

Effects of Tadalafil on Erectile Dysfunction in Men With Diabetes

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OBJECTIVE— To evaluate the efficacy and safety of tadalafil taken as needed before sexual activity by men with diabetes and erectile dysfunction (ED).

RESEARCH DESIGN AND METHODS— Men with type 1 or type 2 diabetes and a minimum 3-month history of ED were randomly allocated to one of three groups: placebo ($n = 71$), tadalafil 10 mg ($n = 73$), or tadalafil 20 mg ($n = 72$) taken up to once daily for 12 weeks. Changes from baseline in mean scores on the erectile function domain of the International Index of Erectile Function (IIEF) and changes from baseline in the proportion of “yes” responses to question 2, “Were you able to penetrate?,” and 3, “Were you able to complete intercourse?,” of the Sexual Encounter Profile were coprimary outcome measures.

RESULTS— A total of 191 (88%) of 216 patients completed the study. Treatment with tadalafil significantly improved all primary efficacy variables, regardless of baseline HbA_{1c} level. Therapy with tadalafil also significantly improved a number of secondary outcome measures, including changes in other IIEF domains, individual IIEF questions, and percentage of positive responses to a global assessment question measuring erection improvement. Treatment with tadalafil did not alter mean HbA_{1c} levels. Tadalafil was well tolerated, with headache and dyspepsia being the most frequent adverse events with active treatment.

CONCLUSIONS— Tadalafil therapy significantly enhanced erectile function and was well tolerated by men with diabetes and ED.

Diabetes Care 25:2159–2164, 2002

Erectile dysfunction (ED) is a common comorbidity in patients with diabetes. As many as 75% of diabetic men will be confronted at some time in their lives with a consistent or recurrent inability to achieve and maintain an erection adequate for sexual performance (1), typically at an earlier age than their counterparts with normal glycemic control (2).

Whereas the incidence of ED increases as a function of age in the general population (3), the gradient is particularly steep in men with diabetes. In one cohort study (4), ED affected >47% of

men with type 1 diabetes aged ≥ 43 years, compared with 1.1% of those aged 21–30 years ($P < 0.0001$). According to one estimate (5), >50% of men will develop ED within 10 years of diabetes onset.

Not only does diabetes increase the risk of ED nearly twofold, but ED may also be the first symptom of diabetes and was significantly predictive of neuropathic symptoms and poor glycemic control in a 5-year prospective study (6). ED and diabetes each affect >150 million people worldwide, and this value is projected to double by the year 2025 (7–9).

Recent trials (10,11) demonstrated that the oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil citrate was effective and well tolerated in men with concomitant ED and diabetes. The mechanism of action for PDE5 inhibitors is well established. In response to sexual stimulation in potent men, nitric oxide (NO) is released by nonadrenergic noncholinergic nerve terminals (12). NO induces relaxation of smooth muscle within the arterioles perfusing the lacunar tissues, sinusoidal endothelium, and trabecular erectile tissues of the corpus cavernosum (13,14). Lacunar expansion against the tunica albuginea surrounding the corpora compresses subtunical venules, resulting in venous congestion, engorgement of the corporal bodies, and thus physiological erection. The smooth muscle-relaxing properties of NO are mediated by cyclic 3',5'-guanosine monophosphate (cGMP), a second messenger that is synthesized by guanylyl cyclase under the influence of NO. Blockade of PDE5, which hydrolyzes cGMP, thus potentiates the physiological NO-mediated erectile response.

Tadalafil is a potent, reversible, and selective inhibitor of PDE5 in development as an oral therapy for mild-to-severe ED of psychogenic, organic, or mixed etiology (15). The objective of this study was to assess the efficacy and safety of tadalafil in men with diabetes and mild-to-severe ED.

RESEARCH DESIGN AND METHODS

This multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 18 sites in Spain from December 1999 through August 2000. A total of 216 men aged ≥ 18 years with a clinical diagnosis of type 1 or type 2 diabetes (mean duration 11.7 years), a minimum 3-month history of mild-to-severe ED, and a stable monogamous relationship with a female partner were eligible. Men with a history of hypertension ($n = 80$; 37%) and hypercholesterolemia ($n = 38$; 18%) were included.

A clinical diagnosis of diabetes was predicated on either current therapy with

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Received for publication 1 February 2002 and accepted in revised form 19 August 2002.

