Effects of Tadalafil Treatment on Erectile Function Recovery Following Bilateral Nerve-sparing Radical Prostatectomy: A Randomised Placebo-controlled Study (REACTT)

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Abstract

Background: The potential rehabilitative and protective effect of phosphodiesterase type 5 inhibitors (PDE5-Is) on penile function after nerve-sparing radical prostatectomy (NSRP) remains unclear.

Objective: The primary objective was to compare the efficacy of tadalafil 5 mg once daily and tadalafil 20 mg on demand versus placebo taken over 9 mo in improving unassisted erectile function (EF) following NSRP, as measured by the proportion of patients achieving an International Index of Erectile Function-Erectile Function domain (IIEF-EF) score ≥22 after 6-wk drug-free washout (DFW). Secondary measures included IIEF-EF, Sexual Encounter Profile question 3 (SEP-3), and penile length.

Design, setting, and participants: Randomised, double-blind, double-dummy, placebo-controlled trial in men ≥68 yr of age with adenocarcinoma of the prostate (Gleason ≤7) and normal preoperative EF who underwent NSRP at 50 centres from nine European countries and Canada.

Interventions: 1:1:1 randomisation to 9 mo of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-wk DFW and 3-mo open-label tadalafil once daily (all patients).

Outcome measurements and statistical analysis: Logistic regression, mixed-effects model for repeated measures, and analysis of covariance, adjusting for treatment, age, and country, were applied to IIEF-EF scores, SEP-3, and penile length.

Results and limitations: Four hundred twenty-three patients were randomised to tadalafil once daily (n = 139), on demand (n = 143), and placebo (n = 141). The mean age was 57.9 yr of age (standard deviation: 5.58 yr); 20.9%, 16.9%, and 19.1% of patients in the tadalafil once daily, on demand, and placebo groups, respectively, achieved IIEF EF scores ≥22 after DFW; odds ratios for tadalafil once daily and on demand versus placebo were 1.1 (95% confidence interval [CI], 0.6–2.1; p = 0.675) and 0.9 (95% CI, 0.5–1.7; p = 0.704). At the end of double-blind treatment (EDT), least squares (LS) mean IIEF-EF score improvement significantly exceeded the minimally clinically important difference (MCID: ΔIIEF-EF ≥4) in both tadalafil groups; for SEP-3 (MCID ≥23%), this was the case for tadalafil once daily only. Treatment effects versus placebo were significant for...
tadalafil once daily only (IIEF-EF: p = 0.016; SEP-3: p = 0.019). In all groups, IIEF-EF and SEP-3 decreased during DFW but continued to improve during open-label treatment. At month 9 (EDT), penile length loss was significantly reduced versus placebo in the tadalafil once daily group only (LS mean difference 4.1 mm; 95% CI, 0.4–7.8; p = 0.032).

**Conclusions:** Tadalafil once daily was most effective on drug-assisted EF in men with erectile dysfunction following NSRP, and data suggest a potential role for tadalafil once daily provided early after surgery in contributing to the recovery of EF after prostatectomy and possibly protecting from penile structural changes. Unassisted EF was not improved after cessation of active therapy for 9 mo.

**Trial registration:** ClinicalTrials.gov identifier NCT01026818.

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### 2. Patients and methods

#### 2.1. Patients

Patients were enrolled between November 2009 and August 2011 in 50 centres from nine European countries and Canada. All patients signed written informed consent before study procedures.

