Effect of Nightly versus On-Demand Vardenafil on Recovery of Erectile Function in Men Following Bilateral Nerve-Sparing Radical Prostatectomy

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Abstract

Background: To date, no data have been available from large, well-designed trials comparing on-demand and nightly dosing of phosphodiesterase type 5 (PDE5) inhibitors on recovery of erectile function in postprostatectomy patients with erectile dysfunction (ED).

Objective: To investigate the effect of early postoperative dosing with vardenafil, administered either nightly or on demand, compared with placebo on recovery of erectile function in men with ED following bilateral nerve-sparing radical prostatectomy (NSRP).

Design, setting, and participants: A randomised, double-blind, double-dummy, multicentre, parallel group study conducted at 87 centres across Europe, Canada, South Africa, and the United States. For inclusion, patients had to be scheduled to undergo bilateral NSRP within 1 mo of screening and have a normal International Index of Erectile Function erectile function domain (IIEF-EF) score of ≥21 at screening. A total of 628 men, aged 18–64 yr, were randomised to treatment. Study design consisted of a 9-mo double-blind treatment period, a 2-mo single-blind washout period, and an optional 2-mo open-label period.

Intervention: Patients received placebo, nightly vardenafil, or on-demand vardenafil.

Measurements: Primary outcome measure was the percentage of subjects with an IIEF-EF score of ≥21 after the 2-mo washout period. Secondary variables included mean per-patient success rates for Sexual Encounter Profile (SEP) questions 2 and 3.

Results and limitations: No statistically significant differences were observed among treatment groups in the proportion of patients with an IIEF-EF score of ≥22 or in SEP success rates after the washout period. On-demand vardenafil treatment resulted in significantly greater IIEF-EF scores and better SEP response rates than placebo over the entire treatment period.

Conclusions: In this study of men with ED following bilateral NSRP, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5 inhibitors in this patient group.

Trial registration: European clinical trials database (EudraCT; available at http://eudract.emea.europa.eu/). Trial registration number: 11336.
1. Introduction

Radical prostatectomy, and particularly nerve-sparing prostatectomy, is the gold-standard therapy for clinically localised prostate cancer in men with a life expectancy of ≥10 yr [1]. Walsh pioneered the understanding of pelvic neuroanatomy and the subsequent development of a surgical technique by which the entire prostate could be removed while preserving the anatomical integrity of the external urethral sphincter and the autonomic nerves surrounding the gland [2,3]. The procedure was termed nerve-sparing radical prostatectomy (NSRP). Although the NSRP technique has continued to evolve, the risk of developing erectile dysfunction (ED) and urinary incontinence—two classic sequelae of this surgery—remains significant [4]. ED following NSRP is caused by the neuropraxia effect that inevitably occurs during the procedure, leading to temporary malfunction of the cavernous nerves [5]. This results in reduced or lack of nitric oxide (NO) release and, ultimately, a continuous state of constriction of the penile vascular smooth muscle. The hypoxic state that follows may lead to the development of fibrosis within the corpus cavernosa [6], eventually leading to cavernous veno-occlusive dysfunction, the typical aetiology of postprostatectomy ED [7].

To prevent the onset of postoperative ED, the concept was introduced of stimulating oxygenation of the corpus cavernosum by pharmacologically stimulating penile erection [8]. The regular administration of intracavernosal injections of alprostadil, started relatively soon after surgery, significantly improved the recovery of spontaneous erections, when compared with no administration. This landmark study led to the consideration of phosphodiesterase type 5 (PDE5) inhibitors as pharmacologic agents for use in postsurgery penile rehabilitation programmes. The rationale for their use is that the formation of NO and cyclic guanosine monophosphate (cGMP) in cavernosal tissue is believed to play a role in the antiapoptotic and antifibrotic defence mechanisms that oppose the deleterious effects of neural injury [9]. By preventing the breakdown of cGMP, PDE5 inhibitors may exert a protective effect on cavernosal smooth muscle, as has been demonstrated in animal models [10,11]. PDE5 inhibitors are also believed to increase nocturnal erections, and this may further protect the function of the corpus cavernosum [12].

A number of studies in animal models of post-prostatectomy neuropraxia have clearly demonstrated a beneficial class effect of PDE5 inhibitors on smooth muscle cells of the corpus cavernosum [10,11,13]. In one study, recovery of spontaneous erections was demonstrated in humans; function was improved by nightly sildenafil use compared with placebo [14]. However, this study was limited due to the inclusion of a relatively small number of patients and the lack of comparison with a patient group that would take the PDE5 inhibitor as required (ie, on demand). To date, data from well-designed, multicentre studies from a large patient cohort are lacking.

