Benign Prostatic Enlargement

A Randomised, Placebo-Controlled Study to Assess the Efficacy of Twice-Daily Vardenafil in the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

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**Abstract**

**Introduction:** Benign prostatic hyperplasia (BPH) is associated with bothersome lower urinary tract symptoms (LUTS) and reduced patient quality of life (QoL). Phosphodiesterase (type) 5 (PDE5) inhibitors such as vardenafil are commonly used for the treatment of erectile dysfunction (ED), but have also been shown to improve the symptoms of BPH. This randomised, double-blind, placebo-controlled study investigated the effects of vardenafil on LUTS and QoL in men with BPH/LUTS, with or without concomitant ED.

**Methods:** Men aged 45–64 yr with BPH/LUTS and an International Prostate Symptom Score (IPSS) ≥12 were randomised to receive either 10 mg vardenafil or placebo twice daily. LUTS were assessed with the use of two primary efficacy parameters, IPSS score and maximum urinary flow rate ($Q_{\text{max}}$), as well as postvoid residual (PVR) urine volume; ED was measured with the use of the erectile function (EF) domain score of the International Index of Erectile Function (IIEF-EF); and QoL was assessed with the Urolife\textsuperscript{TM} QoL-9 questionnaire.

**Results:** After 8 wk of treatment, there was a significant improvement in the IPSS total score in the vardenafil group compared with placebo (–5.9 and –3.6, respectively; $p = 0.0013$). Nominally significant improvements in irritative and obstructive IPSS subscores ($p = 0.0017$ and $p = 0.0081$, respectively), EF ($p = 0.0003$), and Urolife QoL-9 ($p < 0.0001$) were also associated with vardenafil treatment. $Q_{\text{max}}$ and PVR urine volume did not change significantly with treatment, although baseline values were already considered close to normal. Vardenafil was generally well tolerated, with most adverse events considered mild or moderate in severity.

**Conclusions:** Vardenafil treatment significantly improved LUTS, EF, and QoL in men with BPH/LUTS. Vardenafil may be considered a promising treatment option for men with symptoms secondary to BPH.

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1. Introduction

Benign prostatic hyperplasia (BPH) is typically characterised by enlargement of the prostate gland, constriction of the urethra, and the emergence of moderate-to-severe lower urinary tract symptoms (LUTS). It is most prevalent in ageing males, with 50% of men aged 51–60 yr and 90% of men aged 81–90 yr demonstrating histological evidence of BPH, characterized by epithelial and fibromuscular hyperplasia in the transition zone and periurethral areas of the prostate [1,2]. The primary risk factor for BPH is increasing age. Although a variety of other factors have been proposed as affecting the risk of BPH (e.g., obesity, sexual activity, hypertension, smoking, socioeconomic status, ethnicity), no compelling evidence for these has been reported [3,4].

LUTS associated with BPH are bothersome and can disrupt normal daily activities. Irritative LUTS include increased urinary frequency, urgency, and nocturia, whereas obstructive symptoms may comprise incomplete bladder emptying, intermittent urinary flow, a weak urinary stream, and straining to void. The symptoms associated with BPH can have a substantial impact on the quality of life (QoL) of patients, with disruption to sleep, mobility, leisure pursuits, and sexual activities particularly disturbing for patients [5,6]. BPH is often accompanied by age-related comorbidities such as erectile dysfunction (ED), cardiovascular disease, and metabolic syndrome [7,8].

Current medical treatment options for BPH include 5-alpha reductase inhibitors, which block the conversion of testosterone to the more potent dihydrotestosterone, and alpha-adrenergic receptor antagonists, which affect smooth muscle tone by lowering increased sympathetic adrenergic activity, a common contributory factor to BPH symptoms [9]. Nonpharmacological options include transurethral prostatectomy and minimally invasive surgery; however, there are risk factors associated with prostate surgery such as hemorrhage, retrograde ejaculation, and further surgical interventions [10].

