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Impact of Baseline Total Testosterone Level on Successful Treatment of Sexual Dysfunction in Men Taking Once-Daily Tadalafil 5 mg for LUTS/BPH: An Integrated Analysis of Three Randomized Controlled Trials

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Abstract

Introduction—Controversy exists as to whether erectile response to phosphodiesterase type 5 inhibitors (PDE5i) is compromised in men with low total testosterone (TT) levels. This is amplified by reports of improved response to PDE5i therapy following co-administration of testosterone replacement therapy (TRT) in hypogonadal men unresponsive to PDE5i.

Aim—To determine if TT and luteinizing hormone (LH) levels influence efficacy of tadalafil for erectile dysfunction (ED) in men with concomitant lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH).

Methods—This integrated analysis included 1075 men randomized to once-daily tadalafil 5 mg (n=540) or placebo (n=535) for 12 weeks in three prospective clinical trials who had not received concomitant TRT. Subjects were categorized at baseline by low vs. normal TT (n=1049; <300

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Conflicts of Interest:

Dr. John P. Mulhall is a consultant/advisor for Eli Lilly and Company, Nexmed, Absorption Pharmaceuticals, and Meda; consultant/advisor and clinical trial investigator for AMS and Vivus; and clinical trial investigator for Pfizer. Dr. Gerald B. Brock is an advisory board member, investigator, and lecturer for Pfizer, Eli Lilly and Company, GlaxoSmithKline, Bayer, Johnson & Johnson, American Medical Systems, Inc., Coloplast, and Abbott Laboratories. Sidney Glina is an advisory board member of Besins and Eli Lilly and Company; principal investigator for Astellas and Medivation; and speaker for Besins, Eli Lilly and Company, and Probiomed. Simin Baygani and Dr. Craig F. Donatucci are employees and stockholders of Eli Lilly and Company. Professor Mario Maggi is an advisory board member, investigator, or lecturer for Bayer, Eli Lilly and Company, Menarini, Prostrakan, Intercept, and GlaxoSmithKline. These studies and the preparation of this paper were funded in full by Eli Lilly and Company. Data analyses were undertaken by Eli Lilly and Company.

ng/dL vs. 300 ng/dL) and normal vs. high LH levels (n=1058; 9.4 mIU/mL vs. >9.4 mIU/mL). Treatment-group differences in International Index of Erectile Function (IIEF) by hormone subgroups were assessed using analysis of covariance.

Main outcome measures—Changes in IIEF-Erectile Function domain and other domain scores.

Results—The overall study population was comprised of primarily White men (>86%) with a mean age range of 64–70 years. Median baseline TT in the integrated population was 355 ng/dL; levels were <300 ng/dL cutoff for normal in 32.4% of men. Men with low TT reported diabetes (21.8%), cardiovascular disease (54.1%), and hypertension (49.1%) numerically more often than men with normal TT (10.6%, 43.2%, and 36.7%, respectively). Low TT and high LH were associated with numerically, but not statistically significantly, lower 12-week IIEF domain scores than those with normal levels. The changes in most 12-week IIEF domain scores showed that tadalafil was significantly more effective than placebo ($P<0.02$).

Conclusions—Low TT levels at baseline did not negatively influence response to tadalafil in men of advancing age with LUTS/BPH and ED.

Keywords

Erectile dysfunction; benign prostatic hyperplasia; phosphodiesterase type 5 inhibitors; tadalafil; testosterone; luteinizing hormone

INTRODUCTION

Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are common and bothersome conditions in aging men [1]. Testosterone has long been recognized to have a role in erectile function [2]. The relationship of testosterone deficiency to onset of LUTS is less clear [3]. Erectile dysfunction and LUTS/BPH may and often do coexist, and are attributed, in part, to age-related androgen deficiency [4–8].

Testosterone is involved in many key physiologic functions, including expression of nitric oxide synthase (NOS)—the primary neurotransmitter involved in penile erection [2]. Although postulated, no role for NOS in the pathophysiology of LUTS/BPH has yet been documented. Symptoms of low testosterone often appear when blood levels drop below 300 ng/dL [9]. Approximately 20% of men >60 years old and 50% of men >80 years old [10] have low total testosterone (TT) levels. Older men with ED [11] and those with metabolic syndrome [12] are more likely to have low TT levels.

Significant advances in the medical treatment of these conditions have occurred, including the introduction of first-line phosphodiesterase type 5 inhibitor (PDE5i) therapy to treat ED and the approval of the PDE5i tadalafil for treatment of LUTS/BPH. Numerous reports suggest that erectile response to PDE5i is compromised in men with low TT levels [13–19] and that there is an improved response to PDE5i therapy in men with low TT levels following testosterone replacement therapy (TRT) [14,16–23]. However, despite evidence supporting a possible link between low testosterone levels and reduced PDE5i efficacy for

ED, a study in testosterone-deficient men not experiencing prior PDE5i failure suggests that TRT may not enhance the efficacy of PDE5i therapy [24].

