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Author(s)
Marumo, K; Imaoka, T; Fujimoto, K; Watts, S; Stothard, D; McGill, J

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A Comparison of the Efficacy and Tolerability of Tadalafil 10 mg and 20 mg in Japanese Patients With Severe Erectile Dysfunction

Ken Marumo, MD, PhD, Takeshi Imaoka, MD, PhD, Kenjiro Fujimoto, MPh, Steven Watts, PhD, Diane Stothard, PhD, and James McGill, MD

1Department of Urology, Tokyo Dental College, Ichikawa General Hospital, Chiba, Japan
2Lilly Research Laboratories Japan, Kobe, Japan
3Lilly Research Laboratories, Indianapolis, IN, USA

*Correspondence: James McGill, MD, Lilly Research Laboratories, Lilly Corporate Center DC 6063, Eli Lilly and Company, Indianapolis, Indiana USA.
Phone 317-276-7323; email: jmcgill@lilly.com.

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ABSTRACT

Introduction: Tadalafil is a phosphodiesterase 5 inhibitor with documented efficacy in the treatment of erectile dysfunction (ED).

Aim: To compare the efficacy and tolerability of tadalafil 10 mg and 20 mg in men with severe ED.

Methods: A prespecified subgroup analysis was conducted to compare the efficacy of tadalafil 10 and 20 mg measured by the International Index of Erectile Function (IIEF) erectile function (EF) domain and Sexual Encounter Profile (SEP) among patients with severe ED (EF domain score=1-10) in a Japanese placebo-controlled study. We also analyzed the efficacy of the two doses in men with severe ED post hoc by pooling data from three tadalafil clinical trials evaluating these doses using a similar study design (3 placebo-controlled trials; 3 PCTs) and evaluated (post hoc) the presence of organic comorbidities in patients with different levels of response to tadalafil 10 or 20 mg.

Main outcome measures: Mean change in IIEF EF domain and mean per-patient changes in percent “yes” responses to SEP Question 2 (SEP2) and 3 (SEP3).

Results: Patients with severe ED in the Japanese study experienced numerically greater increases (improvements) when taking tadalafil 20 mg compared with 10 mg in the IIEF EF domain (14.3 vs 12.4; \(P=0.355\)), SEP2 (60% vs 57%; \(P=0.781\)), and SEP3 (61% vs 49%, \(P=0.196\)). When sufficiently powered, these observations reached statistical significance in the 3 PCTs: patients with severe ED experienced greater increases when taking tadalafil 20 mg compared with 10 mg in the IIEF EF domain (13.6 vs 10.4; \(P=0.014\)) and SEP3 (56% vs 43%, \(P=0.019\)). Both doses were well tolerated.
Conclusions: Patients with severe ED, and especially those with an organic comorbidity, may derive greater clinical benefits from tadalafil 20 mg compared with 10 mg.

Keywords: efficacy, erectile dysfunction, phosphodiesterase type 5 inhibitors, tadalafil, treatment outcome

Running title: Tadalafil 20 mg for Japanese men with severe ED
INTRODUCTION

In a previous analysis of pooled data from 11 randomized, controlled trials examining the efficacy of the oral phosphodiesterase type 5 (PDE5) inhibitor tadalafil in different clinical subpopulations, including men over 65 years, men with diabetes mellitus, and men with severe erectile dysfunction (ED), it was noted that, in most groups studied, tadalafil 20 mg showed numerically greater improvement in erectile function compared with tadalafil 10 mg. However, the doses were not compared statistically, and, to our knowledge, significantly superior clinical responses to a higher dose of a PDE5 inhibitor compared with a lower dose in ED clinical subpopulations have not been demonstrated.