Phosphodiesterase (PDE) enzymes are involved in the regulation of the nitric oxide (NO)–cyclic GMP–protein kinase pathway and hence influence smooth muscle tone; the presence of these androgen-regulated enzymes in the urogenital tract is well-known [11,12]. Vardenafil is a PDE (type 5) (PDE5) inhibitor registered for symptomatic, on-demand treatment of ED [13]. PDE5 inhibitors have been shown to inhibit prostate stromal cell proliferation in vitro [14]. Furthermore, these agents have demonstrated the potential to induce relaxation of bladder, urethral, and prostatic smooth muscle, and to relieve the irritative symptoms of BPH in vivo [14,15]. There is increasing evidence to support the clinical use of PDE5 inhibitors for relief from LUTS, and randomised, placebo-controlled trials have been performed with sildenafil and tadalafil in this setting [16,17].

The present report describes the first randomised, double-blind, placebo-controlled, study to investigate the effects of twice-daily treatment with vardenafil on irritative and obstructive LUTS as well as QoL in men with BPH/LUTS.

2. Methods

2.1. Study design

This was a randomised, double-blind, placebo-controlled, parallel group, phase 2b, study conducted at 16 centres in Germany between October 2005 and June 2006. The study was conducted in accordance with the guidelines of the International Conference on Harmonisation/World Health Organization Good Clinical Practice standards and the principles of the Declaration of Helsinki. Also, at each centre, the protocol was approved by the appropriate independent ethics committee or institutional review board before commencement of the study.

Men aged 45–64 yr with a history of BPH/LUTS for at least 6 mo before commencing the study and an International Prostate Symptom Score (IPSS) ≥12 at screening were enrolled, and underwent randomised allocation to either 10 mg vardenafil or a matched placebo tablet twice daily (with a 12-h dosing interval). Upon enrolment, patients entered a 4-wk run-in phase, during which no study medication was administered. This was a non-pivotal proof-of-concept study, and a rapid onset of action in terms of LUTS was expected during the treatment phase. A single-blind placebo run-in aiming for limitation of the placebo effect was not included; instead a significant treatment effect versus placebo at end point was assumed to be determined in spite and on top of a placebo effect. Randomisation was subsequently performed according to a code generated by the Biometry Administration Group of Global Biometry at Bayer HealthCare, Germany, by using balanced blocks of treatment group allocation and a 1:1 ratio between the two treatment groups. The packaging site was provided with a copy of the randomisation code, and investigators received sealed, patient-specific “code-break” envelopes. All patients provided written, informed consent before beginning the study.

The main exclusion criteria were contraindications to vardenafil, spinal cord injury, prostatitis, history of prostate or bladder cancer, bladder or urethra stricture, urinary retention (postvoid residual [PVR] volume ≥100 ml), pelvic trauma or surgery, history of any malignancies, and life expectancy of less than 3 yr. Concomitant use of nitrates or NO donors, androgens or anti-androgens, anticoagulants, cytochrome P-450 3A4 inhibitors, any treatment for ED or alpha1-adrenoceptor antagonists was prohibited. (Patients receiving...
alpha1-adrenoceptor antagonists before the study were eligible to participate, provided they had been on a constant dose for at least the previous month and were willing to withdraw from the medication for the duration of the study.) If alpha-blockers were withdrawn at screening, subjects would fail to be eligible for study drug treatment in case of deterioration of any BPH-related symptom during the run-in period (in the opinion of the investigator). Previous or current use of 5-alpha-reductase inhibitors was prohibited. Assessments were carried out 4 and 8 wk after treatment allocation; the maximum treatment duration was 8 wk. Baseline values for all patients were obtained before treatment (at the end of the run-in period).

2.2. Study assessments

The primary efficacy variables of the study were the IPSS total score and the maximum urinary flow rate (Qmax). Secondary variables were the IPSS irritative (storage—frequency, urgency, nocturia) and obstructive (voiding—incomplete emptying, intermittency, weak stream, straining) subscores (in line with American Urological Association terminology [18]), PVR urine volume, Benign Prostatic Hyperplasia Quality of Life Questionnaire 9 (UrolifeTM) (QoL-9) [19] and the erectile function (EF) domain score of the International Index of Erectile Function (IIEF-EF) [20].