The aim of the current study is to determine the effect of baseline hormone levels on sexual response to tadalafil in men with LUTS/BPH and ED [25], which was measured by the International Index of Erectile Function-Erectile Function (IIEF) domain scores.

Patients and Methods

Study design and study population—This integrated analysis was based on data from three previously reported, randomized, double-blind, placebo-controlled studies in men with LUTS/BPH and ED [26–28]. These studies shared similar designs and populations, except that ED was an entry criterion for only one study [27]. Each study had a four-week, single-blind, placebo lead-in period followed by a 12-week, double-blind treatment phase. Subjects were randomized in a 1:1 ratio to tadalafil 5 mg once daily (n=540) or placebo (n=536).

In brief, subjects were aged 45 years with a history of LUTS secondary to BPH for >6 months, International Prostate Symptom Score (IPSS) 13, and a peak urinary flow rate of 4 to 15 mL/s [26–28]. Men in all three studies who were sexually active were asked whether they suffered from ED, and if so was their ED mild, moderate, or severe. Sexually active patients also were asked to complete the IIEF index questionnaire at baseline (after four-week lead-in period and before start of 12-week treatment period) and at the end of the 12-week treatment period [25]. All men included in the final integrated analysis for outcomes had baseline TT and/or luteinizing hormone (LH) levels and had not received TRT.

Single serum TT, LH, and estradiol samples were to be obtained before 10 AM at baseline. All analyses were performed at a central laboratory (Covance Laboratories, Princeton, NJ).

Each study was performed in accordance with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. Institutional review boards for each site approved the study and all men provided written informed consent before initiating any trial procedure or therapy.

Outcome measures—The primary outcome measurement was the change in the IIEF-EF domain score from baseline (randomization visit [end of placebo lead-in period or start of double-blind treatment period]) to endpoint (data collected at week 12 of double-blind period or last post-baseline visit) in the tadalafil and placebo treatment groups. Secondary outcome measurements were the change from baseline to endpoint in the treatment groups for the remaining four IIEF domain scores and IIEF Question 15, with higher scores indicating better EF [25]. All subjects who had baseline and post-baseline IIEF domain scores were included in this treatment-effect analysis regardless of reported erectile function status at baseline.

Efficacy results were compared for subgroups of men with low (<300 ng/dL) vs. normal TT levels (≥ 300 ng/dL) and high (>9.4 mIU/mL) vs. normal LH levels (≤ 9.4 mIU/mL) [29].

Statistical analyses—Analyses in the integrated analysis set were performed on an intent-to-treat basis for all subjects who were randomized and started double-blind study medication. Subject demographics and baseline clinical characteristics, hormone levels, and reported co-administered medications known to affect testosterone levels (eg, opiates) were summarized by treatment group and within each hormone subgroup using descriptive statistics. Pearson's or Spearman's correlation coefficients were calculated to examine relationships between baseline IIEF domain scores and baseline hormone levels (TT, LH, estradiol) whenever appropriate.

All efficacy analyses assessed changes from baseline to endpoint. Changes from baseline to endpoint and differences in these changes between the placebo and tadalafil 5 mg treatment groups were estimated as least-squares means using analysis of covariance (ANCOVA) models for each subgroup defined above. The model included terms for protocol, centered-baseline value, treatment group, geographic region, subgroup category, treatment-by-subgroup category interaction, centered-baseline-by-treatment interaction, and treatment-by-geographic region interaction. In addition, to detect association between baseline hormonal level and change from baseline to endpoint, an ANCOVA model using continuous baseline TT, LH, and estradiol levels as a covariate was performed. The model included terms for protocol, centered-baseline value, treatment group, geographic region, baseline hormone, treatment-by-baseline hormone interaction, centered-baseline-by-treatment interaction, and treatment-by-geographic region interaction. *P* values associated with estimated between-treatment group differences were assessed for significance at a two-sided 0.05 level. Treatment-by-subgroup interaction *P* values were retained in the model if the *P* value was <0.10.

The clinical relevance of IIEF-EF changes in men with low and normal baseline TT levels was interpreted using a minimally clinically important difference (MCID) in treatment response (change in baseline to endpoint for IIEF-EF of 4) [30].

RESULTS

A total of 1076 subjects (540 tadalafil, 536 placebo) comprised the intent-to-treat population [26–28], of which 1050 and 1059 subjects had baseline TT and LH levels, respectively. After excluding one subject who received TRT, 1049 and 1058 subjects with baseline TT and LH levels, respectively, formed the integrated population for the current analysis.

Baseline demographics, medical characteristics, and IIEF domain scores

Baseline demographic and medical characteristics were relatively well balanced between tadalafil and placebo treatment groups within the TT and LH hormone subgroups (Table 1). The integrated study population was primarily comprised of white men (>86%) with a mean age range of 64–70 years.

Medical characteristics at baseline revealed that >79% of men self reported ED, approximately two-thirds of their ED was categorized as moderate to severe in severity, and the majority (>68%) had ED for 1 year (Table 1). Incidence of ED reported at baseline was slightly higher in men with low TT levels and/or high LH levels vs. men with normal levels.