Abbreviations: ECG, electrocardiogram; ED, erectile dysfunction; GAQ, global assessment question; IIEF, International Index of Erectile Function; NO, nitric oxide; PDE5, phosphodiesterase type 5; SEP, Sexual Encounter Profile.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Baseline patient characteristics

	Placebo	Tadalafil 10 mg	Tadalafil 20 mg	Overall
n	71	73	72	216
Age (years)	55.8 ± 9.1	55.9 ± 8.8	55.5 ± 9.0	55.7 ± 9.0
Race				
White	70 (98.6)	73 (100)	72 (100)	215 (99.5)
Black	1 (1.4)	0	0	1 (0.5)
Diabetes duration (years)	11.9 ± 9.6	11.9 ± 9.4	11.2 ± 9.5	11.7 ± 9.5
Type 1 diabetes	8 (11.3)	8 (11.0)	4 (5.6)	20 (9.3)
Type 2 diabetes	63 (88.7)	65 (89.0)	68 (94.4)	196 (90.7)
Diabetes control				
Good: HbA _{1c} <7.0%	15 (21.1)	13 (17.8)	12 (16.7)	40 (18.5)
Fair: HbA _{1c} 7.0–9.5%	42 (59.2)	51 (69.9)	43 (59.7)	136 (63.0)
Poor: HbA _{1c} >9.5%	14 (19.7)	9 (12.3)	17 (23.6)	40 (18.5)
Microvascular complications*	14 (19.7)	15 (20.5)	19 (26.4)	48 (22.2)
Current diabetic therapy				
Insulin only	32 (45.1)	26 (35.6)	20 (27.8)	78 (36.1)
Oral only	29 (40.8)	32 (43.8)	39 (54.2)	100 (46.3)
Insulin + oral	7 (9.9)	9 (12.3)	6 (8.3)	22 (10.2)
None	3 (4.2)	6 (8.2)	7 (9.7)	16 (7.4)
IIEF erectile function domain score	12.1 ± 6.1	12.9 ± 6.9	11.5 ± 5.6	12.2 ± 6.2
ED duration >1 year (%)	66 (93.0)	68 (93.2)	67 (93.1)	201 (93.1)

Data are means ± SE or n (%). *Patients with microvascular complications had a history of diabetic retinopathy, laser treatment for diabetic eye disease, or a urine microalbumin-to-creatinine ratio >3.0 at visit 1.

insulin, metformin, or sulfonylureas or a history within the previous year of two occasions of diagnostic-level hyperglycemia, including 1) fasting plasma, serum, or blood glucose >7 mmol/l (126 mg/dl); 2) randomly obtained plasma, serum, or blood glucose ≥11.1 mmol/l (200 mg/dl) associated with symptoms of polyuria, polydipsia, or unexplained weight loss; or 3) plasma, serum, or blood glucose ≥11.1 mmol/l (200 mg/dl) 2 h after administration of 75 g oral glucose. Any patient with an onset of diabetes before the age of 30 years who had received continuous insulin treatment since diagnosis was considered to have type 1 diabetes.

The vast majority of patients (>72%) had moderate-to-severe ED, an ED history of >1 year (93%), and a diagnosis of type 2 diabetes (>90%) at study onset (Table 1). Patients were eligible for study inclusion irrespective of previous responses to ED treatments, including sildenafil.

Patients with HbA_{1c} >13.0% at the screening visit (visit 1, week -4), a recent history of diabetic ketoacidosis (≥2 episodes), or ≥3 episodes of hypoglycemia requiring assistance as specified by the Diabetes Control and Complications Trial (16) were excluded. However, men with microvascular complications, including

retinopathy, were eligible (n = 48; 22%); most patients (>80%) had fair-to-poor glycemic control (HbA_{1c} >7.0%). Ophthalmologic histories were obtained and analyses of urinary albumin were conducted at the screening visit to determine the presence of diabetic complications at baseline.

Patients with angina during intercourse, unstable angina, or any other evidence of recently diagnosed coronary artery disease, poorly controlled blood pressure (systolic >170 or <90 mmHg or diastolic >100 or <50 mmHg) or orthostatic hypotension, congestive heart failure, arrhythmia, significant renal or hepatic dysfunction, and anemia were also excluded. Also ineligible were men who failed to achieve an erection after radical prostatectomy or pelvic surgery; those who had penile implants, clinically noteworthy penile deformities, or a history of stroke or spinal-cord trauma within 6 months of study onset; and those who were receiving nitrates, antiandrogens, or cancer chemotherapy.