Safety assessments included the monitoring of adverse events (AEs), laboratory parameters, and electrocardiogram (ECG) abnormalities.

2.3. Statistical analyses

The sample size estimation was based on the intention to test two primary efficacy variables in a step-down manner. First the IPSS total score was assessed and, if this was significant, then Qmax was analysed. The estimated sample size provided a power of approximately 80% for each test. Clinically relevant differences were assumed to be 2.2 points (IPSS) and 2 ml/s (Qmax). Analyses for the secondary variables were descriptive and, as such, significance levels were reported as nominal values without any adjustments for multiplicity. Therefore, any significant differences in the secondary variables are referred to as nominally statistically significant.

Efficacy data were analysed for the intention-to-treat (ITT) population—that is, those patients with post-treatment efficacy data—by using a last observation carried forward
A least square (LS) mean with 95% confidence intervals (95%CIs), unless otherwise stated.

Adverse events and laboratory abnormalities were assessed in the safety population—that is, those patients who received at least one dose of vardenafil or placebo.

3. Results

3.1. Study population

The total number of patients enrolled was 222, with 109 randomised to the vardenafil group and 113 to the placebo group (Fig. 1). One patient in the vardenafil group did not receive any medication; therefore, 221 patients were included in the safety population. Six patients did not provide any post-treatment efficacy data; therefore, the ITT population consisted of 215 patients (105 randomised to vardenafil and 110 to placebo). There were minimal differences in the baseline characteristics of the patients allocated to either treatment group (Table 1), and there were little differences in concomitant medications taken between the treatment groups. A total of 10 patients in the vardenafil

### Table 1 - Patients' baseline characteristics (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Vardenafil (n = 108)</th>
<th>Placebo (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.5 ± 5.4</td>
<td>55.4 ± 5.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.3 ± 13.3</td>
<td>85.9 ± 11.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.7 ± 3.9</td>
<td>27.0 ± 3.5</td>
</tr>
<tr>
<td>Ethnicity (n [%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>108 (100%)</td>
<td>111 (98.2%)</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (0.9%)</td>
</tr>
</tbody>
</table>

Values are mean (±SD) unless stated otherwise.

![IPSS score (least square mean)](image)

**Fig. 2** - The least square mean International Prostate Symptom Score (IPSS) total score for the vardenafil and placebo groups (intention-to-treat [ITT] population). A reduced score indicates an improvement in lower urinary tract symptoms (LUTS). * The p value indicates a significant change from baseline for vardenafil versus placebo as analysed with the use of analysis of covariance.

### Table 2 - Efficacy variables for the two treatment groups, at baseline and the end of the 8-wk treatment period

<table>
<thead>
<tr>
<th></th>
<th>Vardenafil (n = 104)</th>
<th>Placebo (n = 110)</th>
<th>Between-group difference in change from baseline (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPSS total score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>16.8</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>8 wk</td>
<td>11.0</td>
<td>13.2</td>
<td>2.3 (0.90–3.64) * p = 0.0013</td>
</tr>
<tr>
<td><strong>IPSS irritative score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.6</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>8 wk</td>
<td>4.9</td>
<td>5.9</td>
<td>1.0 (0.37–1.57) * p (nominal) = 0.0017</td>
</tr>
<tr>
<td><strong>IPSS obstructive score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.3</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>8 wk</td>
<td>6.1</td>
<td>7.4</td>
<td>1.3 (0.34–2.25) * p (nominal) = 0.0081</td>
</tr>
<tr>
<td><strong>Qmax</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>15.9</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>8 wk</td>
<td>17.5</td>
<td>16.9</td>
<td>−0.6 (−2.62 to 1.43) * p = 0.5614</td>
</tr>
<tr>
<td><strong>PVR volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.0</td>
<td>26.9</td>
<td></td>
</tr>
<tr>
<td>8 wk</td>
<td>27.0</td>
<td>28.8</td>
<td>1.8 (−7.39 to 10.99) * p (nominal) = 0.6994</td>
</tr>
<tr>
<td><strong>IIEF-EF score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>15.9</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>8 wk</td>
<td>23.4</td>
<td>17.4</td>
<td>−6.0 (−7.77 to −4.16) * p (nominal) = 0.0001</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; PVR, postvoid residual; IIEF-EF, International Index of Erectile Function-Erectile Function (domain). All values are least square means.
group and 12 in the placebo group had received treatments for genitourinary system disorders before randomisation.