A greater proportion of men with high LH levels had ED for > one year (82.9%) vs. men who had normal LH levels (69.5%). The rate of severe ED was greater in men with high LH levels (21.3%) vs. normal LH levels (12.6%). Rates of diabetes, cardiovascular disease, and hypertension reported at baseline were numerically higher for men with low TT levels (21.8%, 54.1%, and 49.1%) vs. men with normal TT levels (10.6%, 43.2%, and 36.7%). These differences were not observed between men with high vs. normal LH levels.

Baseline IIEF domain scores were generally similar between the tadalafil and placebo groups when categorized by low vs. normal TT levels or high vs. normal LH levels (Table 1). However, men with low TT levels and high LH levels tended to have numerically lower, but not clinically significantly different, IIEF domain scores vs. those with normal TT and LH levels. For example, among tadalafil-treated men, the mean baseline IIEF-EF scores were 16.01 and 15.62 for men with low TT and high LH levels, respectively, vs. 17.36 and 17.08 for men with normal TT and LH levels, respectively.

Baseline endocrine-related hormone levels, concomitant medications, and correlation with baseline IIEF sub-scores

Most men included in this pooled database had TT and/or LH levels available at baseline (97.6% and 95.1%, in the tadalafil and placebo groups, respectively). A total of 1049 men had a median baseline TT level of 355.1 ng/dL and 1058 men had a median baseline LH level of 4.5 mIU/mL (Table 2). Hypogonadism (defined as baseline TT level <300 ng/dL) was diagnosed in 32.4%.

Concomitant medications that may have impacted baseline TT levels were reportedly taken by 3.7% of men. The most commonly used medication was dutasteride, followed by oxycodone/acetaminophen and finasteride.

Baseline IIEF-EF domain scores were weakly positively correlated with baseline TT levels (Pearson correlation = 0.096; Spearman correlation = 0.092), inversely correlated with baseline LH levels (Pearson correlation = -0.078; Spearman correlation = -0.098), and positively correlated with estradiol levels (Pearson correlation = 0.019; Spearman correlation = 0.026). All other IIEF domain scores and hormone levels demonstrated even weaker correlations.

Changes in sexual function

Changes from baseline to endpoint in IIEF domain scores and IIEF Question 15 (erectile confidence) for both treatment groups, available in approximately 900 patients, were categorized by baseline TT and LH levels, and are summarized in Table 3. For most IIEF domain scores, tadalafil was significantly more effective than placebo at the 12-week endpoint ($P < 0.02$). Several exceptions, wherein change in sexual function was similar between treatment groups, were found in men with high baseline LH levels (IIEF-IS and IIEF-SD domain scores) or normal LH levels (IIEF-SD domain score). However, the ANCOVA models for individual IIEF domain scores by hormone level found no significant treatment-by-baseline hormone subgroup interactions (all $P \geq 0.10$).

Additional ANCOVA models, which included baseline TT, LH, and estradiol as a covariate, revealed that baseline hormone levels (with one exception) did not influence the response to tadalafil as measured by IIEF domain scores (all $P > 0.05$; data not shown). The exception was that baseline LH levels were associated with a positive tadalafil treatment response for the IIEF-Orgasmic Function domain score ($P = 0.006$; data not shown).

Minimal clinically important difference

Based on a MCID of 4 from baseline to endpoint, tadalafil was significantly more effective than placebo, regardless of TT level (ie, PDE5i was equally effective for men with low or normal baseline TT levels). For men with a baseline TT of < 300 ng/dL, a MCID was achieved in 57% of tadalafil and 26% of placebo recipients ($P < 0.0001$). Likewise, for men with a baseline TT of ≥ 300 ng/dL, corresponding MCIDs of 53% and 29% were reported ($P < 0.0001$).

DISCUSSION

The advent of PDE5i therapy was a watershed moment for men with ED. Yet, since the time of PDE5i introduction, concern has remained that men with decreased serum testosterone do not fully respond. Given that older men with LUTS/BPH may have coexisting ED due to hormone imbalance, this integrated analysis from three similarly designed trials in men with LUTS/BPH examined this question [26–28]. The present analysis examined the relationships between androgen hormones and response to once-daily tadalafil 5 mg therapy. To reduce confounding effects, men who received TRT were excluded. Within the subgroup of men with normal TT levels (≥ 300 ng/dL) at baseline, the tadalafil group showed greater improvement in IIEF domain scores vs. the placebo group. This finding was similar for the subgroup with low TT levels (< 300 ng/dL). Thus, regardless of baseline TT level (normal vs. low), men treated with tadalafil experienced significantly greater improvement in IIEF domain scores vs. the placebo group. We did find that tadalafil-treated men with low baseline TT levels experienced numerically smaller improvements in most other IIEF domain scores at the 12-week endpoint vs. men with normal TT levels; however, these differences are not considered clinically significant. Of clinical relevance, men receiving tadalafil were two-fold more likely to achieve a MCID of 4 vs. placebo recipients, a statistically significant difference, regardless of baseline TT level.