Vardenafil is a potent PDE5 inhibitor with demonstrated efficacy and tolerability in patients with ED, including postprostatectomy patients [15,16]. The objective of the present study was to investigate the effect of early postoperative dosing with vardenafil, administered either nightly or on demand, compared with placebo on recovery of erectile function in men with ED following NSRP surgery.

2. Methods

2.1. Study design

This was a randomised, double-blind, double-dummy, multicentre, parallel group study conducted at 87 centres across Europe, the United States, Canada, and South Africa between 13 December 2004 and 26 September 2007. All patients provided written, informed consent. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and the principles of the Declaration of Helsinki.

Participants were recruited to the study provided they fulfilled the following criteria at screening: male, aged 18–64 yr, in a heterosexual relationship, and scheduled to undergo bilateral NSRP surgery within approximately 1 mo of screening; an interest in resuming sexual activity as soon as possible after surgery; normal preoperative erectile function (International Index of Erectile Function erectile function domain [IIEF-EF] score of ≥26 at screening without the use of therapy or devices for the improvement of erections and no previous use of therapy or devices for ED); historical total prostate-specific antigen (PSA) level <10 ng/ml; Gleason tumour score ≤7 on biopsy; no tumour perforation of the prostate capsule. At randomisation, all of the above criteria remained valid. In addition, an operating report of bilateral nerve-sparing during the prostatectomy procedure was required (which must have taken place within 1 mo of screening) together with no positive tumour margins, thus confirming lack of perforation of the prostate capsule by the tumour.

Patients were excluded from the study based on the exclusion criteria typically used in studies with PDE5 inhibitors for ED treatment [17].

The following exclusion criteria were applied immediately prior to randomisation: residual prostate cancer or requirement for radiotherapy or adjuvant therapy; need for further surgery due to haemorrhage; and urethral catheter expected to be in place for ≥3 wk due to anastomotic fistula.

The study design is illustrated in Fig. 1. Within 14 d of bilateral NSRP, eligible patients were randomised (in a 1:1:1
ratio) to receive either 9 mo of treatment with 10 mg nightly vardenafil (which could be decreased to 5 mg if required) plus on-demand placebo; 9 mo of treatment with flexible-dose (starting at 10 mg with the option to titrate to 5 mg or 20 mg), on-demand vardenafil plus nightly placebo; or 9 mo of treatment with nightly placebo plus on-demand placebo. Randomisation codes were computer generated by Bayer Schering Pharma, Germany. At the end of the 9-mo treatment period, all patients entered a 2-mo single-blind placebo washout period (with no devices) during which the dose could be up- or down-titrated by the investigator to preserve subject blinding. The open-label period of the study involved 2 mo of treatment with vardenafil on demand at a starting dose of 10 mg for 1 mo, after which the dose could be adjusted to either 5 or 20 mg.

Participants were required to make 11 study centre visits. Visits 1, 2, and 3 took place at screening (1 mo prior to surgery), at surgery, and at randomisation (within 14 d after surgery), respectively. Following initiation of treatment, visits 4, 5, 6, and 7 took place at months 1, 3, 6, and 9, respectively, during the 9-mo double-blind period. Visits 8 and 9 took place at months 10 and 11, respectively, during the single-blind placebo washout period. The final two visits took place at months 12 and 13 during the open-label on-demand period of the study.

2.2. Study population

The safety population consisted of any subject who took at least one dose of study medication and for whom post-medication safety data were collected. The intent-to-treat (ITT) population consisted of subjects who were valid for safety and had a baseline (1 mo presurgery) and one postbaseline measurement for at least one of the following at any double-blind visit: IIEF domains, SEP2, and SEP3 (all post-baseline only), Duke Health profile domains, or Center for Epidemiologic Studies Depression Scale (CES-D) total score. For inclusion in the analysis of the primary efficacy variable, subjects were required to have at least one IIEF-EF measurement during the single-blind placebo washout period. This population is referred to as the modified ITT (mITT). Analyses of all efficacy variables discussed were performed on this mITT population.