The chief objective of the current analysis was to determine the comparative efficacy and tolerability of tadalafil 10 mg and 20 mg in a subpopulation of men with severe ED from a recent Japanese study. Because the Japanese study was originally designed to detect differences between tadalafil and placebo rather than between tadalafil doses, there was a risk of encountering type II error (i.e., the result could lack statistical significance despite numerical superiority). Thus, we also examined (post hoc) efficacy data pooled from the only other tadalafil studies that examined both 10- and 20-mg doses using the same study design [three placebo-controlled trials (3 PCTs)]. This pooled-data analysis was performed to increase the power of detecting a difference between the 10- and 20-mg doses in the subgroup of men with severe ED, should such a difference exist, and to demonstrate the repeatability of the efficacy results reported for Japanese men.
To supplement these analyses and identify potential reasons for suboptimal treatment effects with tadalafil in patients with severe ED, we performed *post-hoc* analyses concerning the presence of organic ED and/or comorbidities that might compromise neurovascular function in Japanese patients. These analyses also were conducted to help identify patients with severe ED to whom tadalafil 20 mg might be prescribed.
METHODS

Study Design

This prespecified subgroup analysis was conducted to compare the efficacy of tadalafil 20 mg and tadalafil 10 mg for severe ED patients involved in a multicenter, randomized, double-blind, parallel-group, placebo-controlled study recently conducted in Japan (Study # H6D-MC-LVDI). Severe ED was defined as a score of 1-10 on the International Index of Erectile Function (IIEF) erectile function (EF) domain after a 4-week treatment-free screening and run-in phase. Primary efficacy endpoints for this study have been reported.

The pooled-data analysis (3 PCTs) contained efficacy and tolerability data from three multicenter, randomized, double-blind, parallel-group, placebo-controlled trials conducted in China, Philippines, and Singapore (Study # H6D-MC-LVDY); Taiwan (Study # H6D-MC-LVCO); and Canada (Study # H6-MC-LVDJ). These trials also were designed to detect differences between tadalafil and placebo rather than between tadalafil doses.

The study design and eligibility criteria for all four of these trials have been published elsewhere. ED severity was determined by the IIEF EF domain score. Three categories were adapted from Cappelleri: mild (score of 17-30), moderate (11-16), and severe (1-10). Patients were randomly allocated in a 1:1:1 or 1:2:2 ratio (placebo:tadalafil 10 mg:tadalafil 20 mg) to treatment with placebo or tadalafil for up to 12 weeks. In the Japanese study, tadalafil 5 mg also was evaluated; however, data for this dose are not included here because the Japanese study did not assess tadalafil 5 mg as a primary efficacy endpoint, and the 3 PCTs did not include tadalafil 5 mg.
In each study, informed consent was obtained from each patient prior to participation, and both the informed-consent document and study protocols were reviewed and approved by responsible institutional review boards.

**Outcome Measures**

**Efficacy**

There were three co-primary measures of efficacy: IIEF EF domain, Sexual Encounter Profile (SEP) diary Question 2 (SEP2: “Were you able to insert your penis into your partner’s vagina?”) and Question 3 (SEP3: “Did your erection last long enough for you to have successful intercourse?”). The co-primary outcome measures, all reported as least-square (LS) mean changes from baseline, were change in the IIEF EF domain score and change in per-patient percent “yes” responses to SEP2 and SEP3 in patients with severe ED in the Japanese study and the 3 PCTs. The IIEF has been validated for use in Japanese populations.6-8

Secondary analyses included: 1) change from baseline in per-patient percent “yes” responses to SEP Question 5 (SEP5; “Were you satisfied overall with this sexual experience?”) and 2) the proportion of patients achieving a score of =26 on the IIEF EF domain (“no ED”7 or normal erectile function).

Patients with severe ED in the Japanese study also were categorized according to the adequacy of their responses to treatment with tadalafil on the IIEF EF domain and SEP3. An “inadequate” treatment effect was arbitrarily defined as a mean per-patient IIEF EF domain score <22 at endpoint or as =50% mean per-patient proportion of “yes” responses to SEP3 at endpoint; consequently, an adequate response was defined as mean per-patient IIEF EF domain score ≥22 at endpoint or >50% mean per-patient proportion.
of “yes” responses to SEP3 at endpoint. Among patients with severe ED who had inadequate or adequate responses to tadalafil, we determined numbers (%) with organic, psychogenic, or mixed etiology, as well as numbers (%) of patients presenting with one of the following organic comorbidities at study entry: hypertension, hyperlipidemia, atherosclerosis-induced disease, diabetes mellitus, or spinal-cord injury. We determined baseline, endpoint, and LS mean change from baseline in the efficacy measures by dose group in Japanese patients with severe ED who did or did not have these organic comorbidities.