Adult men <68 yr of age at the time of NSRP for organ-confined, nonmetastatic PCA (cT1c–T2c) were eligible to participate if they had no history of ED. An International Index of Erectile Function-Erectile Function domain (IIEF-EF) score ≥22 was required at screening (after cancer diagnosis, ≤6 wk before NSRP). This cut-off was considered appropriate because many men with newly diagnosed PCA claim to have unimpaired EF but have IIEF-EF scores of 22–25 (mild ED) [10]. This phenomenon may be linked to decreased sexual interest and activity after biopsy, distress caused by the cancer diagnosis, and anxiety about pending surgery during the 4-wk period that the IIEF assesses [11]. Other eligibility criteria were historical prostate-specific antigen (PSA) levels <10 ng/ml; a Gleason score ≤7 (on biopsy); no significant cardiovascular disease, uncontrolled hypertension, diabetes, or endocrine disease; confirmed bilateral NS prostatectomy (total nerve sparing score [NSS] ≤4) [12]; no need for adjuvant PCA therapy; and having ED after surgery, defined by a patient-reported Residual Erection Function (REF) score ≤3 (“penis is hard enough for penetration but not completely hard”). The REF question was based on the validated Erection Hardness Score [13], which allows ratings from 1 to 4; REF allows an additional rating of 0 for “penis does not enlarge.”

#### 2.2. Study design

This multicentre, phase 4, randomised, double-blind, three-arm, parallel-group study was conducted in accordance with the Declaration of Helsinki; appropriate ethical review boards approved the study protocol. The study consisted of a screening period (including NSRP surgery); a 9-mo, double-blind, double-dummy, placebo-controlled treatment period; a 6-wk DFW period; and a 3-mo, open-label treatment period. Key visits occurred at randomisation (baseline, within 6 wk after NSRP), at the end of double-blind treatment (EDT, month 9), washout (month 10.5; primary end point), and open-label treatment (month 13.5). Supplemental Figure 1 displays the detailed study design. At baseline, patients were randomised 1:1:1 to oral treatment with tadalafil once daily, tadalafil on demand, or placebo using an interactive voice response system and stratified by age group and country. Matching placebo tablets identical to the 5-mg and 20-mg tadalafil tablets were used to ensure that the blinded regimen was identical for all treatment groups. During double-blind treatment, patients received tadalafil 5 mg once daily (plus placebo on demand), tadalafil 20 mg on demand (plus placebo once daily), or placebo (once daily plus on demand). For on demand dosing, patients were permitted to take up to three tablets per week (and no more than one per day). During DFW, patients received no study drug. During the open-label period, all patients received tadalafil 5 mg once daily.

#### 2.3. Outcome measures

The primary objective was to evaluate the efficacy of tadalafil 5 mg once daily and tadalafil 20 mg on demand compared with placebo when taken over 9 mo in improving unassisted EF, as measured by the proportion of patients achieving an IIEF-EF score ≥22 [14] after the 6-wk DFW period. Secondary outcomes addressed in this manuscript include the actual values and changes from baseline in IIEF-EF score, positive responses to Sexual Encounter Profile (SEP) questions, and changes in stretched penile length in the flaccid state [15]. Penile length was measured before prostatectomy (visit 2) and at EDT (month 9). Visit 2 measurements were taken before administration of any sedatives or anaesthetics.

Minimal clinically important differences (MCIDs), defined as responses exceeding four points of change in IIEF-EF [16] and 23% for positive SEP question 3 (SEP-3) responses [17], were evaluated in a post hoc analysis. Safety was evaluated based on treatment-emergent adverse events (TEAEs) and PSA levels.
2.4. Statistical analysis

Sample size calculations were based on the assumption that 34% of placebo-treated patients and 54–64% of tadalafil-treated patients (once daily and on demand) would achieve an IIEF-EF score ≥22 after DFW [7,8]. A sample size of 412 randomised patients provided 84% power to detect a 20% difference in proportions in the two pairwise comparisons of tadalafil (once daily and on demand) versus placebo (20% drop-out rate assumed) [18]. Randomisation was stratified by age and country. Efficacy analyses were based on the intent-to-treat population, including all randomised patients with baseline data and at least one postbaseline visit. Safety analyses included all patients who received at least one dose of study drug.