The study sample size was determined based on the assumption that 30% of placebo-treated subjects and 50–60% of vardenafil-treated subjects (in both treatment groups) would obtain IIEF-EF domain scores of ≥22 after 9 mo of treatment followed by 2 mo without treatment. Based on a 1:1:1 randomisation protocol for the three treatment groups, a total of approximately 372 subjects (124 per treatment group) were required to provide 90% power to detect a statistically significant difference between either of the vardenafil treatment groups and placebo.

2.3. Study assessments and statistical analyses

The primary efficacy variable was the percentage of subjects with an IIEF-EF score ≥22 (defined as mild ED) after the 2-mo washout period, as observed at last observation carried forward (LOCF). The primary comparison was the test for overall treatment differences among the three treatment groups. If found to be significant, pairwise comparisons between vardenafil nightly and placebo as well as vardenafil on demand and placebo would be performed. If both regimens were found to be superior to placebo, a secondary analysis would then be performed to test for superiority. Statistical significance was defined as p < 0.05.

Secondary efficacy variables included the difference among treatment groups in the percentage of subjects with an IIEF-EF score ≥22 at LOCF at the end of the double-blind treatment period and at the end of the open-label period. Data were further analysed for the percentage of patients with IIEF-EF scores ≥17 and ≥26 at LOCF for each period of the study. Statistical analyses were performed as per the primary efficacy variable. Mean per-patient success rates for Sexual Encounter Profile (SEP) questions 2 (“Were you able to insert your penis into your partner’s vagina?”) and 3 (“Did your erections last long enough for you to have successful
intercourse?”) were assessed cumulatively (overall) over the double-blind treatment period, single-blind washout period, and the open-label on-demand period. For the open-label period, SEP3 success rates are given as descriptive statistics only. Statistical analyses were performed using analysis of variance (ANOVA), with effects for treatment and country. For all secondary variables, statistical significance identified as \( p < 0.05 \) was considered nominally significant.

3. Results

3.1. Study population and baseline demographics

A total of 997 men were screened for the study, and 628 were randomised to treatment with placebo, nightly vardenafil, or on-demand vardenafil. In total, 423 patients completed the study. The most common reasons for discontinuation (percentage of subjects valid for safety) were withdrawal of consent (11%), adverse events (6%), and protocol violations (5%). The flow of participants throughout the study is shown in Fig. 2. Of the 628 patients randomised to treatment, 617 were eligible for the safety population, 599 for the ITT population, and 445 for the mITT population. The baseline demographic characteristics of the safety population were generally similar among all three treatment groups (Table 1).

3.2. Efficacy variables

3.2.1. Double-blind treatment period

A significantly greater proportion of patients in the vardenafil on demand group had IIEF-EF scores \( \geq 22 \) compared with those in the placebo group at all double-blind visits (\( p \leq 0.0001 \), data not shown). At double-blind LOCF, the proportions of patients with IIEF-EF scores \( \geq 22 \) were 24.8%, 32.0%, and 48.2% for the placebo, vardenafil nightly, and vardenafil on demand groups, respectively (\( p = 0.0001 \) for vardenafil on demand vs placebo; Fig. 3). The proportion of patients with an IIEF-EF score \( \geq 22 \) was also significantly greater in the vardenafil on demand group than in the vardenafil nightly group at several visits and at double-blind LOCF (\( p = 0.0065 \)). The proportions of patients with IIEF-EF scores \( \geq 26 \) at double-blind LOCF were 16.8%, 20.1% and 36.2%, respectively (\( p = 0.0003 \) for vardenafil vs placebo).

In response to the patient diary question SEP3, significantly greater mean per-patient success rates were observed with vardenafil on demand compared with placebo over the entire double-blind period, as demonstrated by the double-blind overall time point (45.9% versus 25.0%; \( p < 0.0001 \), Fig. 4). In addition, on-demand use of vardenafil also produced significantly greater mean SEP3 success rates than placebo at the double-blind LOCF time point (52.9% vs 31.1%; \( p < 0.0001 \)). Similarly, nightly vardenafil use was associated with significantly greater SEP3 success rates compared with placebo, as demonstrated by the double-blind period overall time point (34.5% versus 25.0%; \( p = 0.0344 \); Fig. 4).

3.2.2. Single-blind washout period

The primary efficacy variable was not met in this study. No statistically significant differences were observed among treatment groups in the percentage
of patients with an IIEF-EF score ≥22 at the end of the 2-mo washout period, as observed at LOCF. Following washout, IIEF-EF scores ≥22 were achieved in 28.9%, 24.1%, and 29.1% of patients for placebo, vardenafil nightly, and vardenafil on demand groups, respectively (Fig. 3).