**Tolerability**

The tolerability of tadalafil was assessed throughout the treatment period by recording adverse events originally volunteered by patients after non-leading questions by the investigators. Treatment-emergent adverse events for each of the four studies have been reported previously.\textsuperscript{2-5}
Statistics

The effects of tadalafil 20 mg on erectile function and on frequencies of
treatment-emergent adverse events were compared with the effects of tadalafil 10 mg in
patients with severe ED in the Japanese study, patients with severe ED in the 3 PCTs, and
in the overall populations.

All patients with a baseline and at least one post-baseline observation were
included in the efficacy analyses. For the IIEF EF domain analysis, missing endpoint data
were imputed with the most recent non-missing post-baseline value using the last
observation carried forward convention. Efficacy analyses were performed on an intent-
to-treat basis. Changes from baseline to endpoint were evaluated using an analysis of
covariance (ANCOVA) model including effects for baseline, treatment group, and site.
For the 3 PCTS, an effect for study was included instead of site in the model mentioned
above. In addition, the model included therapy-by-baseline interaction if \( P < 0.10 \).
Treatment group differences were evaluated within the ANCOVA model by contrasting
model-based LS means. All tests of statistical significance were two-tailed at \( \alpha = 0.05 \).
Given the exploratory nature of these analyses and the associated low power of tests, no
adjustments for multiplicity were utilized.

Analyses comparing the incidences of treatment-emergent adverse events across
treatment groups were performed using \( \chi^2 \) tests.
RESULTS

Patient Characteristics

Among 258 randomized patients in the Japanese study, 99 had severe ED: 33 each in the placebo, tadalafil 10 mg, and tadalafil 20 mg groups. Among 816 total patients in the 3 PCTs, 256 had severe ED: 77 in the placebo group, 95 in the tadalafil 10 mg group, and 84 in the tadalafil 20 mg group. Baseline characteristics of patients with severe ED in the Japanese study are summarized in Table 1.

Efficacy

Primary Efficacy Measures

Japanese study. Among patients with severe ED, changes from baseline to endpoint in all three efficacy measures were numerically higher (improved), although not statistically significantly higher, for tadalafil 20 mg compared with tadalafil 10 mg (Figure 1). The differences between treatment groups in the overall Japanese population were less pronounced.

Patients with severe ED in the pooled 3 PCT data. When a subgroup analysis of men with severe ED was conducted for each individual study within the 3 PCT data set, changes in the three co-primary endpoints were numerically greater for the 20-mg compared with the 10-mg dose, though the differences were not statistically significant (similar to the Japan study). When the data were pooled, changes from baseline in the IIEF EF domain were significantly greater for patients with severe ED taking tadalafil 20 mg compared with 10 mg (13.6 vs 10.4, respectively, \( P=0.014 \); Figure 1A, right panel). Changes in per-patient percent “yes” responses to SEP2 were not significantly greater for patients taking tadalafil 20 mg compared with 10 mg but showed a trend
(\(P=0.054\); **Figure 1B, right panel**). Changes in per-patient percent “yes” responses to SEP3 were significantly greater for patients taking tadalafil 20 mg compared with 10 mg (\(P=0.019\); **Figure 1C, right panel**).

**Secondary Efficacy Measures**

In the Japanese study, the change from baseline in per-patient percent “yes” responses to SEP5 in patients with severe ED was significantly greater for patients taking tadalafil 20 mg compared with 10 mg (50.9% vs. 28.0%, \(P=0.005\)). This difference was less pronounced in the overall Japanese population (47.9% vs 39.3%, \(P=0.076\)).

