Effect of silodosin on specific urinary symptoms associated with benign prostatic hyperplasia: analysis of international prostate symptom scores in 2 phase III clinical studies

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Purpose: Pooled results from 2 randomized, placebo-controlled, US phase III studies (NCT00224107, NCT00224120) showed that silodosin, a uroselective α-blocker, significantly improved International Prostate Symptom Scores (IPSS) in men with symptomatic benign prostatic hyperplasia (BPH). This analysis evaluated the effect of silodosin on each symptom assessed by IPSS questionnaire.

Materials and methods: Study participants (N = 923) were men aged ≥50 years with IPSS ≥13 and Qmax 4–15 mL/s. They received silodosin 8 mg or placebo once daily for 12 weeks. Patient responses to 7 IPSS questions were collected at weeks 0 (baseline), 0.5, 1, 2, 4, and 12 and scored on a 6-point scale. Efficacy of silodosin versus placebo was assessed by analysis of covariance.

Results: For each symptom, the 2 treatment groups had similar mean baseline scores. Decrease in score from baseline (mean ± standard deviation) to last observation was significantly greater with silodosin than with placebo for all symptoms (P < 0.005); symptom improvement with silodosin (versus placebo) was greatest for weak stream (silodosin, −1.1 ± 1.4 versus placebo, −0.5 ± 1.2; P < 0.0001) and smallest for nocturia (silodosin, −0.6 ± 1.1 versus placebo, −0.4 ± 1.2; P = 0.0037). Compared with placebo, silodosin significantly improved nocturia within 1 week (silodosin, −0.5 ± 1.07 versus placebo, −0.3 ± 1.05; P = 0.009) and all other symptoms within 3 to 4 days (P < 0.01).

Conclusions: Silodosin significantly improved all BPH-associated symptoms assessed by IPSS questionnaire within the first week of treatment. All improvements were maintained over the 12-week study period.

Keywords: BPH, symptoms, rapid onset, silodosin, α1A-adrenoceptor antagonist

Introduction
Benign prostatic hyperplasia (BPH) is a chronic condition often associated with lower urinary tract symptoms (LUTS). The severity of BPH-related LUTS appears to depend, at least in part, on smooth muscle tone in the prostate and bladder neck, which is mediated by α1A-adrenoceptors. α-Blockers (α1-adrenoceptor antagonists) have become the therapy of choice for patients with BPH-related LUTS because they provide effective symptom relief, are generally well tolerated, and are relatively inexpensive. However, α-blockers vary in their propensity to cause blood pressure-related adverse events, which have been attributed to the blockade of α1B-adrenoceptors in arterial vessels.
Silodosin is an ρ-blocker that recently has been approved in the United States (US) for treatment of the signs and symptoms of BPH. The pharmacological properties of silodosin are characterized by an exceptionally high selectivity for the ρ₁A versus ρ₁B adrenoceptor subtype.6,7 Moreover, silodosin has been shown to be highly selective for prostatic versus vascular tissue.8–10 Consistent with this observation, results from phase III clinical studies suggest that silodosin carries minimal risk for orthostatic hypotension and overall has excellent cardiovascular tolerability.11,12

Combined efficacy results from the phase III clinical studies showed that silodosin can promote rapid and significant improvement in BPH-associated urinary symptoms and peak urinary flow rate and can substantially improve LUTS-related quality of life.11 Overall symptom improvement was evaluated on the basis of aggregate patient scores for 7 distinct symptoms addressed by the International Prostate Symptom Score (IPSS) questionnaire. This post hoc analysis determined the effect of silodosin on each of the 7 symptoms.

Materials and methods
Patients and study design
This post hoc analysis of combined data from two 12-week randomized, double-blind, placebo-controlled US studies (NCT00224107, NCT00224120, at www.clinicaltrials.gov) evaluated the efficacy and safety of silodosin for the treatment of signs and symptoms of BPH. The study has been described in detail and overall results published.11 Briefly, study participants were at least 50 years of age with an IPSS greater than 13, a peak urinary flow rate (Qmax) of 4 to 15 mL/s, and a postvoid residual volume less than 250 mL. Patients first received single-blind treatment with placebo or silodosin 8 mg once daily for 1 week (week 0.5). Eligible patients were randomly assigned (1:1) to double-blind treatment with placebo or silodosin 8 mg once daily with breakfast for 12 weeks. The primary end point was the change in IPSS from baseline to the last observation. IPSS was assessed during clinical visits at weeks 0 (baseline), 1, 2, 4, and 12 and by phone interview on day 3 or 4 of the placebo run-in period were excluded from randomization.

