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Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: a randomized, double-blind, placebo-controlled study

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Abstract

Introduction: Erectile dysfunction (ED) impacts on both members of the couple. Female partners of men with ED are more likely to report reduced sexual quality of life than women whose partners don't have ED.

Aims: To assess vardenafil efficacy in men with ED and determine the effects of treatment on their female partner's sexual quality of life.

Methods: Study participants comprised men aged 18–64 years with ED and their female partners. Eligible men had ED of ≥ 6 months' duration, and a female partner who was motivated to support their ED treatment. Eligible women had a total Female Sexual Function Index score >23.55 , indicating absence of significant sexual dysfunction. Following a 4-week screening period, the man was randomized to treatment with vardenafil 10 mg or placebo, which could be titrated to 20 or 5 mg after 4 weeks.

Main outcome measures: Primary efficacy variables were: (1) question 3 of the Sexual Encounter Profile questionnaire (SEP3); and (2) the quality of life domain of the modified Sexual Life Quality Questionnaire [mSLQQ-QOL]).

Results: The intent-to-treat population included 343 couples, with 168 and 175 men receiving vardenafil or placebo, respectively. Vardenafil treatment significantly improved both erection maintenance and the female partners' sexual quality of life. Least squares (LS) mean SEP3 overall success rates after 12 weeks of treatment were 9.5 (baseline) *vs* 67.2 (week 12) and 12.4 (baseline) *vs* 24.2 (week 12) in the vardenafil and placebo groups, respectively ($p < 0.0001$). In female partners, LS mean mSLQQ-QOL scores were 28.8 (baseline) *vs* 68.2 (last observation carried forward [LOCF]) in the vardenafil group and 24.6 (baseline) *vs* 40.5 (LOCF) in the placebo group ($p < 0.0001$).

Conclusions: Vardenafil treatment of men with ED improved both their erectile function and the sexual quality of life of their female partners.

Introduction

Erectile dysfunction (ED) has been the focus of much research over the past decade. Epidemiological studies have shown that ED is a prevalent condition, particularly among older men. The Massachusetts Male Aging Study (MMAS) found that 35% of men aged 40–70 years had moderate or severe ED.^{1,2} Similar ED prevalence rates have also been reported in other studies.^{2,3} Clinical research into ED has focused largely on the men's experience of this condition, with treatment efficacy measured in terms of improvements in erectile function and male quality of life.⁴⁻⁹ Studies have increasingly begun to address the impact of ED on the female partner. The Female Experience of Life Events and Sexuality (FEMALES) study¹⁰ showed that female partners of men with ED experienced significantly lower levels of sexual desire, arousal, orgasm and sexual satisfaction after their partner developed ED, compared with prior to the onset of this condition ($p < 0.001$). These changes were also found to be strongly associated with the man's self-reported severity of ED. A study using the Female Sexual Function Index (FSFI) showed that female partners of men with ED had significantly lower total FSFI scores ($p = 0.003$) and demonstrated significant impairments in sexual arousal, lubrication, orgasm, and satisfaction (all $p \leq 0.009$), compared with partners of men without ED.¹¹ Other studies have also reported impaired sexual function and low levels of sexual satisfaction among female partners of men with ED.^{12,13}

In light of these findings, researchers have begun to investigate the impact of ED treatment on the sexual function of female partners of men with ED. A recent double-blind, placebo-controlled study investigating sexual function in 180 female partners of men with ED showed that ED treatment with the PDE-5 inhibitor, sildenafil, led to a significant improvement in FSFI satisfaction domain scores for the female partner ($p < 0.0001$), together with a significant improvement in

treatment satisfaction, as assessed by the ED Inventory of Treatment Satisfaction partner version (EDITS-partner).¹⁴ Earlier research also demonstrated a significant improvement in EDITS-partner scores in women following sildenafil treatment of the man's ED.¹⁵ In the FEMALES study, female partners of men with ED who were receiving PDE-5 inhibitor therapy were significantly more likely to experience sexual desire, arousal and orgasm "almost always" or "most times" compared with those partners of men with ED not taking a PDE-5 inhibitor ($p < 0.05$).¹⁰ Similar significant improvements in female sexual arousal, lubrication, orgasm and satisfaction ($p \leq 0.002$) have also been reported following ED treatment with sildenafil.¹¹

A randomized, double-blind, multicenter, flexible-dose study investigated the impact of vardenafil treatment of ED on the female partner's sexual quality of life.¹⁶ Using the quality of life domain of the modified Sexual Life Quality Questionnaire (mSLQQ-QOL), female partners of men treated with vardenafil had significantly higher sexual quality of life scores than partners of men taking placebo (65.80 *vs* 32.14; $p < 0.0001$). Female partners of men taking vardenafil also experienced significant improvements in FSFI domain scores relating to arousal, desire, lubrication, orgasm and sexual satisfaction, and significantly higher total FSFI scores ($p < 0.01$ *vs* placebo).¹⁷

To date, studies examining female sexual function, satisfaction and quality of life following PDE-5 inhibitor treatment of their partner's ED have typically only included those female partners with normal or undefined sexual function. The aims of the present study were to assess the efficacy of vardenafil treatment in men with ED and determine the impact on sexual quality of life in female partners with an absence of significant sexual dysfunction (i.e. those with normal sexual function or mild sexual dysfunction, defined as a baseline FSFI total score > 23.55). A further aim was to investigate the impact of vardenafil treatment, in conjunction with an educational program, on erection maintenance and sexual quality of life of both members of the couple.

Methods

Study design

This was a randomized, double-blind, placebo-controlled, flexible-dose, parallel group, multicenter comparison of vardenafil *vs* placebo in men with ED and their female partners. The study was conducted between 12 July 2006 and 12 August 2007 at 43 study centers across 6 countries (Belgium, France, Germany, the Netherlands, Spain and South Africa).