After the screening visit, eligible candidates qualified for randomization by making at least four attempts at sexual intercourse during a 4-week treatment-free run-in phase to determine baseline erectile function. Participants were ran-

domly allocated to one of three 12-week treatment arms: tadalafil 10 mg (n = 73) or 20 mg (n = 72) or placebo (n = 71) taken up to once daily as needed. Men were instructed to take one dose of their treatment orally at any time before anticipated sexual activity, with no restrictions on food or alcohol intake.

The effects of tadalafil on erectile function were evaluated using the International Index of Erectile Function (IIEF) (17), a 15-item questionnaire that assesses five domains of male sexual function using 5- to 6-point Likert scales, with 0 or 1 signifying a low frequency or ability and 5 signifying a high frequency or ability. These domains include erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.

The erectile function domain consists of six questions concerning erection frequency (question [Q]1), erection firmness (Q2), frequency of partner penetration (Q3), frequency of maintaining erection after penetration (Q4), ability to maintain erection to completion of intercourse (Q5), and confidence in achieving and maintaining erection (Q15), all during the previous 4 weeks. One co-primary efficacy variable consisted of the

change in mean erectile function domain score from baseline to end point.

Patients also used Sexual Encounter Profile (SEP) diaries to record their sexual experiences. Other coprimary efficacy outcome measures consisted of the changes from baseline to end point in the mean proportions of “yes” responses to SEP-Q2 and SEP-Q3, respectively: “Were you able to insert your penis into your partner’s vagina? (yes/no)” and “Did your erection last long enough to have successful intercourse? (yes/no).”

Secondary outcome measures included the changes from baseline to end point in mean scores on IIEF-Q3 (penetration ability) and IIEF-Q4 (maintenance ability) in each treatment group. In addition, at study end point or early discontinuation, each patient was asked a global assessment question (GAQ), “Has the treatment you have been taking improved your erections? (yes/no).” Proportions of patients achieving more than a five-point gain from baseline to end point in the erectile function domain of the IIEF were also determined for all treatment groups.

Post hoc analyses were also performed to determine the effect of tadalafil treatment on HbA_{1c} levels, the effect of baseline HbA_{1c} level on response to treatment, and the effect of antihypertensive medications on response to treatment.

A medical history was obtained at the first visit; physical examination, 12-lead electrocardiogram (ECG), and urinalysis were performed at visit 1 and end point or early discontinuation; vital signs and clinical laboratory tests were evaluated at every visit or early discontinuation. Patients were also seen within 1–2 weeks after the 12-week end point for appropriate follow-up of adverse events.

The study protocol and informed consent form were reviewed and approved by ethical review boards. Patients and their partners provided written informed consent.

Statistical methods

Each randomized patient was eligible for the efficacy analysis. The analysis of safety included all randomized patients. All analyses were performed with the patients included in the groups to which they were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol.

Patient baseline characteristics were summarized for each treatment group. For continuous patient characteristics, means were compared using ANOVA. Incidences of categorical variables were compared using Pearson’s χ^2 test.

For efficacy analyses, all patients with baseline and postbaseline observations on all variables in the statistical model were included. The IIEF erectile function domain, other domains, and individual items were analyzed using the last-observation-carried-forward convention, applied to each of the baseline and the postbaseline periods. The baseline and end point score for each SEP question was the patient’s percentage of “yes” responses to that question during the run-in and postbaseline periods, respectively.

ANCOVA models of change from baseline in the IIEF (domains and individual items) and SEP variables included terms for baseline value of the efficacy variable, treatment group, investigator site, and the baseline-by-treatment-group interaction. In any model, if the interaction was not significant (i.e., if $P \geq 0.10$), then it was removed from the model and the between-treatment-group P value was obtained from the reduced model.