The proportion of patients with severe ED in the Japanese study with a normal IIEF EF domain score (>26) at endpoint was numerically greater in patients taking tadalafil 20 mg compared with 10 mg (54.6% vs. 39.4%, respectively; \(P=0.218\)). The proportions of patients in the overall Japanese population with normal IIEF EF domain scores were similar between tadalafil 20 mg and 10 mg (**Figure 2**).

Among Japanese patients with severe ED and organic comorbidities, most (70.6%) had inadequate treatment effects to tadalafil 10 mg as assessed by both IIEF EF domain score and SEP3 (**Table 2**). On the other hand, the number (%) of patients with adequate treatment effects to tadalafil 20 mg in the presence of comorbidities increased, such that more than half (55.6%) of patients had adequate treatment effects to tadalafil 20 mg.

As shown in **Figure 3**, Japanese patients with severe ED and organic comorbidity exhibited a dose response in LS mean changes (improvements) from baseline to endpoint in the IIEF EF domain score (**Figure 3A**), as well as in mean per-patient proportions of “yes” responses to SEP2 (**Figure 3B**) and SEP3 (**Figure 3C**), over the dose range
tadalafil 10–20 mg. On the other hand, patients with severe ED but without these comorbidities did not exhibit a dose response across all three endpoints.

**Tolerability**

No patient with severe ED who received tadalafil 20 mg in any study discontinued treatment because of adverse events. Two (0.8%) of 245 patients (all studies) with severe ED discontinued because of adverse events (both in the tadalafil 10 mg group). There were no significant differences between treatment groups in frequencies of treatment-emergent adverse events among patients with severe ED in the Japanese study (Table 3). However, among men with severe ED in the 3 PCTs, there were significant differences between treatment groups in the frequencies of dizziness (0% for placebo, 2.1% for tadalafil 10 mg, and 7.1% for tadalafil 20 mg; \(P=0.026\)) and dyspepsia (0% for placebo, 5.3% for tadalafil 10 mg, and 14.3% for tadalafil 20 mg; \(P=0.001\); data not shown). In pairwise comparisons between tadalafil 10 mg and 20 mg, only dyspepsia showed a significant difference between doses (\(P=0.040\); data not shown).
DISCUSSION

Studies in Japanese and other populations have demonstrated that both doses of tadalafil (10 mg and 20 mg) significantly improve erectile function compared with placebo in men with ED of differing etiology and severity.\textsuperscript{1-5,9-11} Before our analysis, it was unknown whether there was a dose response for tadalafil treatment effects in patients with severe ED. The Japanese study showed improvements in a number of indices of erectile function and sexual satisfaction among Japanese patients with severe ED who received treatment with tadalafil 20 mg compared with 10 mg. Many patients with severe ED and organic comorbidities did not derive adequate treatment effects from tadalafil 10 mg but were more likely to do so when receiving the higher dose.

There was no increase in the incidence or severity of treatment-emergent adverse events for Japanese patients with severe ED taking tadalafil 20 mg compared with 10 mg, and no patient with severe ED who received tadalafil 20 mg discontinued because of adverse events. The findings of no significant differences in adverse events between doses in men with severe ED in the Japanese study may have been due to insufficient power to detect differences, because ED clinical studies are almost invariably powered for efficacy outcomes, not adverse events. Tadalafil was well tolerated at both doses, with only 2 (0.8%) of 245 men with severe ED discontinuing treatment because of adverse events (both in the tadalafil 10 mg group).

In the Japanese study, both tadalafil doses showed significant improvement in erectile function in men with severe ED compared with placebo, but tadalafil 20 mg showed numerically greater improvements in efficacy measures compared with tadalafil 10 mg for patients with severe ED, although statistical significance was not reached.
(likely because of type II error). As noted, the original study was not powered to detect a
difference between tadalafil doses in the total population or in the subset of men with
severe ED (N=99). That a type II error occurred is supported by the results of the analysis
of the 3 PCTs. When the data from these studies were pooled (N=256), the efficacy
endpoints were statistically greater for tadalafil 20 mg compared with 10 mg for patients
with severe ED.