These integrated analyses corroborate previous epidemiologic findings [11,12,31], including that a higher rate of ED was observed in men with low TT levels and high LH levels, and that men with ED and low TT levels had increased comorbidities including metabolic syndrome. Further, consistent with the literature, these findings underscore the known facts that men with ED are at greater risk for cardiovascular disease and sexual dissatisfaction. As expected, analyses herein also revealed that men with ED and low TT and/or high LH levels at baseline presented with lower IIEF domain scores.

The findings of this integrated analysis challenge earlier reports that suggest normalizing testosterone levels is essential towards achieving a response to PDE5i therapy in men with low TT levels [14,16–18,20–23]. Our analysis corroborates and extends earlier reports that support that low androgen levels do not compromise PDE5i efficacy [24,32]. While the

Spitzer et al study claimed that low testosterone levels did not reduce PDE5i efficacy, their study did not conclusively prove that PDE5i efficacy was maintained in the face of androgen hormone deficiency because TT levels were reported to be in the normal range (ie, 364 ng/dL) after the end of the run-in phase (sildenafil only) [24]. Accordingly, Aversa et al asserted that men in the PDE5i group of Spitzer's study were not truly hypogonadal [33]. Goldfischer et al also reported that low testosterone levels do not impair the response to tadalafil in men with ED; however, their population included men who had a partial response to prior treatment with a maximum dose of a PDE5i when given as needed [32]. Considering the heterogeneity of the study populations and potential methodological flaws of these and other previous studies, the present analysis provides more decisive evidence that low serum TT levels do not negatively influence the efficacy of PDE5i therapy in men with ED.

A recent meta-analysis that explored the possible effects of testosterone supplementation on responsiveness to PDE5i in randomized controlled trials vs. uncontrolled studies reported that efficacy of PDE5i was improved with co-administration of testosterone, but only in uncontrolled trials [34]. The authors speculated that the difference in synergistic benefit of testosterone supplementation with PDE5i for male sexual function was likely based on bias introduced by differences in trial design. These data, in addition to this integrated analysis, support claims by the Endocrine Society that testosterone deficiency and ED are separate clinical disorders with distinct pathophysiology [9]. Corona et al also concluded that while TRT will improve hormone levels, it does not consistently correct symptomatic sexual dysfunction [34]. In contrast, Hackett et al reported that in men with type 2 diabetes, ED, and severe hypogonadism (< 231 ng/dL), 30-week TRT significantly raised TT levels from 223 ng/dL at baseline to 286 ng/dL and was associated with significant improvement in sexual function (eg, four-point increase in IIEF-EF; $P = 0.029$) vs. worsening sexual function following placebo (two-point decrease; $P = 0.086$) [35]. However, TRT-treated men with mild hypogonadism (233–346 ng/dL) did not experience improved sexual function, supporting that there are threshold levels associated with a positive sexual function response to TRT.

The findings of this integrated analysis have several limitations. Men with very low TT levels (< 231 ng/dL) were likely excluded at the outset due to each study's strict inclusion criteria. Accordingly, the possible negative effect of very low TT levels on PDE5i efficacy cannot be totally dismissed. Furthermore, only a single TT level was analyzed. Given the intra-assay variability, the levels measured may represent the highest or lowest level experienced by these men and confirmatory measurement is lacking. This analysis also defined men with hypogonadism using a somewhat lower TT level (< 300 ng/dL) [9] than other reports (< 350 ng/dL), which also may explain differences in interpretation of PDE5i response based on hormone level. The influence of ED severity and TT level on PDE5i response was not assessed because of the small subpopulation sizes (eg, $n = 23$ in tadalafil-treated men with severe ED and TT < 300 ng/dL). Because this analysis evaluated only one dose level of tadalafil (5 mg once daily), the effects of low TT on other dosage regimens (2.5 mg once daily and 5, 10, and 20 mg as needed) is unknown. In addition, this analysis only examined TT levels; the possible effect of free T levels on response to tadalafil was not evaluated. Given that the hypothalamic-pituitary response to falling serum testosterone levels becomes less sensitive with aging, another limitation of our analysis is that LH levels were

not adjusted for age. Additionally, hormone levels were available only at baseline and not at the endpoint evaluation. It is conceivable that tadalafil administration in our study might have *per se* normalized at endpoint, as previously described in another PDE5i study [24]. Spitzer et al found that a four-week run-in of sildenafil in hypogonadal men significantly raised TT levels by a mean of 115 ng/dL [24], thus supporting a possible role of PDE5i as the sole treatment in selected men presenting with ED and mildly reduced TT levels [36]. Accordingly, an open-label, retrospective study of 74 ED subjects found that three-month treatment with either sildenafil or tadalafil increased TT levels by 115–173 ng/dL [37]. This integrated analysis with the exception of one study [27], was comprised mostly of men who were not being treated primarily for ED; in fact, mean changes in IIEF-EF scores between tadalafil and placebo in this integrated analysis of men with LUTS/BPH were lower than for men presenting with ED [38]. This is not unexpected as all men who reported sexual activity and completed baseline and Week 12 IIEF domain score assessments were included in the treatment-effect analysis. Accordingly, the inclusion of some men without ED (ie, baseline IIEF score of >26) may have confounded the influence of sexual hormone status on tadalafil's efficacy for erectile function. Yet, exclusion of men without ED would likely have led to a more prominent tadalafil treatment effect.