Men with ED and their female partners were screened during a 4-week unmedicated run-in period. Couples meeting the inclusion criteria were randomly assigned (1:1 ratio) to either vardenafil or placebo using a computer generated code. During the confirmatory phase of the

study, men received 12 weeks of double-blind, on-demand treatment with flexible-dose vardenafil, or matched placebo. Initial treatment comprised vardenafil 10 mg for the first 4 weeks, after which the dose could be adjusted to 5 or 20 mg, depending on efficacy and tolerability, for the remaining 8 weeks of this phase of the study.

Following the confirmatory phase, study participants entered a 12-week exploratory phase to investigate the impact of educational material on a variety of measures of ED treatment efficacy, and patient and partner quality of life. Patients remained on their assigned treatment, and a subgroup of randomly selected couples (split equally between placebo and vardenafil treatment groups) participated in an educational program consisting of a video or DVD containing information on ED, partnership and sex life issues. Couples were instructed to watch the material at home and encouraged to do it in conjunction at their convenience. Vardenafil doses could be titrated to 5 or 20 mg at the start of the exploratory phase (week 12), or within the exploratory phase at the 6-week timepoint (week 18).

Study participants

Male patients were aged 18–64 years, with ED for >6 months and in a stable (≥6 months) heterosexual relationship with a female partner willing to participate in the study and support the male partner's ED treatment. Female partners were aged ≥18 years with an absence of significant sexual dysfunction (as indicated by an FSFI score >23.55). For entry to the confirmatory phase of the study, each couple was required to make at least 4 attempts at sexual intercourse on 4 separate days during the unmedicated run-in period. At least 50% of these attempts were required to be unsuccessful, as defined by a negative answer to any one of the following diary questions: "Were you able to achieve at least some erection (some enlargement of the penis)?" "Were you able to insert your penis into your partner's vagina?" "Did your erection last long enough for you to have successful intercourse?".

Principal exclusion criteria for patients included unstable medical conditions; presence of penile anatomical abnormalities; primary hypoactive sexual desire; spinal cord injury; history of surgical prostatectomy; hereditary degenerative retinal disorders; any underlying cardiovascular condition including unstable angina pectoris; history of myocardial infarction, stroke or life-threatening arrhythmia within the prior 6 months; uncontrolled atrial fibrillation at screening. Further principal exclusion criteria included concomitant use of the following medications: nitrates or nitric oxide donors; androgens; antiandrogens; potent inhibitors of cytochrome P450 3A4; alpha blockers; any investigational drug (including placebo) within 30 days of visit 1; and any ED treatment within 7 days of study day 1 or during the study, including oral medications, vacuum

devices, constrictive devices, injections or urethral suppositories. Principal exclusion criteria for female partners included an FSFI score ≤ 23.55 , unstable medical conditions or a substance abuse disorder likely to affect their ability to complete the study.

All patients and their partners provided written, informed consent. The study was conducted in accordance with International Conference on Harmonization/Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki.

Outcome measures

Primary outcome measures were assessed at week 12/last observation carried forward (LOCF). Patients answered the Sexual Encounter Profile question 3 (SEP3): "Did your erection last long enough for you to have sexual intercourse?". Improvements in female partners' sexual quality of life were assessed using the quality of life domain of the modified Sexual Life Quality Questionnaire (mSLQQ-QOL).

Secondary outcome measures were assessed at week 24. For ED patients, these included mSLQQ-QOL scores at weeks 12, 24 and LOCF; the erectile function domain of the International Index of Erectile Function (IIEF-EF) scores at weeks 4, 12, 18, 24 and LOCF; percentage of patients achieving a return-to-normal erectile function (IIEF-EF >25) at weeks 12, 24 and LOCF; responses to SEP3 and additional diary questions after 4, 12, 18, 24 weeks of treatment and LOCF; responses to the Global Confidence Question (GCQ); scores on the patient active medication module of the Treatment Satisfaction Scale (TSS)¹⁸ at weeks 12, 24 and LOCF; and responses to the Partnership questionnaire ['Partnerschafts-Fragebogen' (PFB)] at weeks 12, 24 and LOCF. Secondary outcome measures for female partners included mSLQQ-QOL scores at week 24 and LOCF, and FSFI scores at week 24 and LOCF.

Adverse event data were collected at all visits after initiation of treatment and for 24 hours after the last dose of study medication.

Statistical analyses

Power analysis indicated that 123 couples per treatment group were required to provide this study with 90% power to detect clinically significant treatment differences of 18% for SEP3 and 15 points for the mSLQQ-QOL score, assuming standard deviations of 36% and 25 points, respectively. After factoring in a dropout rate of 20% and assuming that 35% of screened subjects would not give consent for their partner's involvement, a total of 474 subjects (237 for each treatment arm) were required for randomization.

The intent-to-treat (ITT) population included patients who took at least one dose of study medication and provided baseline or post-baseline efficacy data. Study endpoint analyses were performed for the ITT population. Changes from baseline for the primary efficacy variables were analyzed using analysis of covariance (ANCOVA), with baseline values as the covariate, treatment group and country as independent variables, and cumulated SEP3 success rates or mSLQQ-QOL scores up to, and at, week 12 as dependent variables. Secondary efficacy variables, including patient diary questions; mSLQQ-QOL scores; IIEF-EF domain scores; FSFI domain scores; GCQ responses; TSS and PFB subscores and total scores, were analyzed using ANCOVA as above, and Cochran-Mantel-Haenszel statistics for responder analysis. Analysis of data from the exploratory phase that used educational materials was performed using a 2x2 factorial ANCOVA with interaction effect. Other secondary variables were presented with supporting summary or descriptive statistics.

Any patient who took at least one dose of study medication and who had any post-randomization safety data collected was included in the safety evaluation.

Post hoc analysis

A *post hoc* analysis was performed on the subgroup of female partners with baseline FSFI scores of between 23.55 and 26.0. FSFI total and domain scores were analyzed using ANCOVA and Cochran-Mantel-Haenszel statistics for responder analysis.