According to our analyses, a large proportion of patients with severe ED together
with organic comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, or
atherosclerosis-induced disease, did not obtain adequate treatment effects using tadalafil
10 mg but did achieve adequate efficacy when the tadalafil dose was 20 mg. The change
from baseline to endpoint in each efficacy parameter among patients receiving tadalafil
10 mg was modest and clearly different from the change observed in patients receiving
tadalafil 20 mg. Therefore, when treating men with severe ED and organic comorbidities,
strong consideration should be given to treatment with tadalafil 20 mg.

Certain limitations of our study should be noted. The Japanese study and the
3 PCTs excluded patients with recent unstable and other serious cardiovascular
conditions (e.g. unstable angina, myocardial infarction) and interventions (e.g. coronary
artery bypass graft surgery, percutaneous coronary intervention).2-5 To ensure the safety
of ED treatment and the resumption of sexual activity in men with sexual dysfunction and
cardiovascular disease (or advanced risk), the Second Princeton Consensus Conference
provided guidelines for risk-stratifying patients according to clinical history and exercise
tolerance testing.12 Most (80%) patients with cardiovascular disease stratify into low risk
and are candidates for ED treatment. However, in part because ED is a frequent marker
of cardiovascular disease, all men with ED should have their cardiovascular risk assessed; risk graded as low, intermediate, or high; and be treated or counseled according to the guidelines.12

Although the comparison of efficacy between tadalafil doses in the subgroup of men with severe ED was prespecified in the Japanese study, it nevertheless was not the primary efficacy endpoint, and the results must be regarded as preliminary. Additional prospective, randomized controlled trials involving large numbers of patients with severe ED might help to confirm the hypothesis that patients with severe ED derive significantly greater clinical benefits from treatment with tadalafil 20 mg compared with tadalafil 10 mg. However, our findings in the Japanese severe ED population were consistent with data from 3 PCTs including a larger number of men with severe ED. Although not as strong as a prospective, randomized controlled study, multiple subgroup analyses with convergent findings have more validity than the findings of a single subgroup analysis.

Our definitions of “inadequate” treatment effects based on data from the IIEF EF domain and SEP diary were arbitrary and have not been validated in large populations. In addition, organic comorbidities were defined somewhat subjectively as done in clinical practice by clinical reasoning at study onset rather than consensus diagnostic criteria including laboratory cutpoints. The analysis of treatment effects in patients with severe ED and organic comorbidities did not include a number of other conditions that can compromise erectile function, including prostatectomy; pelvic irradiation, surgery or trauma; certain neurologic conditions (e.g. stroke, multiple sclerosis, Parkinson’s disease); and potentially modifiable lifestyle factors (biobehavioral markers), such as smoking, obesity, and metabolic syndrome.
In summary, although both tadalafil 10 and 20 mg are efficacious for treating ED of all severities, patients with severe ED may derive greater clinical benefits from tadalafil 20 mg compared with 10 mg. Patients with severe ED and organic comorbidities might be particularly likely to benefit from tadalafil at the higher dose. Both doses are well tolerated.

Acknowledgment

Assistance in manuscript preparation was provided by Stephen W. Gutkin, Rete Biomedical Communications Corp. (Ridgewood, NJ). We also thank William H. Cordell, MD (Eli Lilly and Company) for reviewing the manuscript.
REFERENCES