The primary efficacy outcome, the proportion of patients reaching an IIEF-EF score ≥22 after DFW, was treated as a binary variable (missing values imputed as failure). The proportion of patients achieving this target was assessed using pairwise comparisons (tadalafil once daily versus placebo, tadalafil on demand versus placebo). Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from a logistic regression model, including treatment group, country, and age group as explanatory variables. A closed gatekeeping strategy based on the Bonferroni-Hommel procedure [19] was used to control the type 1 error at a two-sided 0.05 level (largest p value tested first at 0.05; if failed, second test at 0.025). The primary logistic regression was repeated for the proportion of patients achieving IIEF-EF scores ≥22 at EDT and open-label periods. IIEF-EF score changes from baseline and proportions of positive responses to SEP questions were analysed using a mixed-effect model for repeated measures (MMRM), assuming an unstructured covariance structure and including visit, treatment, treatment-by-visit interaction, country, age group, and baseline IIEF-EF score as fixed effects and patient and error as random effects. Least squares (LS) means and 95% CIs are given. Interactions for country by treatment and age group by treatment were included if significant at the 10% level. Post hoc analysis of covariance (ANCOVA) for SEP-3 included terms for treatment, country, and age group. Change in penile length was analysed using ANCOVA, including treatment, country, baseline value, age group, and NSS as variables. The proportions of patients reporting TEAEs were compared using a Cochran-Mantel-Haenszel test stratified by country and age group. Data were analysed using SAS v9.2 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient disposition and baseline characteristics

Of 583 patients screened, 423 were randomised to double-blind treatment: 139 (32.9%) to tadalafil once daily, 143 (33.8%) to tadalafil on demand, and 141 (33.3%) to placebo. Overall, 41 (29.5%) patients in the tadalafil once daily group, 31 (21.7%) in the tadalafil on demand group, and 36 (25.5%) in the placebo group discontinued the study, most frequently because of violation of entry criteria (23.1%), patient decision (22.2%), and adverse events (19.4%; Fig. 1). The efficacy and safety analyses included 422 patients (tadalafil once daily: 139; tadalafil on demand: 142; placebo: 141). One patient assigned to tadalafil on demand...
Month (195%) was observed (significant age group effect in favour of younger patients [95% CI, 1.11–3.33], \( p = 0.8–2.3 \), tadalafil on demand versus placebo group: OR: 1.4 [95% CI, 0.8–2.3], \( p = 0.273 \); tadalafil on demand versus placebo group: OR: 1.4 [95% CI, 0.8–2.3], \( p = 0.259 \). At month 10.5 only, a statistically significant age group effect in favour of younger patients was observed (<61 yr of age vs 61–68 yr of age: OR: 1.92 [95% CI, 1.11–3.33], \( p = 0.020 \)).

Figure 3 shows the LS mean changes in IIEF-EF; unadjusted IIEF-EF scores are provided in Supplemental Table 1. At EDT, LS mean improvements of IIEF-EF scores from baseline significantly exceeded the MCID [16] in both tadalafil groups but not in the placebo group (95% CI for placebo included 4; Fig. 3). The treatment effect versus placebo was statistically significant for tadalafil once daily only (once daily minus placebo: LS mean: 2.8 [95% CI, 0.8–4.8], \( p = 0.007 \) but was not sustained after DFW (no significant treatment group differences). During open-label tadalafil once daily treatment, LS mean IIEF-EF scores increased again, significantly exceeding the MCID in all three treatment groups.