Results

Study population and baseline demographics

A total of 352 subjects were randomized (175 to vardenafil and 177 to placebo); 343 patients were included in the ITT analysis and 347 in the safety analysis. Of these, 277 patients completed the study (Figure 1). Mean patient age at enrollment was 52.6 years and mean body mass index was 27.5 kg/m². Patients were diagnosed with ED an average of 3.5 years prior to screening. A significant proportion of patients had used a PDE-5 inhibitor previously (41.2%, 32.0% and 34.9% of patients had used sildenafil, tadalafil or vardenafil, respectively). Treatment groups were well matched for demographic and baseline disease characteristics (Table 1). For female partners, mean baseline FSFI scores were 28.1 in the vardenafil group and 27.4 in the placebo group.

Erectile function

During the 12-week confirmatory phase of the study, vardenafil treatment significantly improved rates of successful intercourse, compared with placebo. Least-squares (LS) mean per-patient SEP3

success rates for men taking vardenafil were 9.5% at baseline *vs* 67.2% at week 12, compared with 12.4% at baseline *vs* 24.2% at week 12 for those taking placebo ($p < 0.0001$; Figure 2).

LS mean IIEF-EF scores increased from 13.3 at baseline to 23.3 at week 12 in the vardenafil group, compared with an increase from 13.3 to 14.9 over the same time period in the placebo group ($p < 0.0001$). A significant difference in LS mean IIEF-EF scores was observed between treatment groups at week 12 ($p < 0.0001$).

In the exploratory phase of the study, couples' participation in the educational program resulted in no further improvement in erectile function in men beyond that achieved with vardenafil treatment alone.

Sexual quality of life

Vardenafil treatment led to significant improvements in male patient sexual quality of life. LS mean mSLQQ-QOL total scores were 33.4 at baseline *vs* 68.6 at week 12/LOCF for vardenafil compared with 33.9 *vs* 44.6, respectively for placebo ($p < 0.0001$, nominal statistical significance; Figure 3). Substantially greater improvements in all individual mSLQQ-QOL domains were observed in patients treated with vardenafil compared with placebo-treated patients (Figure 4).

A significant improvement in female partners' sexual quality of life was also observed following vardenafil treatment of the male partner's ED. LS mean mSLQQ-QOL total scores were 28.8 at baseline *vs* 68.2 at week 12/LOCF in the vardenafil treatment group compared with 24.6 *vs* 40.5 at baseline and week 12/LOCF, respectively, in the placebo group ($p < 0.0001$; Figure 3). Corresponding improvements were seen in all individual mSLQQ-QOL domain scores (Figure 4).

Importantly, in both partners, vardenafil treatment improved mSLQQ-QOL scores for all 10 items to above 50 (where a score of ≥ 50 represents sexual quality of life prior to the onset of ED).

Data from the exploratory phase showed that couples' participation in the educational program did not improve mSLQQ-QOL scores in either partner beyond those achieved with vardenafil treatment alone.

Female sexual function

Overall, there was a nominally statistically significant improvement in female partners' FSFI total scores (Figure 5A), and all individual FSFI domain scores (Figure 5B), at week 12 versus baseline following treatment with vardenafil ($p < 0.0001$). Similarly, a significant difference in favour of

varденафил was observed at week 12/LOCF in FSFI total scores ($p < 0.0001$) and individual domain scores ($p \leq 0.0149$).

In the subgroup of women with baseline FSFI scores of 23.55–26.00, no significant improvement in FSFI total scores for vardenafil at week 12 versus baseline, or between vardenafil and placebo at week 12/LOCF, was observed (Figure 6A). However, vardenafil therapy was associated with nominally statistically significant improvements in the individual FSFI domains for orgasm and sexual satisfaction ($p \leq 0.0267$) (Figure 6B).

Adverse events

Treatment with vardenafil was generally well tolerated. The overall incidence of drug-related, treatment-emergent adverse events was 25.7% for the vardenafil group and 4.0% for the placebo group. The most common drug-related adverse events were headache, flushing, nasal congestion and dyspepsia (Table 2), and most adverse events were mild or moderate in severity. Four adverse events led to discontinuation of the study drug; 3 in the vardenafil group, of which 2 (headache and angina pectoris) were considered related to the trial medication, and 1 in the placebo group. The incidence of serious adverse events was low, with 10 events in five patients in the vardenafil group, of which 1 (angina pectoris) was considered to be related to the study medication. In the placebo group, there were 3 serious adverse events in two patients. There were no clinically important differences between treatment groups, for the change from baseline with regard to vital signs, clinical laboratory examinations or ECG findings. No deaths were reported.

Discussion

Research into the impact of ED and its treatment on sexual function, satisfaction and quality of life has traditionally focused on the man. More recently, attention has shifted towards examining the impact of ED on the female partner, with evidence demonstrating that female partners of men with ED frequently report sexual dysfunction and reduced levels of sexual desire and sexual satisfaction.¹¹⁻¹³ It is therefore important to involve both members of the couple in studies evaluating improvement in sexual satisfaction and quality of life following ED treatment.

The relationship between effective ED treatment and improvement in sexual quality of life of both the male and female partner has previously been demonstrated in couples where the female partner reported normal sexual function.¹⁶ The inclusion criteria of the present study were broadened to include female partners with mild sexual dysfunction (i.e. FSFI score > 23.55). Due to the 'step-down' approach used in this study, it was first necessary to determine the efficacy of vardenafil in men with ED, prior to investigating the effect of treatment on their female partner's

sexual quality of life. Following 12 weeks of treatment with flexible-dose vardenafil, both erectile function and rates of successful intercourse were significantly improved in patients with ED. Overall increases in IIEF-EF scores were indicative of an average improvement from moderate to mild ED. This confirmed the results of earlier studies showing the beneficial effect of vardenafil treatment on the physical symptoms of ED.^{16, 17}

The mSLQQ-QOL measures a variety of parameters of sexual quality of life, covering both the physical and emotional aspects of the sexual experience.¹⁹ Here, we demonstrate consistent improvements in all individual mSLQQ-QOL domain scores for both patients and partners following ED treatment with vardenafil. Moreover, for both members of the couple, total mSLQQ-QOL scores and all individual mSLQQ-QOL domain scores improved to >50, signifying a return to sexual quality of life comparable to that prior to the onset of ED. This demonstrates the broadly beneficial effect of vardenafil therapy on all determinants of sexual quality of life.