Because there were two tadalafil doses being studied, 10 and 20 mg, there were also two separate primary null hypotheses concerning the comparison of 10 mg to placebo and 20 mg to placebo. To reject the null hypothesis of no treatment effect relative to placebo, statistical significance at $P < 0.05$ was required on all three coprimary end points. To protect against type 1 error, the P values from primary-efficacy treatment-group contrasts were adjusted by the method of Dunnett for the comparison of two doses with placebo. Accordingly, rejection of either of the null hypotheses concerning 10 mg tadalafil versus placebo or 20 mg tadalafil versus placebo was interpretable as statistically significant, due to the Dunnett correction for multiple comparisons with respect to dose.

Logistic regression models were used to evaluate GAQ at the end point and the proportion of patients achieving a greater than five-point gain in the erectile function domain of the IIEF. The models included terms for baseline value of the IIEF erectile function domain, treatment group, investigator site, and baseline-by-treatment-group interaction. If the interaction was not significant (i.e., if $P \geq$

0.10), then it was removed from the model and the between-treatment-group P value was obtained from the reduced model.

Change of HbA_{1c} from baseline to end point was evaluated by a ranked ANOVA model. The effect of baseline HbA_{1c} level and concomitant antihypertensive medication use on response to treatment was determined using a model including investigator site, therapy, and baseline HbA_{1c} or antihypertensive medication status.

The analysis of safety included all enrolled patients. Safety was assessed by evaluating all reported adverse events and changes in clinical laboratory values, vital signs, physical examination results, and ECG results. Treatment-emergent adverse events were defined as events that first occurred or worsened after baseline and were summarized by the COSTART preferred term for severity and the relationship to the study drug. Analyses comparing the incidence of treatment-emergent adverse events among treatment groups were performed using Fisher’s exact test across all treatment groups in the study. Treatment-emergent events with incidences of $>3\%$ in tadalafil-treated patients or statistically significant differences between active treatment and control groups are presented.

Changes in continuous laboratory analytes, vital signs, and ECG measurements were evaluated by a ranked ANOVA model with a term for treatment group. Categorical changes in laboratory analytes by treatment group were evaluated by summarizing the proportion of patients whose test values were outside the reference ranges at their final visit and at their maximum and minimum value recorded during the study, as appropriate, for each individual analyte.

RESULTS — Of the 216 men enrolled, 191 (88%) completed treatment. A total of six (3%) patients discontinued because of treatment-emergent adverse events. Of these six, four were randomized to tadalafil treatment: one man in the tadalafil 10-mg group experienced mild pain and three patients in the 20-mg group experienced either moderate myalgia, moderate headache, or severe flushing. The other two patient discontinuations were due to myocardial infarctions: one in the placebo group and one

Table 2—Effects of tadalafil on efficacy variables

Change in efficacy end points*	Treatment group				
	Placebo	Tadalafil 10 mg	P†	Tadalafil 20 mg	P‡
<i>n</i>	71	73		72	
ΔIIEF EF domain	0.1	6.4	<0.001	7.3	<0.001
By HbA _{1c} level					0.5068§
Good: <7.0%	−1.0	9.7	—	8.3	
Fair: 7.0–9.5%	−0.9	6.0	—	6.7	
Poor: >9.5%	3.9	3.8	—	8.3	
By concomitant antihypertensive medication use					<0.001
Yes	−1.8	3.9	—	9.5	
No	1.1	7.9	—	5.5	
ΔSEP-Q2 (%)	−4.1	22.2	<0.001	22.6	<0.001
By HbA _{1c} level					0.649§
Good: <7.0%	−13.7	21.0	—	30.6	
Fair: 7.0–9.5%	−3.3	24.1	—	21.0	
Poor: >9.5%	3.7	13.0	—	21.2	
By concomitant antihypertensive medication use					0.004
Yes	−4.2	16.4	—	33.8	
No	−4.1	25.8	—	13.4	
ΔSEP-Q3 (%)	1.9	28.4	<0.001	29.1	<0.001
By HbA _{1c} level					0.793¶
Good: <7.0%	4.4	35.7	—	34.2	
Fair: 7.0–9.5%	−1.7	27.8	—	28.8	
Poor: >9.5%	9.7	21.1	—	26.8	
By concomitant antihypertensive medication use					0.085
Yes	−4.5	21.9	—	31.9	
No	5.4	32.5	—	26.9	

