

# Effect of estimated prostate volume on silodosin-mediated improvements in the signs and symptoms of BPH: does prostate size matter?

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**Objective:** The uroselective  $\alpha$ -blocker silodosin significantly improved International Prostate Symptom Score (IPSS) in two 12-week, double-blind (DB), placebo-controlled Phase III studies in men aged  $\geq 50$  years with symptoms of benign prostatic hyperplasia (BPH) and maintained symptom improvement during a 9-month open-label (OL) extension. This post-hoc analysis evaluated the effects of estimated prostate volume (EPV) on silodosin-mediated symptom improvement.

**Methods:** Patients were stratified by EPV ( $<30$  mL or  $\geq 30$  mL) calculated from prostate-specific antigen (PSA) concentrations using a published algorithm. Group comparisons were done by analysis of covariance with last observations carried forward.

**Results:** Of 890 patients with PSA baseline data, 192 had EPV  $< 30$  mL and 698 had EPV  $\geq 30$  mL. During DB treatment, silodosin was associated with significant symptom improvement (adjusted mean difference versus placebo) in men with EPV  $< 30$  mL ( $-2.0$ ;  $P = 0.038$ ) and those with EPV  $\geq 30$  mL ( $-3.0$ ;  $P < 0.0001$ ). Among patients who received silodosin during DB treatment, changes from baseline in IPSS to the end of OL extension (mean  $\pm$  standard deviation) were similar for EPV  $< 30$  mL ( $n = 60$ ,  $-7.0 \pm 6.8$ ) and EPV  $\geq 30$  mL ( $n = 242$ ,  $-8.0 \pm 7.1$ ;  $P = 0.416$ ). Also, among patients who received placebo as DB treatment, symptom improvement at the end of OL extension was similar for EPV  $< 30$  mL ( $n = 62$ ,  $-6.2 \pm 8.1$ ) and EPV  $\geq 30$  mL ( $n = 275$ ,  $-6.7 \pm 6.1$ ;  $P = 0.339$ ).

**Conclusion:** Silodosin effectively relieved BPH-related symptoms for up to 12 months, irrespective of prostate size, including in patients with enlarged prostates.

**Keywords:** International Prostate Symptom Score, IPSS, benign prostatic hyperplasia

## Introduction

Lower urinary tract symptoms (LUTS) and urinary flow impairment are typical consequences of benign prostatic hyperplasia (BPH).  $\alpha$ -Blockers ( $\alpha$ 1-adrenoceptor antagonists) are the treatment of choice for the rapid relief of BPH-associated symptoms.<sup>1</sup>

The severity of LUTS is believed to be controlled largely by smooth muscle tone in the prostate and bladder neck, which is mediated primarily by  $\alpha_{1A}$ -adrenoceptors.<sup>2,3</sup> Silodosin is a uroselective  $\alpha_{1A}$ -adrenoceptor antagonist for the treatment of the signs and symptoms of BPH. Its pharmacologic profile is characterized by exceptionally high selectivity for  $\alpha_{1A}$ - versus  $\alpha_{1B}$ -adrenoceptors<sup>4,5</sup> and consequently high selectivity for prostatic versus vascular tissue.<sup>6-8</sup> The low affinity of silodosin for  $\alpha_{1B}$ -adrenoceptors is believed to be responsible for the high level of cardiovascular safety of silodosin, including its low potential for causing orthostatic hypotension.<sup>9</sup>

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Combined efficacy results from two 12-week randomized, placebo-controlled, double-blind, Phase III studies have demonstrated that silodosin provides rapid and significant relief from BPH-related symptoms.<sup>10</sup> Moreover, silodosin-mediated symptom improvement was maintained in a 9-month open-label (OL) extension of the two Phase III studies.<sup>11</sup>

Although  $\alpha$ -blockers are known to provide effective relief of BPH-related LUTS, they do not affect prostate size or hyperplastic growth.<sup>1</sup> This post-hoc analysis of data from the two silodosin Phase III studies and the OL extension study seeks to determine the influence of estimated prostate volume (EPV) on the efficacy of silodosin in improving BPH-associated symptoms.