Treatment with vardenafil was generally well tolerated, with the majority of adverse events being consistent with the normal side-effect profile of PDE-5 inhibitors.

Overall, these data show that effective treatment of ED with vardenafil (as indicated by increased mean IIEF-EF scores and SEP3 success rates) can lead to improved sexual quality of life for both members of the couple. This confirms previous research findings,^{16, 17} and builds upon them by showing that benefits of vardenafil treatment on the female partner also extend to those partners with mild sexual dysfunction, as measured by the FSFI, a validated diagnostic instrument. Men cite concern for their partner's sexual satisfaction as one of the key factors influencing their treatment seeking for ED,²⁰ and female sexual satisfaction is also believed to be associated with men's adherence to ED therapy^{14, 21} and consistency of use of PDE-5 inhibitors. Improvements in female sexual satisfaction, such as those seen here with vardenafil treatment, may foster long-term treatment success in male patients, including those whose partners have mild sexual dysfunction. Conversely, a lack of improvement may predict either discontinuation or reduced use of PDE-5 inhibitors by the male partner. Couples' participation in an educational program during the second (exploratory) phase of this study provided no benefits in terms of additional improvement in erectile function, rates of successful intercourse or sexual quality of life of either partner, beyond those achieved with 12 weeks of vardenafil treatment alone. It is to notice that compliance with the requirements of the exploratory phase couldn't be accurately assessed. Furthermore many couples were PDE5i users, and it is likely that they were either already properly instructed or refused to watch what could be considered by them an useless material. Therefore we acknowledge this as an

important limitation of the study, since the real utility of such educational intervention can't be properly evaluated.

Conclusion

Vardenafil treatment was well tolerated and highly efficacious for the treatment of ED, leading to significant improvements in erectile function in male patients and improved sexual QOL for both patients and their female partners, including those with mild sexual dysfunction.

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Table 1. Patient characteristics at baseline (safety population).

	Placebo (n=176)	Vardenafil (n=171)
Age at enrollment (years)		
Mean (SD)	52.8 (8.4)	52.3 (8.7)
Min-max	23.0-67.0	24.0-67.0
Body mass index (kg/m²)		
Mean (SD)	27.9 (4.4)	27.2 (3.8)
Min-max	19.3-43.2	16.7-37.0
Race, n (%)		
White	113 (64.2)	107 (62.6)
Black	8 (4.5)	6 (3.5)
Asian	12 (6.8)	10 (5.8)
Missing	43 (24.4)	48 (28.1)
Marital status, n (%)		
Married	142 (80.7)	140 (81.9)
Divorced	16 (9.1)	10 (5.8)
Widowed	1 (0.6)	3 (1.8)
Never married	17 (9.7)	18 (10.5)
Smoking history, n (%)		
Past or present smoker	102 (58.0)	102 (59.6)
Non-smoker	73 (41.5)	67 (39.2)
Passive smoker	1 (0.6)	2 (1.2)
Time since ED onset (years)		
Mean (SD)	5.5 (4.6)	5.7 (5.6)
Min-max	0.6-27.1	0.6-44.9
Time since ED first diagnosed (years)		
Mean (SD)	3.4 (3.0)	3.7 (3.7)
Min-max	0-16.9	0-22.6
Etiology of ED, n (%)		
Organic	51 (29.0)	48 (28.1)
Psychogenic	25 (14.2)	40 (23.4)
Mixed	100 (56.8)	83 (48.5)

Table 2. Incidence of most common drug-related, treatment-emergent adverse events occurring in either treatment group (safety population).