### 3.2. Efficacy

Baseline IPSS total scores did not differ significantly between the two treatment groups; however, 8-wk treatment with vardenafil was associated with a significant improvement in IPSS scores compared with placebo (5.9 and 3.6 point reduction, respectively; difference = 2.3 [95%CI, 0.90 – 3.64]; p = 0.0013; Fig. 2 and Table 2). The LS mean baseline Qmax values were 15.9 ml/s for the vardenafil and placebo groups. There were small improvements in Qmax in the vardenafil and placebo groups (+1.6 ml/s and +1.0 ml/s respectively; difference = –0.6 [95%CI, –2.62 to 1.43]); however, there was no significant difference between the two groups (p = 0.5614; Table 2).

When the IPSS total score was separated into the obstructive and irritative scores, the vardenafil group retained a nominally statistically significant treatment advantage compared with placebo (p = 0.0081 and p = 0.0017, respectively; Fig. 3 and Table 2).

The LS mean baseline PVR urine volume was 28.0 ml for the vardenafil group and 26.9 ml for the placebo group. The change in PVR volume from baseline after 8 wk did not differ significantly between the vardenafil and placebo groups (–1.0 ml and 1.9 ml, respectively; difference = 1.8 [95%CI, –7.39 to 10.99]; p = 0.6994; Table 2).

There was a nominally statistically significant improvement in erectile function after 8 wk in the vardenafil group versus the placebo group, as assessed by the IIEF-EF score, with a 7.5 point increase in the vardenafil group and a 1.5 point increase in the placebo from baseline (difference = –6.0 [95%CI, –7.77 to –4.16]; p = 0.0001; Fig. 4 and Table 2).

Vardenafil treatment was associated with a nominally statistically significant improvement in the total Urolife QoL-9 score compared with placebo (difference = –9.3 [95%CI, –12.79 to –5.71]; p < 0.0001). In particular the “interference with activities” and the “perceived sexual life” subscores demonstrated nominally statistically significant improvements from baseline after 8 wk of vardenafil treatment (p = 0.0059 and p < 0.0001, respectively; Fig. 5). There was no significant improvement in the “well-being” subscore for the vardenafil group compared with placebo (p = 0.0980).

### 3.3. Safety

Overall, AEs were reported in 32 patients in the vardenafil group (29.6%) and in 18 patients in the placebo group (15.9%). The most common treatment-emergent AEs were headaches, flushing, and...
dyspepsia (Table 3). Two patients in the vardenafil group and three in the placebo group experienced serious AEs. The serious AEs reported in the vardenafil group were myocardial infarction, chest pain, and cardiac rehabilitation therapy (all occurring in the same patient), and hypertensive crisis; haematochezia, a meniscus injury, and knee surgery occurred in the placebo group. None of the serious AEs was considered to be related to the study medication.

Mean laboratory parameters were within the normal ranges at all times, and changes in these parameters during the study were minor and not considered clinically relevant. During the treatment phase, four patients demonstrated ECG abnormalities for which a history of previous myocardial infarction could not be ruled out; however, no other clinical signs were exhibited. Only one of these patients received vardenafil; thus, there was no obvious relationship between ECG abnormalities and vardenafil administration.