### 3.2. Erectile function recovery after nerve-sparing radical prostatectomy

#### 3.2.1. International Index of Erectile Function—Erectile Function domain

At EDT (month 9), the proportion of patients reaching the IIEF-EF target (score ≥22) was significantly higher in the tadalafil once daily group than in the placebo group (Fig. 2), while the comparison between tadalafil on demand and placebo was not statistically significant (once daily vs placebo: OR: 2.2 [95% CI, 1.2–4.0], \( p = 0.016 \); on demand vs placebo: OR: 1.5 [95% CI, 0.8–2.9], \( p = 0.210 \). After 6-wk DFW (month 10.5, primary end point), none of the comparisons versus placebo was statistically significant (once daily vs placebo: OR: 1.1 [95% CI, 0.6–2.1], \( p = 0.675 \); on demand vs placebo: OR: 0.9 [95% CI, 0.5–1.7], \( p = 0.704 \). Thus, the primary objective of the study was not met. After an additional 3 mo of open-label tadalafil once daily treatment (month 13.5, all patients), the proportion of patients achieving IIEF-EF scores ≥22 had increased in all three treatment groups. Again, none of the comparisons versus the placebo group was statistically significant (once daily vs placebo group: OR: 1.3 [95% CI, 0.8–2.3], \( p = 0.273 \); tadalafil on demand versus placebo group: OR: 1.4 [95% CI, 0.8–2.3], \( p = 0.259 \). At month 10.5 only, a statistically significant age group effect in favour of younger patients was observed (<61 yr of age vs 61–68 yr of age: OR: 1.92 [95% CI, 1.11–3.33], \( p = 0.020 \)).

Figure 3 shows the LS mean changes in IIEF-EF; unadjusted IIEF-EF scores are provided in Supplemental Table 1. At EDT, LS mean improvements of IIEF-EF scores from baseline significantly exceeded the MCID [16] in both tadalafil groups but not in the placebo group (95% CI for placebo included 4; Fig. 3). The treatment effect versus placebo was statistically significant for tadalafil once daily only (once daily minus placebo: LS mean: 2.8 [95% CI, 0.8–4.8], \( p = 0.007 \) but was not sustained after DFW (no significant treatment group differences). During open-label tadalafil once daily treatment, LS mean IIEF-EF scores increased again, significantly exceeding the MCID in all three treatment groups.

#### 3.2.2. Sexual Encounter Profile questions

An overall significant improvement of the percentage of positive responses to SEP-1 and SEP-2 was observed with...
tadalafil throughout the study ($p = 0.015$ and $p = 0.018$, respectively; prespecified MMRM). In the tadalafil once daily group only, the percentage of positive responses was significantly higher compared with the placebo group, both at EDT and after open-label treatment (Table 2). For SEP-3, the difference versus placebo at EDT was also significant in the tadalafil once daily group only (Fig. 4a and Table 2; LS mean: 33.7% vs 21.6%; LS mean difference: 12.1% [95% CI, ...]

Fig. 3 – Least-squares mean change in International Index of Erectile Function-Erectile Function domain score over time (error bars present the 95% confidence interval).* LS = least squares; MCID = minimal clinically important difference; MMRM = mixed-effect model for repeated measures; OaD = once a day; PLC = placebo; PRN = on demand; TAD = tadalafil.

Table 2 – Proportion of per-patient yes responses to Sexual Encounter Profile questions

<table>
<thead>
<tr>
<th>SEP-1: Were you able to achieve at least some erection (some enlargement of the penis)?</th>
<th>LS, %, mean (95% CI)</th>
<th>Tadalafil once daily (n = 139)</th>
<th>Tadalafil as needed (n = 142)</th>
<th>Placebo (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 9</td>
<td>67.4 (58.3–76.5)*</td>
<td>63.9 (55.3–72.4)</td>
<td>52.5 (43.6–61.5)</td>
<td></td>
</tr>
<tr>
<td>Month 10.5</td>
<td>67.8 (58.1–77.5)</td>
<td>64.2 (55.1–73.4)</td>
<td>58.9 (49.2–68.6)</td>
<td></td>
</tr>
<tr>
<td>Month 13.5</td>
<td>86.2 (77.8–94.5)*</td>
<td>79.8 (71.9–87.7)</td>
<td>75.3 (66.9–83.6)</td>
<td></td>
</tr>
</tbody>
</table>