During the single-blind washout period, there were also no significant differences among the three treatment groups in the proportion of patients with IIEF-EF scores ≥17 or ≥26. Mean per-patient success rates for intercourse completion, measured using SEP3, were not significantly different among treat-

Table 1 – Demographic characteristics of the safety population

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Placebo n = 206</th>
<th>Vardenafil nightly n = 207</th>
<th>Vardenafil on demand n = 204</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marital status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>185 (90)</td>
<td>181 (87)</td>
<td>188 (92)</td>
</tr>
<tr>
<td>Divorced</td>
<td>9 (4)</td>
<td>19 (9)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Widowed</td>
<td>6 (3)</td>
<td>3 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Never married</td>
<td>6 (3)</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>201 (98)</td>
<td>200 (97)</td>
<td>198 (97)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (2)</td>
<td>4 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Not determined</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mean age (yr)</strong></td>
<td>57.1</td>
<td>57.4</td>
<td>56.8</td>
</tr>
<tr>
<td><strong>Mean weight (kg)</strong></td>
<td>83.8</td>
<td>82.9</td>
<td>84.5</td>
</tr>
<tr>
<td><strong>Mean height (cm)</strong></td>
<td>176.0</td>
<td>176.7</td>
<td>176.9</td>
</tr>
<tr>
<td><strong>Mean BMI (kg/m²)</strong></td>
<td>27.0</td>
<td>26.5</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>Alcohol consumption, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>53 (26)</td>
<td>37 (18)</td>
<td>43 (21)</td>
</tr>
<tr>
<td>Light</td>
<td>111 (54)</td>
<td>134 (65)</td>
<td>131 (64)</td>
</tr>
<tr>
<td>Moderate</td>
<td>40 (19)</td>
<td>34 (16)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>Heavy</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Smoking status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>101 (49)</td>
<td>109 (53)</td>
<td>107 (53)</td>
</tr>
<tr>
<td>Passive smoker</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Past or present smoker</td>
<td>105 (51)</td>
<td>97 (47)</td>
<td>97 (48)</td>
</tr>
</tbody>
</table>

Overall percentages for each section may not total 100% due to rounding.
ment groups over the entire single-blind washout period (overall time point; Fig. 4).

### 3.2.3. Open-label on-demand period

During the open-label period, all patients used vardenafil on demand. There were no significant differences between the proportions of patients with IIEF-EF scores ≥22 at the open-label period LOCF, regardless of original treatment group. The proportions were 47.8%, 52.6%, and 54.2% for placebo, vardenafil nightly, and vardenafil on demand groups, respectively (Fig. 3). The proportions of patients with IIEF-EF scores ≥26 were 32.5%, 37.8%, and 39.9%, respectively. There were no significant differences among groups.

Mean SEP3 success rates at open-label LOCF were 57.1%, 59.8%, and 62.6% for patients who had previously taken placebo, vardenafil nightly, and vardenafil on demand (during the double-blind treatment period), respectively.

### 3.2.4. Adverse events

In total, 39 patients discontinued the study due to adverse events. There were no relevant differences between treatment groups in the percentage of patients that discontinued the study due to adverse events across treatment groups (placebo, 5%; vardenafil nightly, 8%; vardenafil on demand, 6%). The nature and overall incidence of adverse events during the double-blind period was similar between vardenafil nightly and on demand treatment groups (Table 2). Among the most common adverse events were headache, flushing, and nasopharyngitis. During the open-label period of the study, the incidences of adverse events were similar across treatment groups.

Two deaths occurred over the duration of the study, one prior to randomisation and the other 39 d after the final dose of study medication. Neither death was considered by the study investigators to be related to the study medication.