CONCLUSIONS

Previous studies on the association of androgen hormone levels and PDE5i response have produced conflicting results. While some authors propose that low TT levels reduce the effects of PDE5i, this contention was not supported by our integrated analyses in older men with ED and LUTS/BPH. Once-daily tadalafil 5 mg therapy for 12 weeks significantly improved IIEF-EF and most other domain scores compared with placebo in men with low and normal TT levels. Our findings suggest that tadalafil can be used successfully in men with LUTS/BPH and coexisting ED, regardless of their gonadal status; however, confirmation is needed in men with very low TT levels. Clinicians should consider initiating PDE5i therapy at the initial consultation for ED, there is no need to wait for confirmation of a normal serum testosterone level. Testosterone Replacement Therapy as a supplement to PDE5i therapy should be reserved for those patients whose clinical laboratory values repeatedly confirm low serum testosterone and who have demonstrated a suboptimal therapeutic response.

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Demographics, Baseline Medical Characteristics, and Baseline IIEF domain scores^a

Subject Characteristic	Hormone Subgroup							
	TT < 300 ng/dL (N=340)		TT 300 ng/dL (N=709)		LH > 9.4 mIU/mL (N=94)		LH 9.4 mIU/mL (N=964)	
	Placebo (n=179)	Tadalafil (n=161)	Placebo (n=339)	Tadalafil (n=370)	Placebo (n=49)	Tadalafil (n=45)	Placebo (n=474)	Tadalafil (n=490)
Demographics								
Age (years), mean (SD)	63.9 (8.9)	64.1 (7.6)	63.8 (9.1)	63.6 (8.6)	70.2 (9.5)	69.5 (7.9)	63.2 (8.7)	63.2 (8.2)
Ethnicity, n (%)								
Hispanic or Latino	32 (17.9)	28 (17.4)	89 (26.3)	95 (25.7)	14 (28.6)	5 (11.1)	106 (22.4)	118 (24.1)
Not Hispanic or Latino	147 (82.1)	133 (82.6)	250 (73.7)	275 (74.3)	35 (71.4)	40 (88.9)	368 (77.6)	372 (75.9)
Race, n (%)								
White	162 (90.5)	140 (87.0)	293 (86.4)	321 (86.8)	42 (85.7)	40 (88.9)	419 (88.4)	425 (86.7)
Black or African American	2 (1.1)	0 (0.0)	10 (2.9)	10 (2.7)	1 (2.0)	2 (4.4)	11 (2.3)	8 (1.6)
Asian	1 (0.6)	7 (4.3)	1 (0.3)	1 (0.3)	1 (2.0)	0 (0.0)	1 (0.2)	8 (1.6)
Multiple	0 (0.0)	1 (0.6)	1 (0.3)	2 (0.5)	0 (0.0)	1 (2.2)	1 (0.2)	2 (0.4)
American Indian or Alaskan Native	14 (7.8)	13 (8.1)	34 (10.0)	36 (9.7)	5 (10.2)	2 (4.4)	42 (8.9)	47 (9.6)
BMI (kg/m ²), mean (SD)	30.2 (4.3)	29.0 (4.3)	27.4 (4.1)	26.8 (3.7)	28.2 (3.7)	26.5 (4.5)	28.4 (4.5)	27.6 (4.0)
Medical characteristics								
Erectile dysfunction ^b								
Yes	151 (84.4)	134 (83.2)	266 (78.5)	299 (80.8)	43 (87.8)	38 (84.4)	380 (80.2)	398 (81.2)
No	28 (15.6)	27 (16.8)	73 (21.5)	71 (19.2)	6 (12.2)	7 (15.6)	94 (19.8)	92 (18.8)
Erectile dysfunction severity ^b								
Mild	32 (17.9)	30 (18.6)	75 (22.1)	75 (20.3)	11 (22.4)	5 (11.1)	96 (20.3)	100 (20.4)
Moderate	89 (49.7)	81 (50.3)	156 (46.0)	172 (46.5)	24 (49.0)	21 (46.7)	227 (47.9)	234 (47.8)
Severe	30 (16.8)	23 (14.3)	35 (10.3)	52 (14.1)	8 (16.3)	12 (26.7)	57 (12.0)	64 (13.1)
Erectile dysfunction duration								
< 1	21 (11.7)	14 (8.7)	28 (8.3)	48 (13.0)	2 (4.1)	1 (2.2)	47 (9.9)	61 (12.4)
1 year	130 (72.6)	120 (74.5)	238 (70.2)	251 (67.8)	41 (83.7)	37 (82.2)	333 (70.3)	337 (68.8)
Diabetes, n (%)								
Yes	35 (19.6)	39 (24.2)	39 (11.5)	36 (9.7)	8 (16.3)	5 (11.1)	67 (14.1)	70 (14.3)