Baseline, mean (SD) Silodosin (n = 466) Placebo (n = 457)
Irritative symptoms
Frequency (Q2) 3.5 (1.10) 3.5 (1.05)
Urgency (Q4) 3.0 (1.32) 3.0 (1.27)
Nocturia (Q7) 2.8 (1.19) 2.8 (1.19)
Obstructive symptoms
Incomplete emptying (Q1) 3.1 (1.27) 3.1 (1.25)
Intermittency (Q3) 3.1 (1.25) 3.1 (1.31)
Weak stream (Q5) 3.6 (1.16) 3.6 (1.16)
Straining (Q6) 2.2 (1.43) 2.2 (1.37)

Abbreviations: IPSS, International Prostate Symptom Scores; Q, question; SD, standard deviation.

Analysis
This post hoc analysis evaluated changes in individual symptom scores as assessed by IPSS questions. All randomized study participants (N = 923) who provided baseline data for the primary efficacy variable (total IPSS) were included in the analysis; 466 patients received silodosin and 457 received placebo.11 The IPSS questionnaire assesses 7 distinct urinary symptoms. Frequency (question [Q2]), urgency (Q4), and nocturia (Q7) are classified as irritative symptoms. Incomplete emptying (Q1), intermittency (Q3), weak stream (Q5), and straining (Q6) are classified as obstructive symptoms. Severity of each symptom is scored on a 6-point scale.11

Mean changes in score from baseline with 95% confidence intervals (CIs) were calculated for observed cases at each time point. For additional analyses at week 12, the last post-baseline observation was carried forward to impute missing data. Comparison of treatment effects was performed by analysis of covariance (ANCOVA), with baseline as a covariate. No adjustments were made for multiple statistical comparisons. ANCOVA results were reported as P values (for the test of null hypothesis of no difference between treatments). A 2-sided significance level of 5% was applied to all statistical tests.

Results
For each IPSS symptom, mean baseline values for the silodosin and placebo groups were similar (Table 1). Mean baseline scores ranged from 2.2 points for straining to 3.6 points for weak stream (Table 1). For each IPSS symptom, improvement from baseline to week 12 (last observation carried forward) was significantly greater in patients who received silodosin than in those who received placebo (Table 2). The difference between silodosin-related and placebo-related mean changes from baseline to week 12 (last observation carried forward) was smallest for nocturia (0.2 points) and greatest for weak stream (0.6 points) (Table 2).
All symptom improvements occurred rapidly. Maximum or close to maximum improvement with silodosin versus placebo was achieved at 0.5 or 1 week (Figure 1). For all IPSS symptoms except nocturia, the difference in improvement between silodosin and placebo treatment groups was significant at week 0.5 (observed cases). For nocturia, the difference between treatments was significant at week 1 (Table 2). Symptom improvement with silodosin, expressed as mean percentage reduction in IPSS from baseline to the last observation, ranged from 16.7% for nocturia to 38.2% for straining. Mean symptom improvement was 20.7% and 24.0% for frequency and urgency, respectively, and 25.2% (incomplete emptying) or greater for all obstructive symptoms (Figure 2). In contrast, mean symptom improvement with placebo was 10.9% (frequency) or less for irritative symptoms and 16.9% (straining) or less for obstructive symptoms (Figure 2).

Discussion
Combined efficacy data from 2 phase III studies with a total of 923 patients demonstrated that once-daily administration of silodosin 8 mg rapidly led to significant improvement

![Figure 1](https://www.dovepress.com/)

**Figure 1** Change from baseline (week 0) in score for specific International Prostate Symptom Score (IPSS) irritative (A) or obstructive (B) symptoms. Error bars indicate 95% confidence intervals.

**Abbreviations:** BL, baseline; CFB, change from baseline; LO, last observation after baseline.
in total IPSS and irritative and obstructive symptom sub-
scores\textsuperscript{11} and statistically significant improvement (versus
placebo) in each of the 7 individual symptoms assessed
by the IPSS questionnaire. Except for nocturia, significant
improvement was achieved by day 3 or 4 – the earliest
assessment time point after treatment initiation. Nocturia
improved significantly within 1 week of treatment initiation.
A previous analysis of patients’ responses to IPSS Q8, which
assesses quality of life related to BPH-associated urinary
symptoms, showed that patients who received silodosin
generally experienced substantially greater improvement
in symptom-related quality of life than those who received
placebo.\textsuperscript{11}