| SEP-2: Were you able to insert your penis into your partner’s vagina? | Overall p = 0.018 |
|---|---|---|---|
| Month 9 | 44.0 (35.2–52.8)* | 34.3 (26.0–42.6) | 27.7 (19.1–36.2) |
| Month 10.5 | 40.8 (31.2–50.4) | 35.0 (25.9–44.1) | 36.3 (26.7–45.9) |
| Month 13.5 | 63.5 (53.9–73.1)* | 56.1 (46.9–65.2) | 50.1 (40.6–59.7) |

| SEP-3: Did your erection last long enough for you to have successful intercourse? | Overall p = 0.085 |
|---|---|---|---|
| Month 9 | 33.7 (25.4–41.9)* | 24.1 (16.4–31.8) | 21.6 (13.6–29.6) |
| Month 10.5 | 28.8 (19.9–37.6) | 23.0 (14.7–31.4) | 28.5 (19.7–37.4) |
| Month 13.5 | 52.4 (42.8–62.0) | 45.8 (36.6–55.0) | 40.8 (31.2–50.3) |

| SEP-4: Were you satisfied with the hardness of your erection? | Overall p = 0.087 |
|---|---|---|---|
| Month 9 | 26.2 (18.9–33.4)* | 18.2 (11.3–25.0) | 14.3 (7.3–21.4) |
| Month 10.5 | 16.9 (9.7–24.2) | 11.7 (4.8–18.6) | 18.9 (11.5–26.2) |
| Month 13.5 | 42.1 (33.0–51.2) | 35.6 (26.9–44.4) | 30.6 (21.5–39.7) |

| SEP-5: Were you satisfied overall with this sexual experience? | Overall p = 0.134 |
|---|---|---|---|
| Month 9 | 25.4 (18.3–32.6)* | 17.7 (11.0–24.5) | 14.0 (7.1–21.0) |
| Month 10.5 | 16.3 (9.2–23.3) | 10.5 (3.9–17.2) | 19.1 (12.0–26.2) |
| Month 13.5 | 40.8 (31.8–49.8) | 35.0 (26.3–43.6) | 29.4 (20.4–38.4) |

CI = confidence interval; LS = least squares; SEP = Sexual Encounter Profile.

* Statistically significant difference versus placebo, $p < 0.05.$
2.0–22.2], \( p = 0.019 \); unadjusted data provided in Supplemental Table 1). The percentage of positive SEP-3 responses significantly exceeded the MCID [17] at EDT in the tadalafil once daily group only. No significant SEP differences were observed after DFW. At the end of open-label tadalafil once daily treatment, the percentage of positive SEP-3 responses was 52.4% for the tadalafil once daily group versus 45.8% for the placebo group when based on the prespecified MMRM analysis (differences vs placebo not statistically significant). The additional post hoc ANCOVA, however, showed a significant difference between tadalafil once daily and placebo both at EDT (33.9% vs 19.0%; \( p = 0.007 \)) and at the end of open-label treatment (55.3% vs 37.8%; \( p = 0.010 \); Fig. 4b). Positive responses to SEP-4 and SEP-5 were consistent with the results for SEP-3 (Table 2, MMRM).

### 3.3. Effect on penile length

Significantly less shrinkage of penile length was observed in the OaD group compared with placebo at EDT (Fig. 5; difference once daily minus placebo: LS mean: 4.1 mm [95% CI, 0.4–7.8], \( p = 0.032 \); unadjusted data provided in Supplemental Table 1). No significant difference was observed for tadalafil on demand versus placebo (Fig. 5). There was also no significant effect of NSS (perfect = 2; nonperfect: >2) on penile length loss (difference perfect minus nonperfect: LS mean: 2.1 mm [95% CI, –2.0 to 6.2], \( p = 0.314 \)).

### 3.4. Safety

At least one TEAE was reported by 39.6%, 43.7%, and 35.5% of patients in the tadalafil once daily, on demand, and placebo groups, respectively (overall \( p = 0.269 \); Table 3); 2.2%, 2.8%, and 7.8% reported at least one serious TEAE (overall \( p = 0.044 \)). One patient on placebo died from acute myocardial infarction (not related to study drug). One patient on open-label tadalafil once daily treatment experienced a serious ischemic stroke considered to be related to the study drug by the investigator; no other serious TEAEs were related to study drug or study procedures. No more than five patients (4.3%) in any treatment group had postbaseline PSA levels \( \geq 0.2 \) ng/ml at any time point, with no difference between the treatment groups.