Table 1. Characteristics of Japanese patients with severe erectile dysfunction* at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=33)</th>
<th>10 mg (n=33)</th>
<th>20 mg (n=33)</th>
<th>Total (N=132)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD) yr</td>
<td>56.7 (±10.4)</td>
<td>56.1 (±11.9)</td>
<td>51.3 (±12.4)</td>
<td>55.0 (±11.3)</td>
</tr>
<tr>
<td>Age &gt;65 yr, n</td>
<td>7 (21.2%)</td>
<td>9 (27.3%)</td>
<td>6 (18.2%)</td>
<td>28 (21.2%)</td>
</tr>
<tr>
<td>Mean (±SD) body mass index, kg/m²</td>
<td>24.1 (±2.8)</td>
<td>23.6 (±3.2)</td>
<td>23.7 (±3.5)</td>
<td>23.9 (±3.3)</td>
</tr>
<tr>
<td>Duration of ED = 1 yr, n</td>
<td>32 (97.0%)</td>
<td>30 (90.9%)</td>
<td>29 (87.9%)</td>
<td>119 (90.2%)</td>
</tr>
<tr>
<td>Etiology of ED, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>15 (45.5%)</td>
<td>8 (24.2%)</td>
<td>10 (30.3%)</td>
<td>49 (37.1%)</td>
</tr>
<tr>
<td>Organic</td>
<td>15 (45.5%)</td>
<td>14 (42.4%)</td>
<td>13 (39.4%)</td>
<td>53 (40.2%)</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>3 (9.1%)</td>
<td>11 (33.3%)</td>
<td>10 (30.3%)</td>
<td>30 (22.7%)</td>
</tr>
<tr>
<td>Comorbid condition, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (33.3%)</td>
<td>11 (33.3%)</td>
<td>10 (30.3%)</td>
<td>42 (31.8%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (18.2%)</td>
<td>8 (24.2%)</td>
<td>11 (33.3%)</td>
<td>34 (25.8%)</td>
</tr>
<tr>
<td>Prior ED therapy, n</td>
<td>18 (54.5%)</td>
<td>19 (57.6%)</td>
<td>13 (39.4%)</td>
<td>71 (53.8%)</td>
</tr>
<tr>
<td>Current smokers, n</td>
<td>11 (33.3%)</td>
<td>7 (21.2%)</td>
<td>14 (42.4%)</td>
<td>49 (37.1%)</td>
</tr>
</tbody>
</table>

*Score of 1-10 on the erectile function domain of the International Index of Erectile Function.

†Includes 33 patients randomized to tadalafil 5 mg who were not involved in efficacy comparisons.
Table 2. Proportions of patients with severe erectile dysfunction and adequate and inadequate treatment effects*† by dose group in the Japanese study

<table>
<thead>
<tr>
<th>Tadalafil</th>
<th>10 mg group</th>
<th>20 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With or without organic comorbidities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without</td>
<td>With</td>
</tr>
<tr>
<td>IIEF EF domain*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocated patients, N</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Patients with inadequate effects, n</td>
<td>3 (18.8%)</td>
<td>12 (70.6%)</td>
</tr>
<tr>
<td>Patients with adequate effects, n</td>
<td>13 (81.3%)‡</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td>SEP3†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocated patients, N</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Patients with inadequate effects, n</td>
<td>3 (20.0%)</td>
<td>12 (70.6%)</td>
</tr>
<tr>
<td>Patients with adequate effects, n</td>
<td>12 (80.0%)</td>
<td>5 (29.4%)</td>
</tr>
</tbody>
</table>

*Inadequate treatment effect assessed by International Index of Erectile Function erectile function (IIEF EF) domain: mean per-patient IIEF EF domain score <22 at endpoint.
†Inadequate treatment effect assessed by Sexual Encounter Profile question 3 (SEP3; successful intercourse): mean per-patient proportion of “yes” responses =50% over the last 4 weeks.
‡Column does not add to 100% because of rounding.
### Table 3. Treatment-emergent adverse events reported by patients with severe erectile dysfunction in the Japanese study

<table>
<thead>
<tr>
<th>Adverse event:</th>
<th>Placebo (n=33)</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg (n=33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg (n=33)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.1%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (3.0%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (6.1%)</td>
<td>1 (3.0%)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1 (3.0%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (3.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>0 (0.0%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>0 (0.0%)</td>
<td>1 (3.0%)</td>
</tr>
</tbody>
</table>

*Includes only events occurring in ≥3% of patients in active treatment groups, including 33 patients randomized to tadalafil 5 mg who were not involved in efficacy comparisons.