Given that IPSS subscores for specific symptoms usual-
ly are not reported for individual patients, the clinical
significance of some of the improvements demonstrated
by our analysis is difficult to gauge. Consideration of
whether a treatment effect is clinically meaningful is furth-
er complicated by the magnitude of positive placebo effect
that is often seen when BPH-related LUTS are assessed
by questionnaire.\textsuperscript{14} Validation of the original American
Urological Association symptom index, which comprises
the 7 symptom-related items of the IPSS, showed a vari-
able degree of correlation of each item with the overall
score, ranging from 0.54 to 0.83.\textsuperscript{13} The study recorded
mean changes in scores following prostatectomy of $-1.5$
(frequency), $-1.0$ (urgency), $-0.8$ (nocturia), $-1.5$ (empty-
ning), $-1.8$ (intermittency), $-2.4$ (weak stream), and $-1.6$
(hesitancy).\textsuperscript{13} In light of these data, the mean changes from
baseline to week 12 observed in our study appear to be of
clinical significance, particularly those observed for all
irritative symptoms (Table 2). Reductions over 12 weeks
in total IPSS were 6.4 points for silodosin and 3.5 points
for placebo.\textsuperscript{11} This illustrates a highly significant treatment
effect of silodosin in terms of statistical significance com-
pared with the placebo effect\textsuperscript{11} and clinically meaningful
symptom improvement.\textsuperscript{15} In this post hoc analysis, silodosin
on average improved each symptom score (except that for
nocturia) by 21% to 38% over the baseline score. These
values are substantially higher than the corresponding
values for placebo (8.8% to 17%).

\begin{table}
\centering
\textbf{Table 2 Differences in treatment-related IPSS changes from baseline}\textsuperscript{a}
\begin{tabular}{lllll}
\hline
\textbf{IPSS questions} & \textbf{Week} & \textbf{Change from baseline, mean (SD)} & \textbf{Silodosin (n = 466)} & \textbf{Placebo (n = 457)} & \textbf{P value}\textsuperscript{b} \\
\hline
\textbf{Irritative symptoms} & & & & & \\
\text{Frequency (Q2)} & 0.5 & $-0.5 (1.08)$ & $-0.3 (0.96)$ & & 0.0002 \\
& 12 & $-0.9 (1.34)$ & $-0.5 (1.16)$ & & $<0.0001$ \\
\text{Urgency (Q4)} & 0.5 & $-0.4 (1.21)$ & $-0.3 (1.14)$ & & 0.0075 \\
& 12 & $-0.8 (1.36)$ & $-0.4 (1.27)$ & & $<0.0001$ \\
\text{Nocturia (Q7)} & 0.5 & $-0.4 (1.06)$ & $-0.3 (1.03)$ & & 0.0968 \\
& 1 & $-0.5 (1.07)$ & $-0.3 (1.05)$ & & 0.0091 \\
& 12 & $-0.6 (1.14)$ & $-0.4 (1.15)$ & & 0.0037 \\
\textbf{Obstructive symptoms} & & & & & \\
\text{Incomplete emptying (Q1)} & 0.5 & $-0.6 (1.14)$ & $-0.3 (0.97)$ & & $<0.0001$ \\
& 12 & $-0.9 (1.42)$ & $-0.6 (1.22)$ & & $<0.0001$ \\
\text{Intermittency (Q3)} & 0.5 & $-0.7 (1.19)$ & $-0.4 (1.10)$ & & 0.0002 \\
& 12 & $-1.1 (1.41)$ & $-0.6 (1.33)$ & & $<0.0001$ \\
\text{Weak stream (Q5)} & 0.5 & $-0.8 (1.29)$ & $-0.4 (1.03)$ & & $<0.0001$ \\
& 12 & $-1.1 (1.41)$ & $-0.5 (1.21)$ & & $<0.0001$ \\
\text{Straining (Q6)} & 0.5 & $-0.7 (1.16)$ & $-0.3 (1.21)$ & & $<0.0001$ \\
& 12 & $-0.9 (1.32)$ & $-0.5 (1.24)$ & & $<0.0001$ \\
\hline
\end{tabular}
\textsuperscript{a}Week 12 (last observation carried forward); \textsuperscript{b}Silodosin versus placebo.
\textbf{Abbreviations:} IPSS, International Prostate Symptom Score; Q, question; SD, standard deviation.
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Symptom improvement (mean reduction in International Prostate Symptom Scores [IPSS] from baseline to last observation) as a percentage of baseline values.}
\end{figure}
The results of this analysis support previous observations that silodosin is a fast-acting agent that provides significant BPH symptom relief within a few days. The short duration of the study precludes evaluation of the long-term effect (beyond 12 weeks) of silodosin on each of the 7 IPSS symptoms. In a 40-week open-label extension of the 2 placebo-controlled phase III studies of silodosin, patients who had received silodosin in the double-blind studies on average maintained symptom improvement with continued silodosin treatment during the open-label study. In the open-label study, symptoms also were assessed by IPSS total score and IPSS irritative and obstructive subscores.

**Conclusion**

Silodosin, a highly uroselective α-blocker, rapidly and significantly improved all irritative and obstructive BPH-related symptoms assessed by the IPSS questionnaire, and the improvements were maintained over the study period of 12 weeks. Together with the previously reported evidence of its efficacy and excellent cardiovascular tolerability, our results support consideration of silodosin as a valuable new treatment option for patients with symptomatic BPH.

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**Disclosure**

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