Subject Characteristic	Hormone Subgroup							
	TT < 300 ng/dL (N=340)		TT 300 ng/dL (N=709)		LH > 9.4 mIU/mL (N=94)		LH 9.4 mIU/mL (N=964)	
	Placebo (n=179)	Tadalafil (n=161)	Placebo (n=339)	Tadalafil (n=370)	Placebo (n=49)	Tadalafil (n=45)	Placebo (n=474)	Tadalafil (n=490)
No	144 (80.4)	122 (75.8)	300 (88.5)	334 (90.3)	41 (83.7)	40 (88.9)	407 (85.9)	420 (85.7)
Cardiovascular disease, n (%)								
Yes	102 (57.0)	82 (50.9)	147 (43.4)	159 (43.0)	24 (49.0)	24 (53.3)	228 (48.1)	219 (44.7)
No	77 (43.0)	79 (49.1)	192 (56.6)	211 (57.0)	25 (51.0)	21 (46.7)	246 (51.9)	271 (55.3)
Hypertension, n (%)								
Yes	87 (48.6)	80 (49.7)	125 (36.9)	135 (36.5)	20 (40.8)	20 (44.4)	195 (41.1)	196 (40.0)
No	92 (51.4)	81 (50.3)	214 (63.1)	235 (63.5)	29 (59.2)	25 (55.6)	279 (58.9)	294 (60.0)
IIEF Domain scores								
IIEF-EF Score, mean (SD)	16.62 (8.41)	16.01 (8.76)	17.28 (8.45)	17.36 (8.10)	14.51 (7.53)	15.62 (8.65)	17.29 (8.44)	17.08 (8.29)
IIEF-IS Score, mean (SD)	7.27 (3.77)	7.24 (3.99)	7.74 (3.47)	7.82 (3.44)	6.15 (3.22)	7.31 (3.58)	7.72 (3.56)	7.67 (3.63)
IIEF-OF Score, mean (SD)	6.40 (3.34)	6.15 (3.43)	6.76 (3.22)	6.58 (3.16)	5.97 (3.42)	6.46 (3.29)	6.72 (3.22)	6.46 (3.26)
IIEF-OS Score, mean (SD)	5.30 (2.38)	5.40 (2.58)	5.71 (2.55)	5.70 (2.41)	4.97 (2.57)	5.41 (2.53)	5.61 (2.49)	5.63 (2.46)
IIEF-SD Score, mean (SD)	6.22 (1.98)	6.14 (1.90)	6.47 (1.92)	6.31 (1.82)	6.56 (1.80)	5.92 (2.14)	6.36 (1.94)	6.31 (1.81)
IIEF-SC question, mean (SD)	2.45 (1.11)	2.44 (1.13)	2.52 (1.14)	2.55 (1.07)	2.21 (1.06)	2.33 (1.06)	2.52 (1.13)	2.54 (1.10)

Abbreviations: BMI = body mass index; ED = erectile dysfunction; IIEF = international index of erectile function; IIEF-EF = IIEF erectile function domain score; IIEF-OF = IIEF orgasmic function; IIEF-IS = IIEF sexual desire; IIEF-IS = IIEF intercourse satisfaction domain score; IIEF-OS = IIEF overall satisfaction domain score; IIEF-SC = IIEF sexual confidence question (confidence in the ability to get and keep an erection); kg/m² = kilograms per squared meter; LH = luteinizing hormone; mIU/mL = milli international units per milliliter; ng/dL = nanograms per deciliter; N = number of subjects in the analysis population; n = number of subjects per category with non-missing data; SD = standard deviation; TT = total testosterone.

^aThe primary analysis population included all subjects who were randomized and started study medication, excluding subjects with concomitant testosterone therapy.

^bErectile function and severity status was self reported.

Table 2Baseline Sexual Hormone Levels in Primary Analysis Population^a

Hormone	Placebo (N=535)	Tadalafil 5mg (N=540)	Total (N=1075) ^b
Total Testosterone (ng/dL)			
n	518	531	1049
Mean (SD)	364.0 (130.32)	377.9 (129.23)	371.0 (129.90)
Median	347.0	363.1	355.1
Min, Max	96.0, 1028.2	40.1, 875.5	40.1, 1028.2
Luteinizing Hormone (mIU/mL)			
n	523	535	1058
Mean (SD)	5.4 (4.80)	5.3 (3.29)	5.4 (4.11)
Median	4.4	4.6	4.5
Min, Max	0.3, 57.2	0.6, 24.0	0.3, 57.2
Follicle Stimulating Hormone (mIU/mL)			
n	522	531	1053
Mean (SD)	8.6 (8.22)	8.4 (7.86)	8.5 (8.04)
Median	6.4	6.2	6.3
Min, Max	0.3, 64.9	1.2, 76.7	0.3, 76.7
Sex Hormone Binding Globulin (nmol/L)			
n	145	150	295
Mean (SD)	38.2 (15.19)	37.1 (14.05)	37.6 (14.61)
Median	36.7	34.3	35.1
Min, Max	14.0, 103.0	11.8, 94.2	11.8, 103.0
Estradiol (pg/mL)			
n	518	533	1051
Mean (SD)	33.7 (13.02)	34.4 (11.95)	34.0 (12.49)
Median	33.5	34.6	34.1
Min, Max	9.0, 108.7	9.0, 66.5	9.0, 108.7
Prolactin (ng/mL)			
n	514	531	1045
Mean (SD)	9.2 (4.78)	10.2 (8.07)	9.7 (6.67)
Median	8.0	8.3	8.2
Min, Max	0.5, 47.4	0.5, 113.1	0.5, 113.1
Inhibin B (pg/mL)			
n	489	506	995
Mean (SD)	56.2 (39.31)	57.8 (42.58)	57.0 (40.99)
Median	51.0	49.5	50.0
Min, Max	6.5, 238.0	6.5, 289.0	6.5, 289.0
Thyroid Stimulating Hormone (μIU/mL)			
n	523	535	1058
Mean (SD)	1.7 (1.73)	1.9 (3.44)	1.8 (2.73)