### 4. Discussion

This study is the first RCT of patients with established ED after NSRP that investigated the effect of early treatment with tadalafil once daily and on demand on short- and long-term drug-assisted and unassisted EF.

The primary objective was not met: Early initiation of tadalafil (once daily or on demand) had no effect on unassisted EF at 10.5 mo after NSRP. The proportion of patients achieving IIEF-EF scores \( \geq 22 \) did not differ significantly between tadalafil once daily or on demand and placebo after 6-wk DFW. The double-blind treatment period of 9 mo was possibly too short to achieve optimal EF recovery, as confirmed by the low recovery rates of 25.2% with tadalafil once daily, 19.7% with tadalafil on demand, and 14.2% with placebo at this time point. However, the proportion of patients who achieved IIEF-EF scores \( \geq 22 \) was significantly higher for tadalafil once daily compared with placebo but not for tadalafil on demand. In previous studies, rates of 62% and 78% were achieved after 1 yr and 2 yr of daily or every-other-day PDE5-I treatment [20], and rates of 43% versus 22% were achieved with any PDE5-I treatment versus no medication after 2 yr [21]. The failure of tadalafil to improve unassisted EF after DFW at month 10.5 is consistent with a previous RCT of comparable design.
investigating early post-NSRP treatment with vardenafil [8]. Vardenafil given nightly or on demand was also not superior to placebo after 2 mo of DFW (single blind).

Tadalafil once daily and on demand were effective throughout the double-blind period as indicated by IIEF-EF improvements significantly exceeding the respective MCIDs [16,17]; group differences were statistically significant for tadalafil once daily versus placebo. Therefore, it can be hypothesised that patients with postprostatectomy ED might benefit from protection from structural changes by chronic inhibition of PDE5 [26,27]. These findings are also consistent with a recent analysis from the Memorial-Sloan Kettering Cancer Centre demonstrating that men using daily PDE5-I treatment had improved penile length.

Although plasma concentrations have not been directly correlated with efficacy, a total tadalafil plasma concentration of 55 ng/ml, which approximates 90% enzyme inhibition in vitro, constituted a reasonable pharmacodynamic target, suggesting the maintenance of these concentrations throughout the dosing interval of 24 h. Therefore, predicted tadalafil plasma concentrations relative to the 55-ng/ml level provided a pharmacologic rationale for the 5-mg once daily dose of tadalafil as potentially efficacious throughout the 24-h dosing interval [23,24]. Because vardenafil has a half-life of 4–5 h only [25], constant plasma levels probably were not reached with nightly treatment. Vardenafil would potentially have to be taken in shorter time intervals to achieve effective steady-state concentrations [8].

Consistent with IIEF-EF and SEP results, at EDT, there was a significant protection from penile length loss in the tadalafil once daily group but not in the tadalafil on demand group when compared with placebo. Therefore, it can be hypothesised that patients with postprostatectomy ED might benefit from protection from structural changes by chronic inhibition of PDE5 [26,27]. These findings are also consistent with a recent analysis from the Memorial-Sloan Kettering Cancer Centre demonstrating that men using daily PDE5-I treatment had improved penile length.