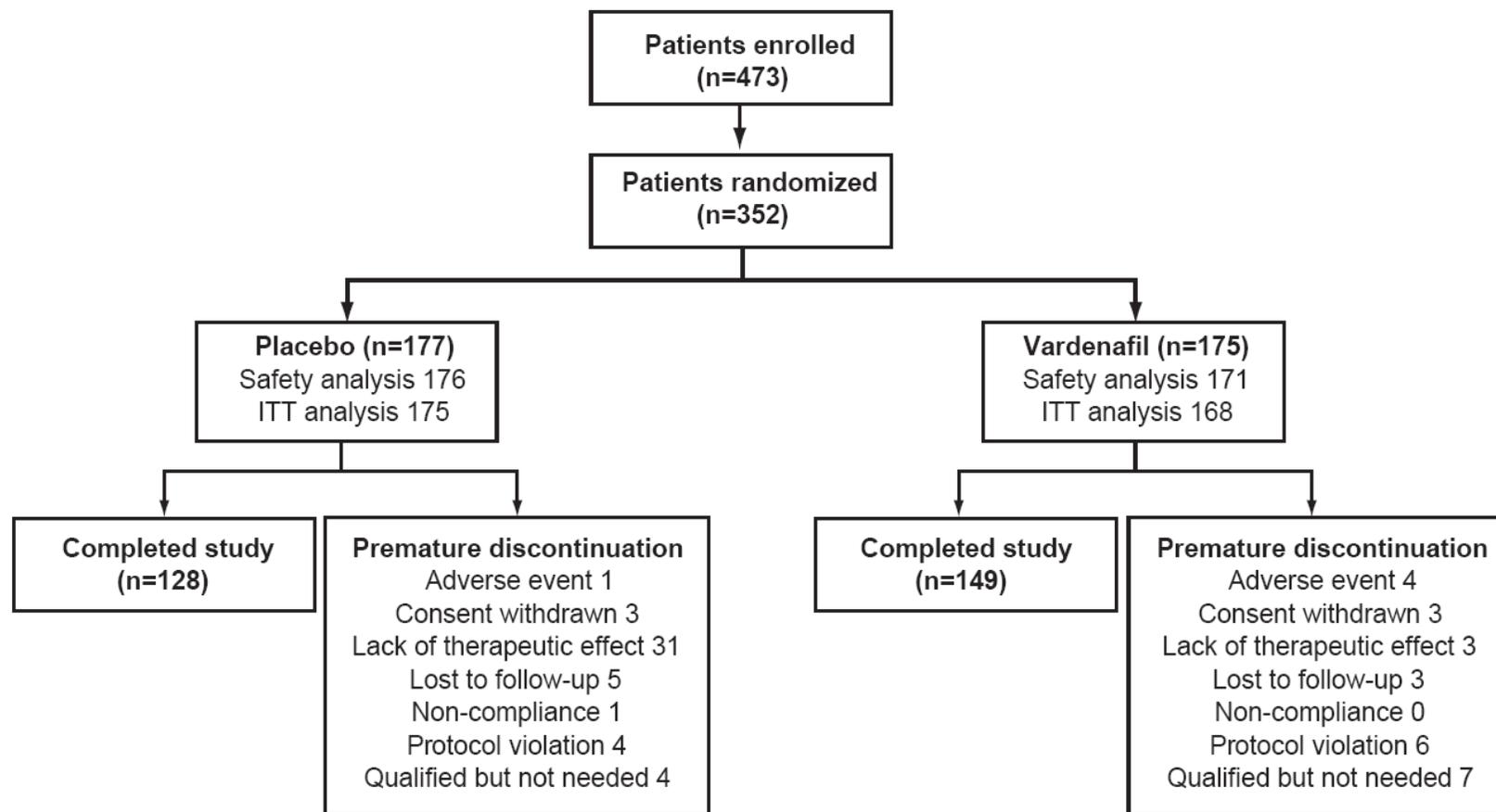
Adverse event, n (%)	Placebo (n=176)	Vardenafil (n=171)
Any event	7 (4.0)	44 (25.7)
Headache	3 (1.7)	26 (15.2)
Flushing	0 (0)	10 (5.8)
Nasal congestion	1 (0.6)	8 (4.7)
Dyspepsia	0 (0)	3 (1.8)

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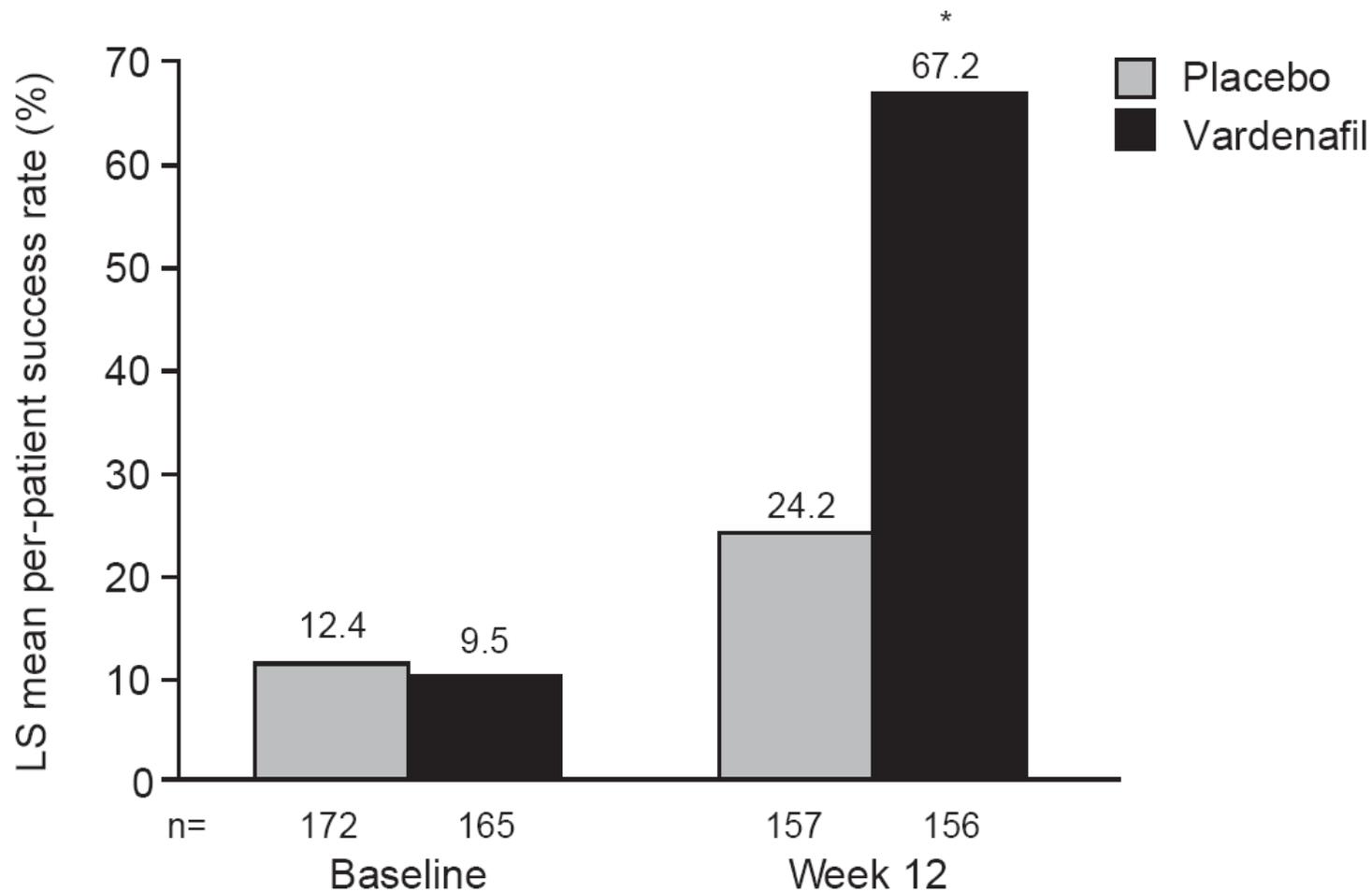
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Figure 1. Patient disposition during study.