### Discussion

The results from this study demonstrate that treatment with vardenafil significantly improves LUTS, ED, and QoL in men with BPH/LUTS. The data presented are consistent with preclinical literature for vardenafil [14,15] and recently published in vivo data for other PDE5 inhibitors [16,17].

The total IPSS score and obstructive and irritative IPSS subscores were significantly improved after vardenafil therapy compared with placebo. Because this was a proof-of-concept study, there was no placebo run-in phase, which may be considered standard methodology in BPH clinical trials; despite the omission of this phase, a significant improvement was seen in the IPSS score over and above any placebo effects that may have occurred. Improvements in the IPSS total score with vardenafil reported in the current study (mean difference vs. placebo, −2.3 points) are similar to those reported for the alpha-adrenergic receptor antagonists, alfo-

### Table 3 – Treatment-emergent adverse events affecting at least 2% of patients receiving either vardenafil or placebo (safety population)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Vardenafil (n = 108)</th>
<th>Placebo (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>32 (29.6%)</td>
<td>18 (15.9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (13.0%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (7.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>7 (6.5%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (4.6%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Gastrointestinal reflux disease</td>
<td>3 (2.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (2.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values shown are the number of patients affected (%).
The improvements in LUTS seen in the current study concur with data from other studies of PDE5 inhibitors in men with BPH [16,17]. The first of these studies evaluated once-daily sildenafil in men aged >45 yr with an IIEF-EF score <25 and IPSS ≥12; after 12 wk, sildenafil produced significantly greater improvement in IPSS than placebo (−6.32 vs. −1.93, p < 0.0001) [16]. In the second study, men with LUTS secondary to BPH demonstrated significantly greater improvement after 12 wk of therapy with once-daily tadalafil versus placebo (−3.8 vs. −1.7; −7.1 vs. −4.5 when the run-in period was included) [17]. The varying dosing regimens, treatment durations, and patient populations involved in the available studies, however, mean that well-designed comparator studies are necessary before accurate comparisons between PDE5 inhibitors can be made. Despite this, the current study adds to the increasing body of evidence suggesting that PDE5 inhibitors could have an active role in the treatment of LUTS associated with BPH, most likely through the NO–cyclic GMP pathway, because PDE isoforms and NO have been identified in prostate tissue [12,23].

Although there were small improvements in Qmax in both vardenafil- and placebo-treated patients, no significant treatment difference emerged. These findings mirror the effects of other PDE5 inhibitors (tadalafil and sildenafil) on urinary flow rate in men with BPH [16,17]. In the current study there was no upper limit for patients’ Qmax, and baseline Qmax values were close to normal. Thus, an obstruction-lowering effect of the PDE5 inhibitor, vardenafil, may not be expected in the population studied. In addition, because of the age restrictions on the current label for vardenafil, the upper age limit of patients in this study (64 yr) may have prevented entry into the study of a proportion of the clinical population of men with BPH/LUTS. Consequently, recruitment of patients with a lower mean baseline Qmax value and a greater upper age limit may be necessary to better assess the efficacy of vardenafil for BPH/LUTS.

Vardenafil was administered at a dose of 10 mg twice daily in this study. This regimen was chosen on the basis that the 10-mg dose is generally effective in the treatment of ED, but is well below the maximum permitted dose of 20 mg [24]. Also, although the half-life of vardenafil is 4–5 h, experience indicates that it is effective for up to 12 h after administration [24]. Thus, the present twice-daily dosage was chosen to provide continuous effectiveness and favourable tolerability, without causing drug accumulation.

The data presented here and those reported in previous studies on PDE5 inhibitors have consistently demonstrated significant beneficial effects of treatment on LUTS as measured with the use of the IPSS questionnaire [16,17]. However, measurements of Qmax and PVR urine volume have not revealed significant treatment effects on bladder outlet obstruction. It remains unclear whether this finding is due to the lack of a clinically meaningful effect on bladder outlet obstruction, or if it is a reflection of the patient populations recruited in these studies. As with the current study, the studies on sildenafil and tadalafil reported by McVary and colleagues [16,17] recruited patients with baseline Qmax values close to normal levels. Although the NO–cyclic GMP pathway is likely to be important, the precise action of PDE5 inhibitors on smooth muscle, urothelium, and sympathetic adrenergic tone is not known; further studies are required to elucidate the mechanism of action of PDE5 inhibitors on LUTS and bladder outlet obstruction. A future study of the clinical effect of PDE5 inhibitors in selected patients with LUTS, benign prostatic enlargement, and decreased urinary flow rates may provide some insight in this respect.