Data are % unless otherwise indicated. *Changes from baseline to end point in mean erectile function domain scores (unitless) or in proportions (%) of “yes” responses to SEP-Q2 (“Were you able to insert your penis into your partner’s vagina? [yes/no]”) or SEP-Q3 (“Did your erection last long enough to have successful intercourse? [yes/no]”). †P for comparison of tadalafil 10 mg vs. placebo; ‡P for comparison of tadalafil 20 mg vs. placebo; §interaction P for difference in response to therapy by baseline HbA_{1c} level; ||interaction P for difference in response to therapy by antihypertensive medication status.

who was randomized to the 20-mg group but never took the study drug. Five patients (2%) randomized to tadalafil discontinued because of perceived lack of efficacy, including three in the 10-mg arm and two in the 20-mg arm. Protocol violations or failure to meet entry criteria accounted for four (2%) discontinuations, including two men in the placebo arm, while eight patients (4%) discontinued because of physician decision (*n* = 4; two in placebo group) or personal conflict/patient decision (*n* = 4; two in placebo group).

Therapy with tadalafil (particularly at 20 mg) significantly enhanced erectile function across all three coprimary efficacy outcome variables: IIEF erectile function domain, erection vaginal penetration rates (SEP-Q2), and successful intercourse rates (SEP-Q3) (all *P* < 0.001; Table 2).

Tadalafil treatment did not significantly change HbA_{1c} levels from baseline

to end point (−0.2% both in the tadalafil 10- and 20-mg groups vs. 0% in the placebo group; *P* = 0.083), and baseline HbA_{1c} level did not influence response to tadalafil treatment (Table 2). However, concomitant antihypertensive medication use did influence response to treatment. Those who were treated with concomitant antihypertensive medications appeared to respond better to tadalafil 20 mg than those who were not (Table 2).

Tadalafil therapy at each dose significantly increased scores on IIEF-Q3 (penetration ability) and IIEF-Q4 (maintenance ability) versus placebo (*P* < 0.001) and improved scores on intercourse satisfaction (10 mg vs. placebo *P* = 0.001; 20 mg vs. placebo *P* = 0.012), orgasmic function (10 mg vs. placebo *P* = 0.001; 20 mg vs. placebo *P* = 0.014), and overall satisfaction (*P* < 0.001) domains from baseline to end point. Men who received tadalafil were also more likely to experience an increase more than five

points in erectile function domain score than patients randomized to the control group: ~44% of those on 10 mg, 56% on 20 mg, and 13% on placebo (both *P* < 0.001).

At end point, each dose of tadalafil also significantly enhanced patients’ erections according to responses to the GAQ. The proportions of positive responses to the GAQ in the tadalafil 10- and 20-mg groups were 56 and 64%, respectively, compared with 25% in the control group (both *P* < 0.001).

Tadalafil at 10 and 20 mg improved erectile function irrespective of the type of diabetes, presence of microvascular complications, or type of diabetes treatment. Treatment with tadalafil was well tolerated, with the majority of events being mild or moderate and transient. The most common treatment-emergent events in the tadalafil groups were dyspepsia and headache (Table 3). Only the incidence of dyspepsia was significantly different

Table 3—Treatment-emergent adverse events occurring in >3% of patients in all treatment groups

	Placebo	Tadalafil 10 mg	Tadalafil 20 mg	P
n	71	73	72	
≥1 Event	22 (31.0)	29 (39.7)	32 (44.4)	0.247
Dyspepsia	0	8 (11.0)	8 (11.1)	0.005
Headache	2 (2.8)	7 (9.6)	6 (8.3)	0.234
Myalgia	1 (1.4)	4 (5.5)	3 (4.2)	0.540
Flu syndrome	3 (4.2)	3 (4.1)	3 (4.2)	1.00
Back pain	1 (1.4)	1 (1.4)	4 (5.6)	0.330
Flushing	0	2 (2.7)	3 (4.2)	0.332

Data are n (%).

across treatment groups: ~11% in either the 10- or 20-mg group, compared with 0% in the control arm ($P = 0.005$). No treatment-related visual disturbances were reported. Electrocardiograms, clinical laboratory values, and vital signs exhibited no clinically significant changes.

CONCLUSIONS— Therapy with tadalafil consistently enhanced erectile function, significantly improving patients' ability to achieve and maintain erections.