ITT, intent-to-treat.

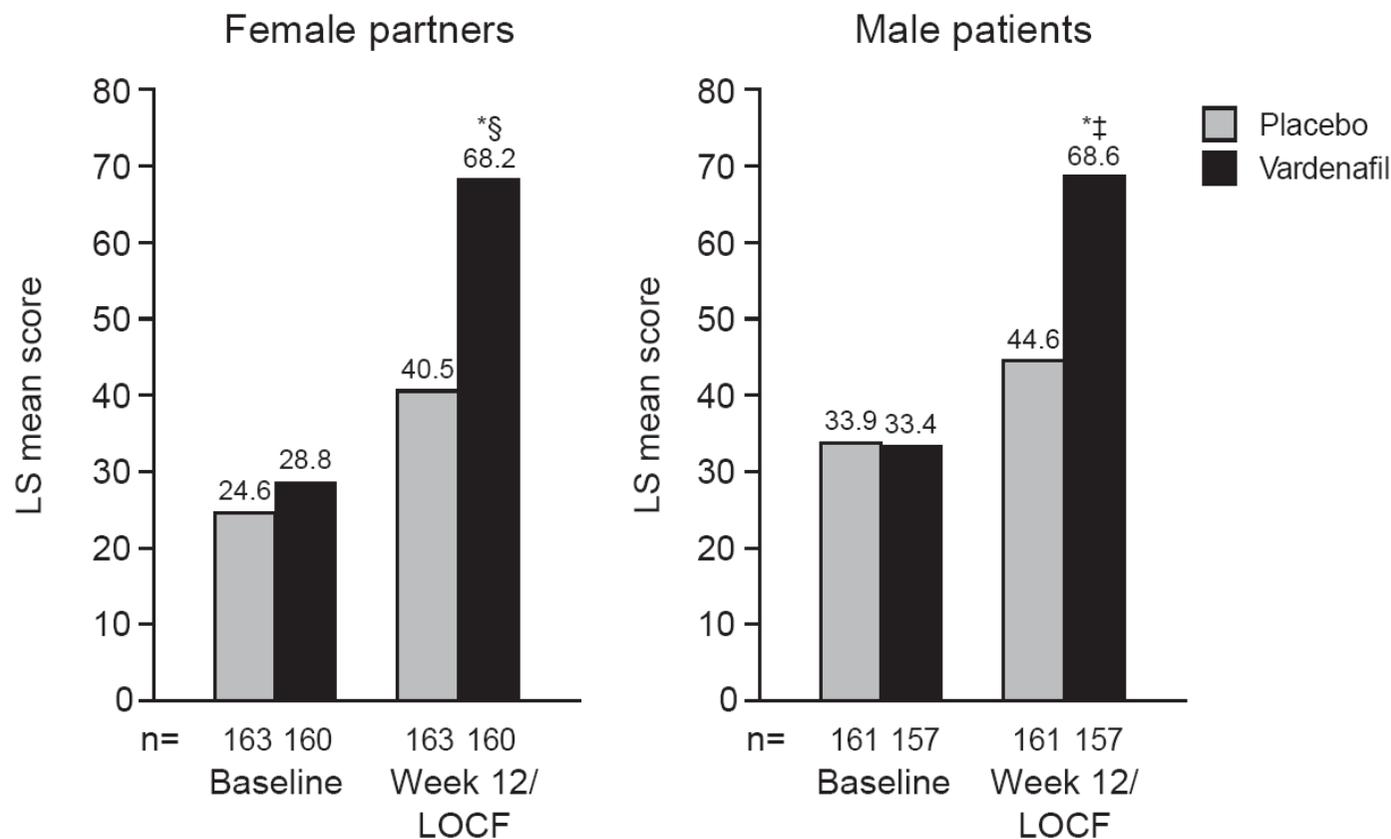
Figure 2. Least squares mean per-patient SEP3 success rates at baseline and week 12 (ITT population).



*p<0.0001 for vardenafil vs placebo at week 12; p<0.0001 for vardenafil at week 12 vs baseline.

ITT, intent-to-treat; LS, least squares; SEP, Sexual Encounter Profile question.

Figure 3. Patient and partner mSLQQ-QOL total scores at baseline and week 12/LOCF (ITT population).