### 4. Discussion

This randomised, double-blind, double-dummy, parallel group, multicentre study investigated the efficacy and safety of two vardenafil treatment

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**Table 2 – Most common adverse events occurring during the double-blind period (safety population)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo n = 206</th>
<th>Vardenafil nightly n = 207</th>
<th>Vardenafil on demand n = 204</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, n (%)</td>
<td>115 (56)</td>
<td>141 (68)</td>
<td>136 (67)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (5)</td>
<td>21 (10)</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5 (2)</td>
<td>11 (5)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Flushing</td>
<td>3 (1)</td>
<td>13 (6)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (4)</td>
<td>14 (7)</td>
<td>13 (6)</td>
</tr>
</tbody>
</table>

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*Fig. 4 – Sexual Encounter Profile (SEP) question 3 patient success rates for the overall double-blind treatment and single-blind washout study periods.*
regimens versus placebo for the treatment of ED following bilateral NSRP surgery. This study recruited a large number of patients and was designed to reflect the real-life general population of patients who undergo NSRP surgery. This study was rigorous in design and blinding, and the inclusion of the on-demand dosing regimen enabled comparison of the currently recommended guidelines for the use of PDE5 inhibitors with a proposed nightly dosing regimen, which has been suggested to have potential rehabilitative effects on erectile function.

The results clearly show that nightly dosing with vardenafil did not have any effect beyond that of on-demand use. No statistically significant differences were observed among treatment groups in either the proportion of patients with mild or no ED (an IIEF-EF score ≥22) or in differences among groups in SEP3 success rates after the 2-mo single-blind washout period (where patients were taking placebo).

Importantly, this study showed that on-demand use of vardenafil during the double-blind treatment period was associated with significantly greater IIEF-EF scores at all double-blind visits compared with placebo as well as with significantly better SEP3 response rates over the entire double-blind treatment period. In addition, the IIEF-EF scores and SEP3 success rates were higher for the vardenafil on demand group compared with the nightly group. These data indicate that the use of on-demand vardenafil is of greater benefit than nightly treatment in patients following NSRP surgery, and, in general, support the on-demand use of PDE5 inhibitors following NSRP surgery over a daily dosing regimen. These findings are consistent with those of previous studies of vardenafil in this difficult-to-treat population of men with ED, which demonstrated significant improvements in key indices of erectile function following on-demand treatment [15,16].

During the open-label period of this study, mean SEP3 per-patient success rates of approximately 60% were achieved following 2 mo of on-demand vardenafil treatment, regardless of treatment group during the double-blind period, indicating that nerve preservation and end organ responsiveness are viable entities in a general urologic setting. This intercourse completion rate is considered favourable for post-NSRP surgery patients after 1 yr, further supporting the efficacy of vardenafil on demand in this difficult-to-treat population.

A recent study in 43 men with preserved nocturnal erections following unilateral or bilateral NSRP assessed the effect of nightly low-dose sildenafil use on erectile function. The results showed that, in this small patient group, sildenafil significantly improved IIEF-5 (the abridged 5-item version of the International Index of Erectile Function) scores and time to recovery of erectile function, compared with no treatment [12]. Clear limitations of the study are that it was not placebo-controlled and was performed at a single centre (a centre of surgical excellence), which does not reflect general worldwide urological practice. Furthermore, 95% of patients had nocturnal erections following catheter removal. This is not typical of the post-surgical situation in general urological practice. Another, earlier study suggested that nightly sildenafil use for 9 mo improved the return of spontaneous erections [14]. However, as with the aforementioned study, only a small number of patients were recruited, and the study design did not compare nightly dosing with the use of on-demand PDE5 inhibitor therapy. While these small pilot studies demonstrated proof of concept, a large multicentre study such as the present study was required to fully investigate the theory of the effects of nightly dosing.

The finding that on-demand dosing is more effective in improving both erectile function and sexual intercourse completion rates within this patient population prompts reconsideration of the current practice of prescribing nightly PDE5 inhibitor therapy, as on-demand use of vardenafil is equally effective in men with ED following NSRP.

5. Conclusions

In this study of men with ED following bilateral NSRP—a notoriously difficult-to-treat patient population—vardenafil was efficacious when used on demand according to the product label. In contrast to the prophylactic use of PDE5 inhibitors for penile rehabilitation and treatment of ED in men following NSRP surgery, this first robustly designed and evidence-based multicentre study provides data to support a paradigm shift towards on-demand dosing with PDE5 inhibitors for the treatment of ED in men in this patient group.

Author contributions:

- Study concept and design: Montorsi, Brock, Van Poppel, Graefen, Tiemo Bandel (Bayer HealthCare AG).
- Analysis and interpretation of data: JoAnn Shapiro (Bayer HealthCare Pharmaceuticals Inc.), Dieter Neuser (Bayer HealthCare AG).
- Drafting of the manuscript: Montorsi, Brock, Lee, Stief.
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References