After 12 weeks of treatment taken whenever patients anticipated sexual activity, without restrictions on food or alcohol intake, nearly two-thirds (64%) of patients in the tadalafil 20-mg group and more than half (56%) in the tadalafil 10-mg group reported improved erections. Similarly, increases in the proportions of positive responses to SEP questions concerning patients' ability to penetrate their partner and maintain erection to successful completion of intercourse in the present trial were significantly higher in the tadalafil 10- and 20-mg groups than in the placebo arm. Treatment with tadalafil at 10 and 20 mg improved these outcomes regardless of baseline HbA_{1c} level.

These findings, taken together with the observed mean improvements of 6.4 and 7.3 points on the erectile function domain of the IIEF, warrant comment given the level of morbidity in this patient population. At baseline, >72% of men had moderate or severe ED, >80% had HbA_{1c} >7.0%, and >20% had microvascular complications, including 23 (11%) men with retinopathy and 14 (6%) with neuropathy. The percentage of men reporting improved erections in this study (56 and 64% for 10 and 20 mg, respec-

tively) is consistent with data from a previous, flexible, dose-escalation study (10) with sildenafil, in which 56% of diabetic men responded at 12 weeks that treatment had improved their erections. The sildenafil study excluded men with either diabetic retinopathy or autonomic neuropathy.

Further, patients in the present trial were included irrespective of previous response to ED therapy, including sildenafil. The fact that tadalafil therapy improved erectile function domain scores by more than five points, which is consistent with an improvement from, for instance, severe to moderate ED (18), in a significant proportion of men with longstanding fairly advanced diabetes is clinically noteworthy.

The pathophysiology of diabetic ED has yet to be completely elucidated, but in vitro work (14) demonstrated that corporal smooth muscle from men with diabetes exhibited diminished autonomically mediated or endothelium-dependent relaxation compared with tissues from nondiabetic counterparts. A more recent immunohistochemical study (19) suggested that advanced glycation end products (e.g., pentosidine and pyrraline) in diabetic men, when deposited within the penile tunica and corporal collagen, might result in downregulation of NO synthesis through modulation of endothelial and/or inducible NO synthase enzymatic activity. Therefore, treatment with a PDE5 inhibitor, which potentiates the effects of NO, is a rational therapeutic alternative in a setting of potentially attenuated NO output. However, improvements in erectile function were not as pronounced in this population as in ED patients without diabetes in other studies. A recent placebo-controlled trial (15) in-

volving 179 men with ED and no history of diabetes that also included a tadalafil 10-mg arm demonstrated positive response rates of 81% on the GAQ at end point at this dose (vs. 56% in the 10-mg group within the present trial).

We observed that nearly 40% of men also had baseline hypertension, a condition that could substantially alter endothelium-dependent relaxation in penile resistance arteries. Antihypertensive medications themselves have also been implicated in ED (20). In this study, men taking concomitant antihypertensive medications had greater improvements in erectile function with tadalafil at 20 mg than those not taking antihypertensives. These results may indicate that men with more severe endothelial dysfunction derive a greater benefit from the NO-potentiating effect of tadalafil at 20 mg. It is clear that hypercholesterolemia (e.g., oxidized LDL cholesterol) can also compromise NO production by endothelial NO synthase (21,22). A total of 38 (18%) men had hypercholesterolemia in the present study.

Tadalafil was well tolerated in this study. The chief adverse events were mild-to-moderate dyspepsia and headache, and the incidences of these events were consistent with data from a previous study in a general population (15). Even in these patients, who are more prone to ophthalmic sequelae of diabetes, no patient reported treatment-related visual (i.e., color discrimination) defects.

When taken as needed with no restrictions on either food or alcohol intake or the timing of dose administration relative to the onset of sexual intercourse, tadalafil significantly enhanced erectile function and was well tolerated in men with diabetes and ED.

Acknowledgments— Funding for this study was provided by Lilly ICOS LLC.

The authors would like to acknowledge the investigators in this study: Antonio Allona Almagro, José Luis Arrondo, Ander Odriozola Astobieta, Martín Caballero Gomez, Venancio Chantada Abal, Natalio Antonio Cruz Navarro, Luis Fiter Gomez, Rafael Gutierrez del Pozo, Fernando Jiménez Cruz, Enrique Lledó García, Antonio Martín Morales, Luis Martínez Piñeiro, Ignacio Moncada Iribarren, Jose M Pomerol Montseny, Luis Resel Estevez, Luis Rodríguez Vela, Jesús Romero Maroto, and Iñigo Sáenz de Tejada.

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