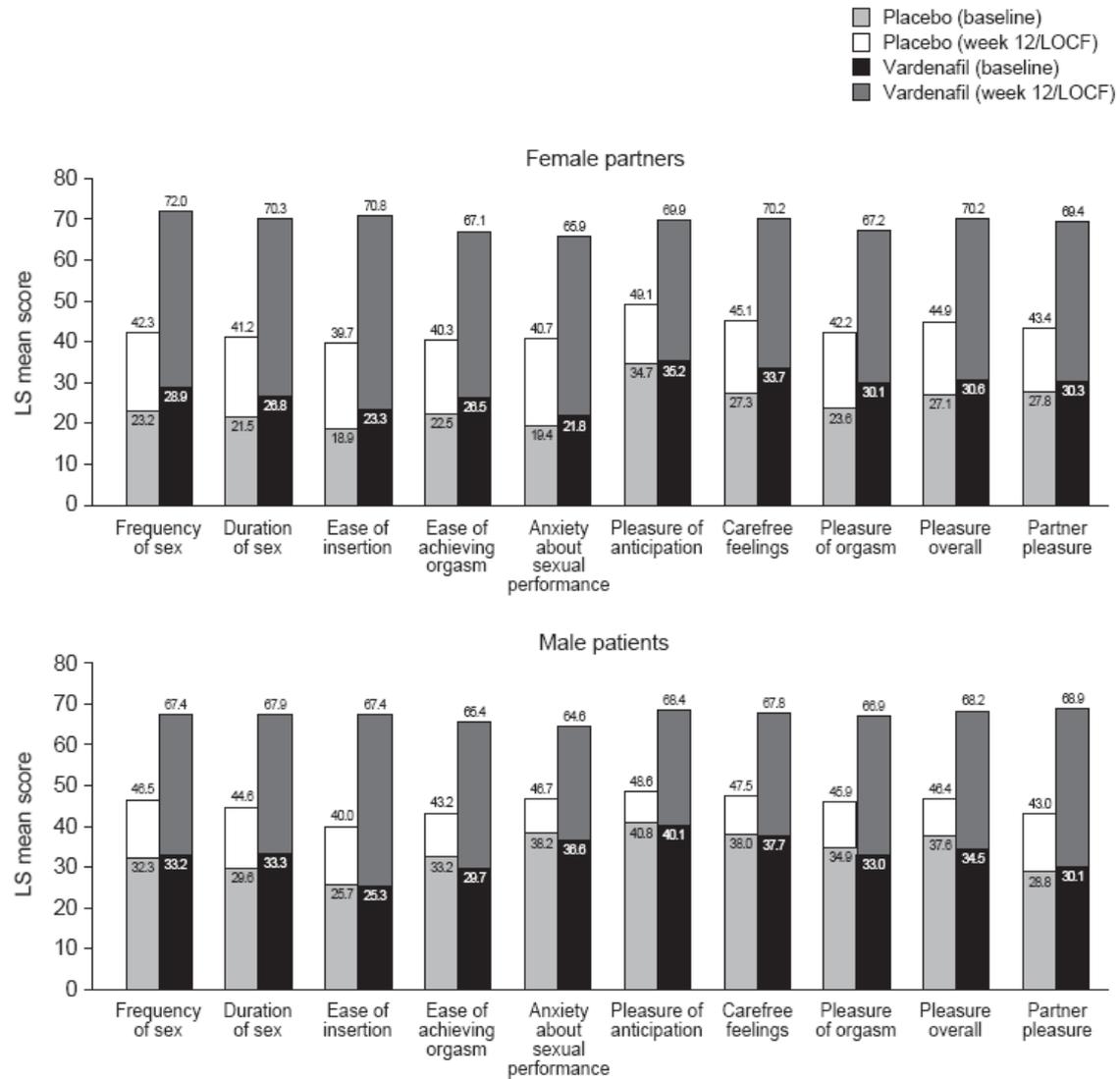


*p<0.0001 for vardenafil *vs* placebo at week 12/LOCF; §p=0.0013, †p=0.0091 for vardenafil at week 12/LOCF *vs* baseline.

ITT, intent-to-treat; LS, least squares; LOCF, last observation carried forward; mSLQQ-QOL, quality of life domain of the modified Sexual Life Quality Questionnaire.

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Figure 4. Patient and partner scores for individual mSLQQ-QOL domains at week 12/LOCF (ITT population).



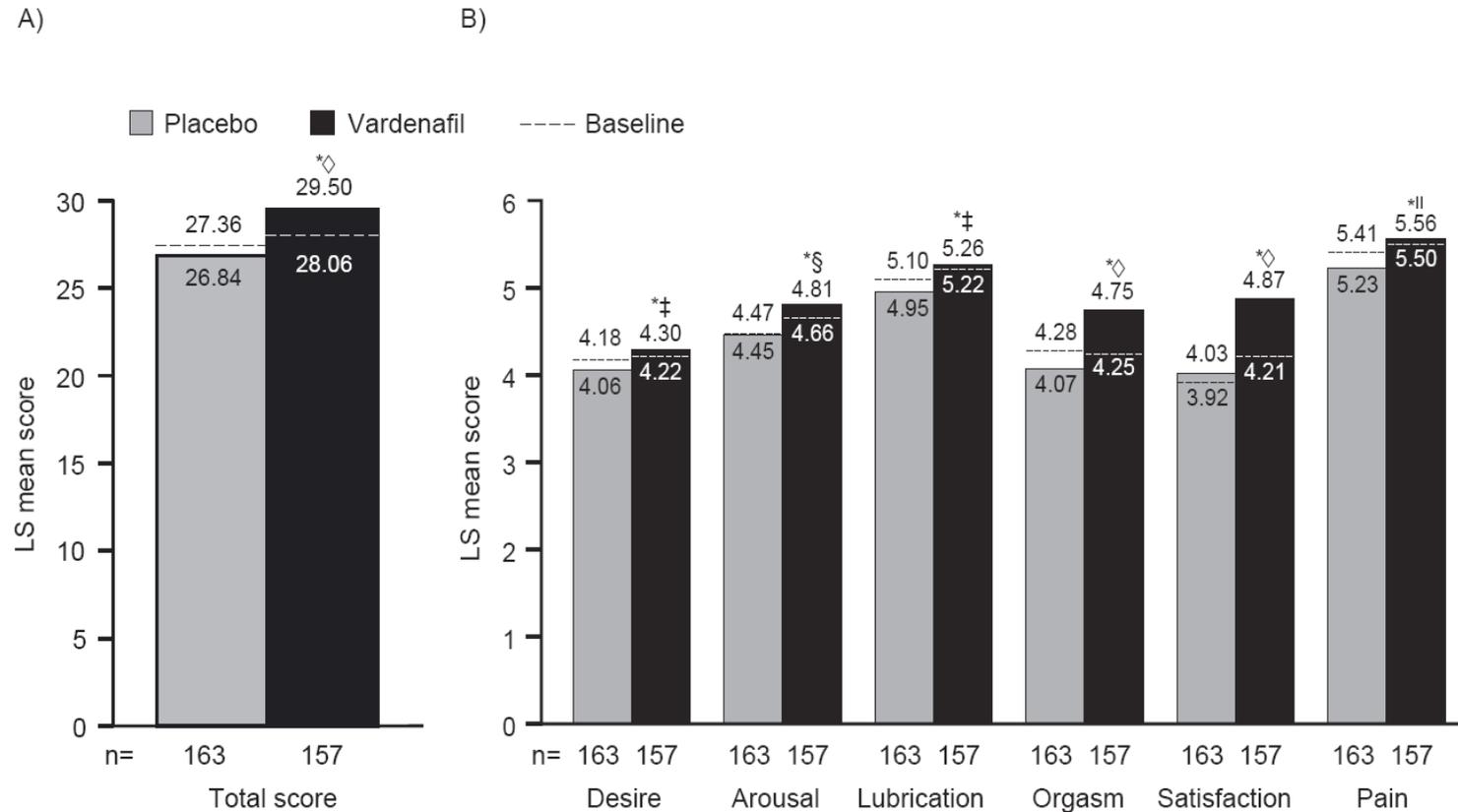
ITT, intent-to-treat; LS, least squares; LOCF, last observation carried forward; mSLQQ-QOL, quality of life domain of the modified Sexual Life Quality Questionnaire.

Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: a randomized, double-blind, placebo-controlled study

J Sex Med. 2011 Oct; 8 (10): 2831-40

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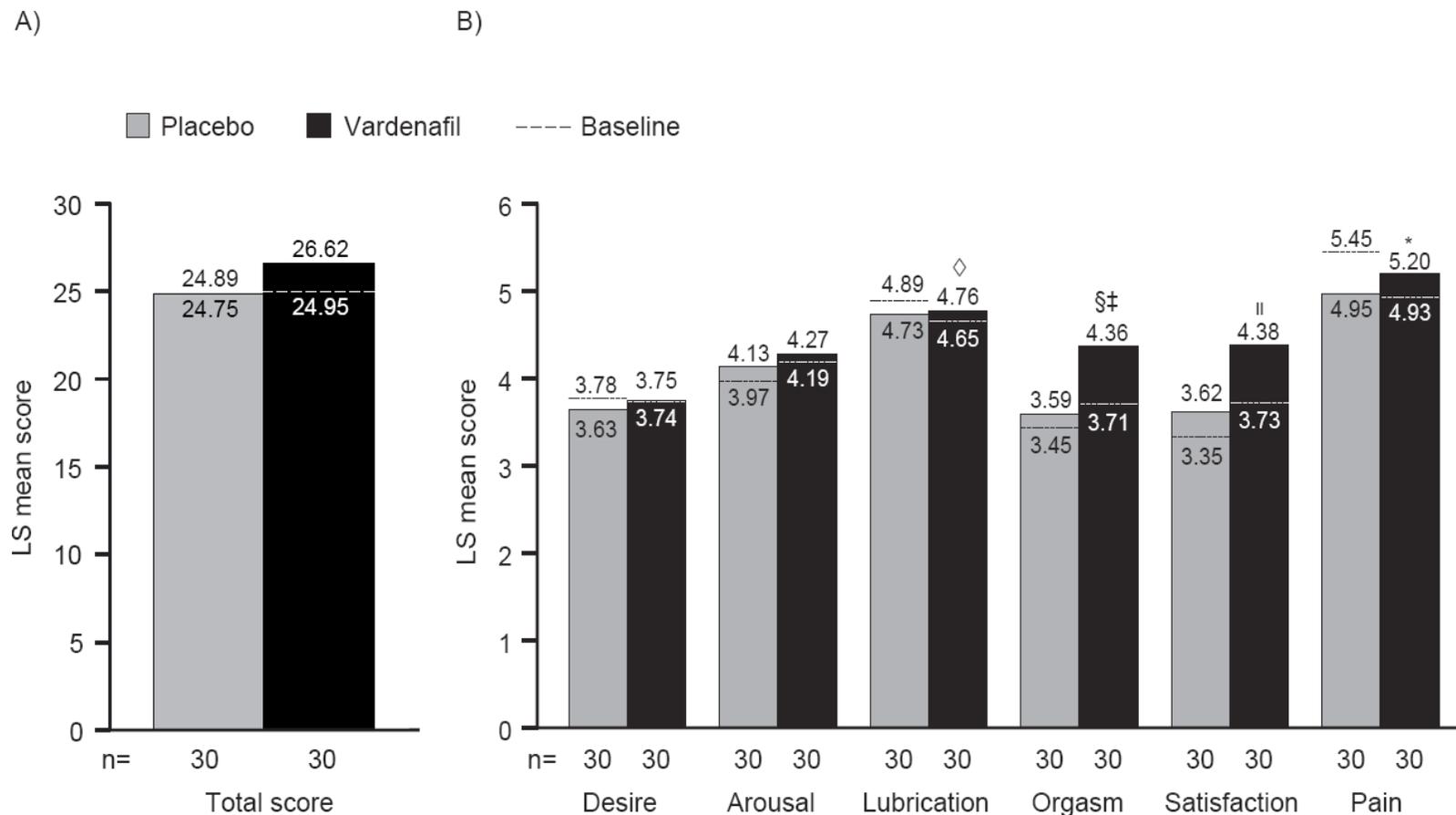
Figure 5. FSFI total scores and individual FSFI domain scores of female partners at week 12/LOCF.



‡p < 0.0001, §p = 0.0014, †p = 0.0091, ¶p = 0.0149 for vardenafil vs placebo at week 12/LOCF; *p < 0.0001 for vardenafil at week 12/LOCF vs baseline.

LOCF, last observation carried forward; LS, least squares.

Figure 6. FSFI total scores and individual FSFI domain scores at week 12/LOCF for female partners with baseline FSFI total scores of 23.5–26.0.



‡p=0.0245, ‖p=0.0267 for vardenafil vs placebo at week 12/LOCF; *p=0.0151, †p=0.0189, §p=0.0275 for vardenafil at week 12/LOCF vs baseline.

LOCF, last observation carried forward; LS, least squares.