Hormone	Placebo (N=535)	Tadalafil 5mg (N=540)	Total (N=1075) ^b
Median	1.4	1.4	1.4
Min, Max	0.0, 18.4	0.1, 67.0	0.0, 67.0

Abbreviations: max = maximum; mg = milligrams; min = minimum; mIU/mL = milli international units per milliliter; ng/dL = nanograms per deciliter; nmol/L=nanomoles per liter; ng/mL=nanograms per milliliter; pg/mL=picograms per milliliter; µIU/mL=macro international units per milliliter; N = number of subjects in the analysis population; n = number of subjects per category; SD = standard deviation.

^aThe primary analysis population includes all subjects who were randomized and started study medication excluding subjects with concomitant testosterone therapy.

^bOne subject randomized to the placebo treatment arm was receiving concomitant testosterone therapy; this subject was excluded from the primary analysis.

Table 3

Summary and analysis of mean changes in International Index of Erectile Dysfunction (IIEF) Domain Scores and Sexual Confidence Question (last observation carried forward at Week 12) by Baseline Hormone Level and Hypogonadism Classification

Tadalafil 5 mg												Treatment Difference	
Placebo													
IIEF Domain/Hormone/HG Subgroup													
n													
Baseline (SD)													
Endpoint (SD)													
LS Mean Change (SE)													
n													
Baseline (SD)													
Endpoint (SD)													
LS Mean Change (SE)													
95% CI													
Treatment-by-subgroup Interaction P-value													
IIEF-EF													
J Sex Med. Author manuscript; not certified for publication and review.													
TT 300 ng/dL													
292													
17.2 (8.5)													
18.5 (8.9)													
-0.3 (0.7)													
325													
17.4 (8.1)													
22.7 (8.1)													
3.9 (0.7)													
4.2 (0.6)													
3.0, 5.3													
0.832													
TT <300 ng/dL													
147													
17.1 (8.3)													
17.5 (9.7)													
-1.1 (0.8)													
136													
16.1 (8.8)													
21.5 (8.6)													
3.2 (0.9)													
4.4 (0.8)													
2.7, 6.0													
LH 9.4 mIU/mL													
407													
17.4 (8.4)													
18.3 (9.2)													
-0.8 (0.7)													
425													
17.2 (8.3)													
22.5 (8.2)													
3.5 (0.7)													
4.4 (0.5)													
3.4, 5.3													
LH >9.4 mIU/mL													
37													
14.9 (7.4)													
17.0 (9.2)													
-0.4 (1.3)													
38													
15.5 (8.7)													
21.7 (9.2)													
3.5 (1.3)													
3.8 (1.6)													
0.6, 7.0													
0.748													
IIEF-IS													
TT 300 ng/dL													
293													
7.7 (3.5)													
7.9 (3.8)													
-0.5 (0.3)													
325													
7.8 (3.4)													
9.6 (3.5)													
1.1 (0.3)													
1.6 (0.3)													
1.1, 2.1													
0.941													
TT <300 ng/dL													
147													
7.5 (3.7)													
7.3 (4.5)													
-0.9 (0.4)													
136													
7.3 (4.0)													
8.9 (4.2)													
0.7 (0.4)													
1.6 (0.4)													
0.9, 2.4													
LH 9.4 mIU/mL													
408													
7.8 (3.5)													
7.8 (4.1)													
-0.7 (0.3)													
425													
7.7 (3.6)													
9.5 (3.7)													
1.0 (0.3)													
1.7 (0.2)													
1.3, 2.1													
LH >9.4 mIU/mL													
37													
6.3 (3.1)													
6.9 (3.7)													
-0.5 (0.6)													
38													
7.3 (3.6)													
8.6 (4.0)													
0.4 (0.6)													
0.9 (0.7)													
-0.5, 2.3													
0.296													
IIEF-OF													
TT 300 ng/dL													
293													
6.7 (3.2)													
7.0 (3.3)													
-0.0 (0.3)													
325													
6.6 (3.2)													
8.0 (2.9)													
1.0 (0.3)													
1.0 (0.2)													
0.6, 1.5													
0.146													
TT <300 ng/dL													
147													
6.5 (3.3)													
6.2 (3.8)													
-0.7 (0.3)													
136													
6.2 (3.4)													
7.7 (3.2)													
0.9 (0.3)													
1.6 (0.3)													
1.0, 2.3													
LH 9.4 mIU/mL													
408													
6.7 (3.2)													
6.8 (3.5)													
-0.3 (0.3)													
425													
6.5 (3.2)													
8.0 (3.0)													
1.0 (0.3)													
1.2 (0.2)													
0.9, 1.6													
LH >9.4 mIU/mL													
37													
6.0 (3.3)													
6.0 (3.5)													
-0.7, (0.5)													
38													
6.4 (3.3)													
7.6 (3.3)													
0.6 (0.5)													
1.3 (0.6)													
0.0, 2.6													
0.933													
IIEF-OS													
TT 300 ng/dL													
293													
5.7 (2.6)													
6.1 (2.5)													
0.3 (0.2)													
325													
5.7 (2.4)													
7.5 (2.3)													
1.7 (0.2)													
1.4 (0.2)													
1.1, 1.7													
0.600													
TT <300 ng/dL													
147													
5.4 (2.4)													
6.1 (2.7)													
0.5 (0.2)													
136													
5.5 (2.6)													
7.4 (2.2)													
1.7 (0.3)													
1.3 (0.2)													
0.8, 1.7													
LH 9.4 mIU/mL													
408													
5.7 (2.5)													
6.1 (2.6)													
0.3 (0.2)													
425													
5.7 (2.5)													
7.5 (2.2)													
1.6 (0.2)													
1.3 (0.1)													
1.1, 1.6													
LH >9.4 mIU/mL													
37													
5.0 (2.6)													
5.6 (2.8)													
0.2 (0.4)													
38													
5.4 (2.6)													
7.5 (2.7)													
1.9 (0.4)													
1.6 (0.5)													
0.7, 2.6													
0.533													
IIEF-SD													
TT 300 ng/dL													
293													
6.5 (1.9)													
6.5 (2.0)													
0.1 (0.2)													
324													
6.3 (1.8)													
7.0 (1.7)													
0.8 (0.2)													
0.7 (0.1)													
0.4, 0.9													
0.572													
TT <300 ng/dL													
147													
6.3 (2.0)													
6.4 (2.0)													
0.2 (0.2)													
135													
6.1 (1.9)													
6.9 (1.7)													
0.7 (0.2)													
0.5 (0.2)													
0.2, 0.9													
LH 9.4 mIU/mL													
408													
6.4 (1.9)													
6.5 (2.0)													
0.5 (0.2)													
423													
6.3 (1.8)													
7.0 (1.7)													
0.5 (0.2)													
-0.1 (0.3)													
-0.7, 0.5													
0.380													