†\(P\) values are for overall differences, including tadalafil 5 mg dose, from a \(?^2\) statistic and are not reported when total \(n<3\).
Figure 1. Treatment effects of tadalafil 10 mg and 20 mg on the International Index of Erectile Function erectile function (IIEF EF) domain (panel A), the mean per-patient proportion of “yes” responses to Sexual Encounter Profile Question 2 (SEP2; panel B), and the mean per-patient proportion of “yes” responses to SEP3 (panel C) in patients with severe erectile dysfunction (filled circles) and all patients (open circles) in the Japanese study (left panels) and in the three placebo-controlled trials (3 PCTs; right panels). All values shown are for LS mean change from baseline. Error bars signify standard errors. P values are shown for all comparisons of 20 mg versus 10 mg. Changes from baseline for tadalafil 10 mg and 20 mg treatment groups for all measures were significantly improved compared with placebo both in the Japanese study and the 3 PCTs (P<0.001).²⁻⁵

Figure 2. Proportions of patients with severe erectile dysfunction whose mean International Index of Erectile Function erectile function (IIEF EF) domain scores were ≥26 (normal erectile function) following treatment with tadalafil 20 mg or 10 mg in the Japanese study. Values above each bar represent the percentage of patients with IIEF EF domain score ≥26 at endpoint in each treatment group. Values below each bar represent total number of patients in each group (excluding those with erectile function domain =26 at baseline in all patients in Japanese study).
Figure 3. Treatment effects of tadalafil 10 mg and 20 mg on the International Index of Erectile Function erectile function (IIEF EF) domain (panel A), per-patient proportion of “yes” responses to Sexual Encounter Profile Question 2 (SEP2; panel B), and per-patient proportion of “yes” responses to SEP3 (panel C) in patients with severe erectile dysfunction and with (filled circles) or without (open circles) organic comorbidity in the Japanese study. All values shown are for LS mean changes from baseline. Error bars signify standard errors.
Figure 1A

Japanese study

3PCTs

Change from baseline to endpoint LS Mean IIEF EF Domain Score

Placebo 10 mg 20 mg

Tadalafil

P=0.355

P=0.777

P=0.014

P=0.019
Figure 1B

Japanese study

Placebo 10 mg 20 mg

P=0.781

P=0.895

3PCTs

- All ED patients
- Severe ED patients

P=0.054

P=0.031

Change from baseline to postbaseline
LS mean per-patient proportion SEP2 "Yes"
Figure 1C

Japanese study

3PCTs

Placebo 10 mg 20 mg Placebo 10 mg 20 mg

Tadalafil

P=0.196

P=0.469

P=0.019

P=0.087

Change from baseline to postbaseline LS mean per-patient proportion SEP3 "Yes"
Figure 2

Japanese study

Proportion of men at endpoint with IIEF EF domain Score ≥26

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline &lt; 26</th>
<th>Baseline &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Tadalafil 10mg</td>
<td>51.8%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Tadalafil 20mg</td>
<td>46.8%</td>
<td>54.6%</td>
</tr>
</tbody>
</table>

All Patients

Severe ED Patients
Figure 3A

Mean Change from baseline in IIEF EF domain score

- Open circle: Without Organic Comorbidity
- Solid circle: With Organic Comorbidity

Placebo 10mg 20mg

Without Organic Comorbidity:
- Placebo: 2.70
- 10mg: 5.70
- 20mg: 18.10

With Organic Comorbidity:
- Placebo: 6.30
- 10mg: 11.30
- 20mg: 17.70
Figure 3B

Placebo 10mg 20mg

LS Mean Per-Patient Percent Change from baseline in SEP2

Without Organic Comorbidity
With Organic Comorbidity
Figure 3C

- ○ Without Organic Comorbidity
- ● With Organic Comorbidity

LS Mean Per-Patient Percent Change from baseline in SEP3

Placebo 10mg 20mg

Without Organic Comorbidity:
- Placebo: 10.10
- 10mg: 30.50
- 20mg: 69.10

With Organic Comorbidity:
- Placebo: 23.50
- 10mg: 50.30
- 20mg: 75.20