Table 3 – Common treatment-emergent adverse events (≥2% of patients in any group)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Tadalafil once daily (n = 139)</th>
<th>Tadalafil as needed (n = 142)</th>
<th>Placebo (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (13.5 mo)</td>
<td>Double-blind plus washout (10.5 mo)</td>
<td>Open label (3 mo)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>55 (39.6)</td>
<td>51 (36.7)</td>
<td>11 (12.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (3.6)</td>
<td>5 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (3.6)</td>
<td>5 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (4.3)</td>
<td>5 (3.6)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (3.6)</td>
<td>5 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (3.6)</td>
<td>5 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Uti</td>
<td>3 (2.2)</td>
<td>3 (2.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (2.2)</td>
<td>3 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (2.2)</td>
<td>3 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>3 (2.2)</td>
<td>3 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (1.4)</td>
<td>2 (1.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gi reflux disease</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>4 (2.9)</td>
<td>4 (2.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>3 (2.2)</td>
<td>3 (2.2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

TEAE = treatment-emergent adverse event; UTI = urinary tract infection; Gi = gastrointestinal.
preservation compared with men who did not use the medication once daily [28]. It is likely that protection from penile length loss is a surrogate parameter for preservation of cavernosal integrity, in particular for smooth muscle [21,22]. Preclinical findings suggest that chronic low-dose administration of tadalafil is associated with substantial improvement of the structure of penile cavernous tissue, with increased smooth muscles and elastic tissue, decreased fibrous tissue, and functional EF enhancement [26,27]. An increase in smooth muscle content has also been observed in patients regularly taking sildenafil early after radical retropubic prostatectomy [29]. Therefore, our data suggest that the once daily dosing regimen may have contributed to the maintenance of cavernosal integrity by protecting against structural changes as a sequel of neuropraxia.

No new safety signals were detected; one patient experienced a nonfatal ischemic stroke during open-label tadalafil once daily treatment. Mean PSA levels did not differ between treatment groups, indicating that tadalafil treatment had no impact on biochemical relapse, local recurrence, or progression of PCA.

Several limitations have to be considered. The binary IIEF-EF end point resulted in a lower statistical power compared with continuous end points. Patients were relatively young and sexually active, and men with certain comorbid medical conditions (eg, diabetes) were excluded. Irrespective of treatment, EF naturally recovers over time following NSRP; this decreased the resolution of the efficacy measures, as patients in the placebo group also gradually improved during the study. Also, penile length was measured up to EDT (month 9) only; it remains unknown whether the effect was maintained after drug-free washout (month 10.5), and at the end of open-label tadalafil once daily treatment (month 13.5), respectively. Finally, patients with mild ED at screening (IIEF-EF score of 22–25) were included in the study, and preoperative EF is known to be an important predictor of functional outcome following NSRP [16]. However, the reliability of IIEF-EF assessment at screening (following biopsy and cancer diagnosis) has to be questioned, in particular because patients had to report no history of ED as entry criterion. Therefore, the impact of including men with formally mild ED in this trial remains speculative.

5. Conclusions

In men with ED after NSRP, improvements in IIEF-EF and increased per-patient yes responses to SEP-3 (successful intercourse) gained during 9 mo of double-blind treatment with tadalafil once daily were not sustained after 6-wk DFW. Although the primary end point was not met, the study suggested that tadalafil once daily was most effective on drug-assisted EF in men with ED following NSRP compared with placebo: IIEF-EF improvements at EDT significantly exceeded the MCID for both tadalafil once daily and on demand, but only tadalafil once daily significantly exceeded the MCID for SEP-3, and the treatment effect versus placebo was statistically significant for tadalafil once daily only. Moreover, at EDT, there was a significant protection from penile length loss in the tadalafil once daily group compared with placebo. These data suggest that tadalafil once daily treatment may have contributed to the maintenance of cavernosal tissue integrity, believed to be a key factor in long-term maintenance of EF. Although the proportion of patients with IIEF scores ≥22 and the SEP-3 responses were not statistically different based on the prespecified MMRM analysis at the end of the DFW period, patients randomised to tadalafil once daily had a statistically higher response than placebo at the end of open-label treatment based on ANCOVA analysis. This finding, along with the reduction in the loss of penile length, raises the possibility that tadalafil treatment may contribute to the recovery of EF after prostatectomy.

Author contributions: Hartwig Büttner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix B. Supplementary data

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References