IIEF Domain/Hormone/HG Subgroup	Placebo			Tadalafil 5 mg			Treatment Difference		
	n	Baseline (SD)	Endpoint (SD)	LS Mean Change (SE)	n	Baseline (SD)	Endpoint (SD)	LS Mean Change (SE)	Treatment Difference LS Mean (SE)
									95% CI
LH >9.4 mIU/mL	37	6.6 (1.8)	6.5 (1.8)	0.4 (0.3)	38	5.9 (2.2)	7.0 (1.8)	0.7 (0.3)	0.3 (0.5)
<i>IIEF-SC question</i>									
TT 300 ng/dL	293	2.5 (1.2)	2.8 (1.1)	0.2 (0.1)	325	2.5 (1.1)	3.3 (1.1)	0.8 (0.1)	0.5 (0.1)
TT <300 ng/dL	147	2.5 (1.1)	2.8 (1.2)	0.2 (0.1)	136	2.4 (1.1)	3.4 (1.1)	0.9 (0.1)	0.6 (0.1)
LH 9.4 mIU/mL	408	2.5 (1.1)	2.8 (1.2)	0.2 (0.1)	425	2.5 (1.1)	3.4 (1.1)	0.8 (0.1)	0.6 (0.1)
LH >9.4 mIU/mL	37	2.2 (1.1)	2.5 (1.0)	0.1 (0.2)	38	2.3 (1.1)	3.3 (1.0)	0.8 (0.2)	0.7 (0.2)

Abbreviations: CI = confidence interval; HG = hypogonadism; IIEF = international index of erectile function; IIEF-EF = IIEF erectile function domain score; IIEF-SD = IIEF sexual desire; IIEF-OF = IIEF orgasmic function; IIEF-IS = IIEF intercourse satisfaction domain score; IIEF-OS = IIEF overall satisfaction domain score; IIEF-SC = IIEF sexual confidence question (confidence in the ability to get and keep an erection); LH = luteinizing hormone; LS = least squares; mg = milligrams; mIU/mL = milli international units per milliliter; n = number of subjects per category; ng/mL = nanograms per milliliter; SD = standard deviation; SE = standard error; TT = total testosterone.