 mg group. Erectile dysfunction severity was similar among patients treated with tadalafil and placebo^[22].

Table 4 Most common treatment-emergent adverse events

Event	Placebo (n = 308)	Tadalafil (n = 804)
Headache	6%	14%
Dyspepsia	2%	10%
Back pain	5%	6%
Rhinitis (nasal congestion)	4%	5%
Myalgia	2%	5%
Vasodilatation (flushing)	2%	4%

(Data from Brock *et al.*^[20].)

Tadalafil 20 mg significantly increased the cumulative proportion of successful intercourse attempts at 16 min after dose administration as compared with placebo ($P = 0.012$). An additional analysis examined the incidence of achievement of an erection sufficient for vaginal penetration that led to successful intercourse with at least one of four doses. Such patients were defined as responders. In this analysis, 52% of patients receiving tadalafil 20 mg were considered responders within 30 min and 32% were responders within 16 min. Among responders, 47% of all tadalafil 20 mg doses resulted in an erection adequate for successful intercourse within 20 min, 61% within 25 min and 80% within 30 min^[22].

In that study tadalafil was well tolerated. Adverse events were generally mild to moderate in severity. The most commonly reported adverse events were headache, myalgia, dyspepsia, nausea, vasodilatation (flushing) and back pain. No serious adverse events were reported^[22].

Efficacy and safety of tadalafil in patients with erectile dysfunction and diabetes

The prevalence of ED is significantly higher in men with diabetes as compared with those without. Accordingly, the risk for ED is increased threefold among men with diabetes mellitus^[24,25]. In a 12-week, randomized, placebo-controlled study, the efficacy and safety of tadalafil were examined in 216 men with diabetes and ED^[26]. The patients were randomly assigned to the following groups: placebo (n = 71), tadalafil 10 mg (n = 73) and tadalafil 20 mg (n = 72). Patients were 18 years of age or older with type 1 or type 2 diabetes who had a history of ED for at least 3 months, ranging in severity and aetiology. The mean age was 55.8 years in the placebo group, 55.9 years in the tadalafil 10 mg group and 55.5 years in the tadalafil 20 mg group. In all treatment groups, ED of organic aetiology was most common. Baseline ED severity was similar among placebo and tadalafil treated patients.

Table 5 Summary of major efficacy variables at end-point in the population with diabetes and erectile dysfunction

Efficacy variables	Tadalafil treatment group						Overall <i>P</i> value
	Placebo (n = 71)		10 mg (n = 73)		20 mg (n = 72)		
	EP	Change	EP	Change	EP	Change	
Primary							
IIEF erectile function domain (mean score)	12.2	0.1	19.3	6.4**	18.7	7.3**	<0.001
SEP question 2 (achieving erections [mean % of success])	30%	-4%	57%	22%**	54%	23%**	<0.001
SEP question 3 (maintaining erections [mean % of success])	20%	2%	48%	28%**	42%	29%**	<0.001
Secondary							
GAQ (improved erection [%])	25%	-	56%**	-	64%**	-	<0.001
IIEF intercourse satisfaction domain (mean score)	8.1	0.9	9.7	2.5**	9.3	2.3*	<0.001
IIEF overall satisfaction domain (mean score)	4.8	0.1	6.1	1.7**	6.0	1.6**	<0.001

EP=end-point; GAQ=Global Assessment Question; IIEF=International Index of Erectile Function; SEP=Sexual Encounter Profile.
P* < 0.05; *P* ≤ 0.001. (Data from Sáenz de Tejada *et al.*[26].)

Following 12 weeks of treatment, erectile function, as assessed by the mean change from baseline to end-point in the IIEF erectile function domain scores, was significantly improved for tadalafil 10 mg and 20 mg when compared with placebo (Table 5). The mean change in IIEF erectile function domain scores was 6.4 for tadalafil 10 mg and 7.3 for tadalafil 20 mg, versus 0.1 for placebo (*P* < 0.001 for tadalafil 10 mg and 20 mg relative to placebo). The proportions of patients who were able to achieve erections sufficient for vaginal penetration (SEP question 2; 'Were you able to insert your penis into your partner's vagina?') following treatment with tadalafil 10 mg and 20 mg were significantly greater than with placebo (*P* < 0.001). In addition, tadalafil treatment increased the proportion of successful intercourse attempts (SEP question 3; 'Did your erection last long enough for you to have successful intercourse?') as compared with treatment with placebo (*P* < 0.001). The proportions of patients who reported improved erections (based on answer to the GAQ) in the tadalafil 10 mg and 20 mg treatment groups were significantly greater than that reported in the placebo treatment group. Tadalafil 10 mg and 20 mg also significantly improved IIEF domains of intercourse satisfaction and overall satisfaction as compared with placebo (*P* < 0.05; Table 5). Treatment with tadalafil improved erectile function regardless of diabetes type[26].

The safety and tolerability profiles of tadalafil in that study were consistent with the known characteristics of the drug. The most commonly reported treatment-emergent adverse events in the patients treated with tadalafil were dyspepsia and headache (Table 6), and these were the only treatment-emergent adverse events reported in more than 5% of patients. With the exception of dyspepsia, no statistically significant differences were reported among the three treatment groups in the incidence of any treatment-emergent adverse event. No clinically significant differences in laboratory measurements or vital signs among the three treatment groups were observed.

Table 6 Most common treatment-emergent adverse events in patients with diabetes and erectile dysfunction

Event	Placebo (n = 71)	Tadalafil (n = 145)
Dyspepsia	0%	11%
Headache	3%	9%
Myalgia	1%	5%
Back pain	1%	3%
Vasodilatation (flushing)	0%	3%

(Data from Sáenz de Tejada *et al.*[26].)

Conclusion

The pharmacokinetic profile of tadalafil indicates that tadalafil is rapidly absorbed, is predominantly eliminated by the liver, and is distributed in the tissues. The half-life of tadalafil (17.5 h) supports results from clinical trials that indicated a period of responsiveness of up to 24–36 h after dosing. Based on integrated analyses of phase 3 efficacy and safety studies, treatment with tadalafil when administered with the following directions from the clinical trial protocols, "patients were instructed to self-administer treatment as needed prior to sexual activity with no restriction on timing of sexual activity after dosing and no restriction on timing of food or alcohol intake relative to dosing," resulted in robust improvements in erectile function and was well tolerated in men with ED. In addition, treatment with tadalafil in men with diabetes and ED resulted in improvements in erectile function superior to those reported with placebo treatment.

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