A significant improvement in erectile function was also associated with vardenafil treatment in the current study. This finding is unsurprising considering vardenafil’s role as a first-line treatment for ED [13]. Whereas the presence of ED was not an inclusion criterion, approximately 60% of patients reported ejaculatory problems or ED before starting the present study, although baseline IIEF-EF scores (15.9 in both treatment groups) were higher than those reported in previous studies of vardenafil in men with severe ED [25,26]. ED is a common comorbidity in men with BPH, with approximately 30% of men with ED demonstrating evidence of BPH [6]. Donatucci et al (2004) [25] reported that 37–41% of BPH patients had a baseline IIEF-EF score ≤10, a score representative of severe dysfunction. Whereas a direct causal link between BPH and ED has not been identified, epidemiological data suggest that these two conditions are associated [8,27]. In addition, rho-kinase activity, increased sympathetic tone, and changes to the NO–cyclic GMP pathway in prostatic and corpus cavernosum tissue are thought to be contributing factors to both conditions [27]. Here, vardenafil demonstrated efficacy for the treatment of both LUTS and ED, suggesting that it may represent an efficacious treatment option for men with BPH/LUTS and concomitant ED.
QoL is!an important consideration when treating BPH [5]; this parameter was assessed in the current study with the Urolife QoL-9 questionnaire. Significant improvements in QoL were observed after treatment with vardenafil. Most notable of which were improvements in subscores representative of QoL factors considered particularly important by men with BPH/LUTS (i.e., “interference with activities”, “perceived sexual life”) [5]. Improved self-esteem in patients has also been reported after vardenafil treatment in men with ED [28]. The significant improvement in the “interference in activities” subscore suggests that vardenafil not only improves sexual function but also those daily activities that are commonly affected by LUTS.

Vardenafil was generally well tolerated in men with LUTS, and the AE profile was consistent with those previously reported for other PDE5 inhibitors [29]. Most AEs were considered mild or moderate in severity, with the number of serious AEs comparable between the vardenafil and placebo groups. Serious AEs seen in the present study were not considered related to the medication.

It is too soon to consider details of the potential role for PDE5 inhibitors in the management of patients with symptomatic BPH. However, the fact that these agents generate improvement in erectile function as well as LUTS suggests that they might be of particular value in patients with both these conditions. Further data are clearly required to ascertain the risk–benefit profile of PDE5 inhibitors relative to the existing treatment options for patients with LUTS.

5. Conclusions

Treatment with vardenafil therapy was well tolerated and significantly improved LUTS, erectile function, and QoL in men with BPH/LUTS. With its favourable safety and efficacy profiles, vardenafil may be considered a promising treatment option for men with symptoms secondary to BPH.

**Author contributions:** Christian G. Stief 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.

**Study concept and design:** Stief, Porst, Ulbrich, Beneke, Neuser.
**Acquisition of data:** Stief, Porst.
**Analysis and interpretation of data:** Stief, Porst, Ulbrich, Beneke, Neuser.
**Drafting of the manuscript:** Stief, Porst, Ulbrich, Beneke, Neuser.
**Critical revision of the manuscript for important intellectual content:** Stief, Porst, Ulbrich, Beneke, Neuser.
**Statistical analysis:** Beneke.

**Obtaining funding:** Ulbrich, Beneke, Neuser, Stief, Porst.
**Administrative, technical, or material support:** Ulbrich, Beneke, Neuser.
**Supervision:** Stief, Ulbrich.
**Other (specify):** none.

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