## Methods

### Patients and treatment

This post-hoc analysis used combined data from two 12-week double-blind, placebo-controlled, Phase III studies (ClinicalTrials.gov identifiers NCT00224107 and NCT00224120) and the OL extension study (NCT00224133) in patients with BPH-related symptoms.<sup>10,11</sup> Study participants were men aged  $\geq 50$  years with International Prostate Symptom Score (IPSS)  $\geq 13$ , peak urinary flow of 4–15 mL/s, voided volume  $\geq 125$  mL, and postvoid residual urine volume  $< 250$  mL. Of the 923 study participants in the two studies, 457 received placebo and 466 received

silodosin 8 mg/d. Change from baseline in IPSS was the primary endpoint.<sup>10</sup> A total of 661 patients participated in the OL extension.<sup>11</sup>

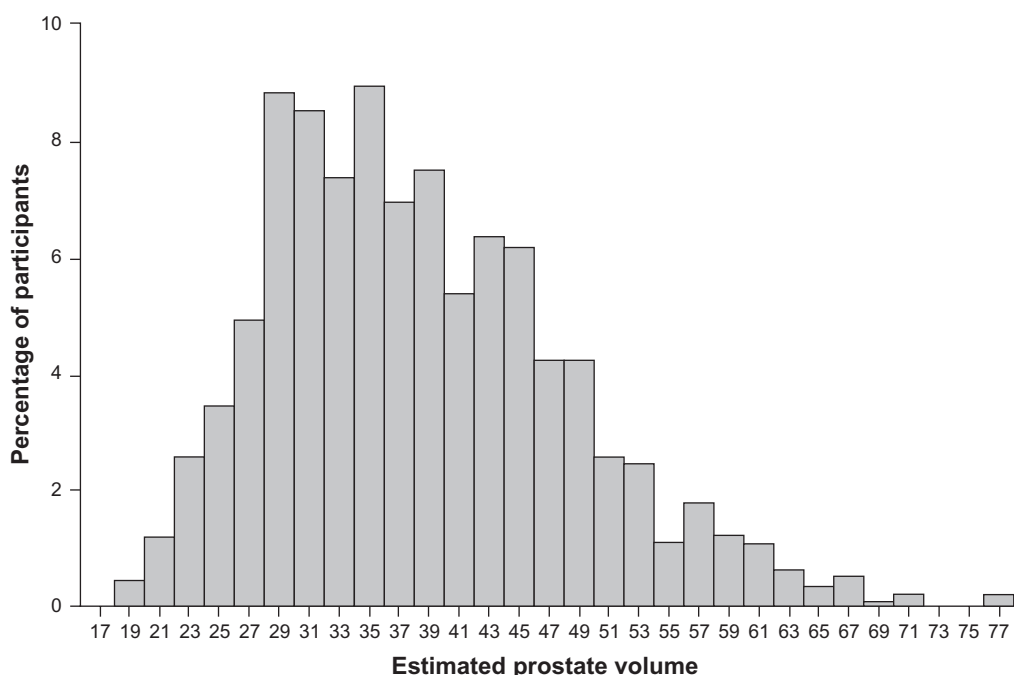
### Assessments and analyses

To assess the effect of EPV on silodosin-mediated symptom improvement, prostate volume (PV) was estimated from prostate-specific antigen (PSA) serum concentrations using the following equation:  $\log PV = a + b \log PSA + c (\text{age} - 60) + d (\text{age} - 60) \times \log PSA$ .<sup>12</sup> A patient was assigned retrospectively to one of two subgroups based on whether or not the EPV met the clinical criterion for pathologic prostate enlargement ( $\geq 30.00$  mL).<sup>13</sup> Serum PSA concentrations were determined by immunometric assay (Siemens Healthcare Diagnostics IMMULITE Series instrument, linear range 0.01–20.00 ng/mL). All group comparisons were performed by analysis of covariance with baseline as the covariate and last observation carried forward (LOCF) to impute missing data. A 5% significance level ( $\alpha = 0.05$ ) with no adjustment for multiple comparisons was applied for all statistical tests.

## Results

### Effect of EPV on symptom improvement during double-blind treatment (12 weeks)

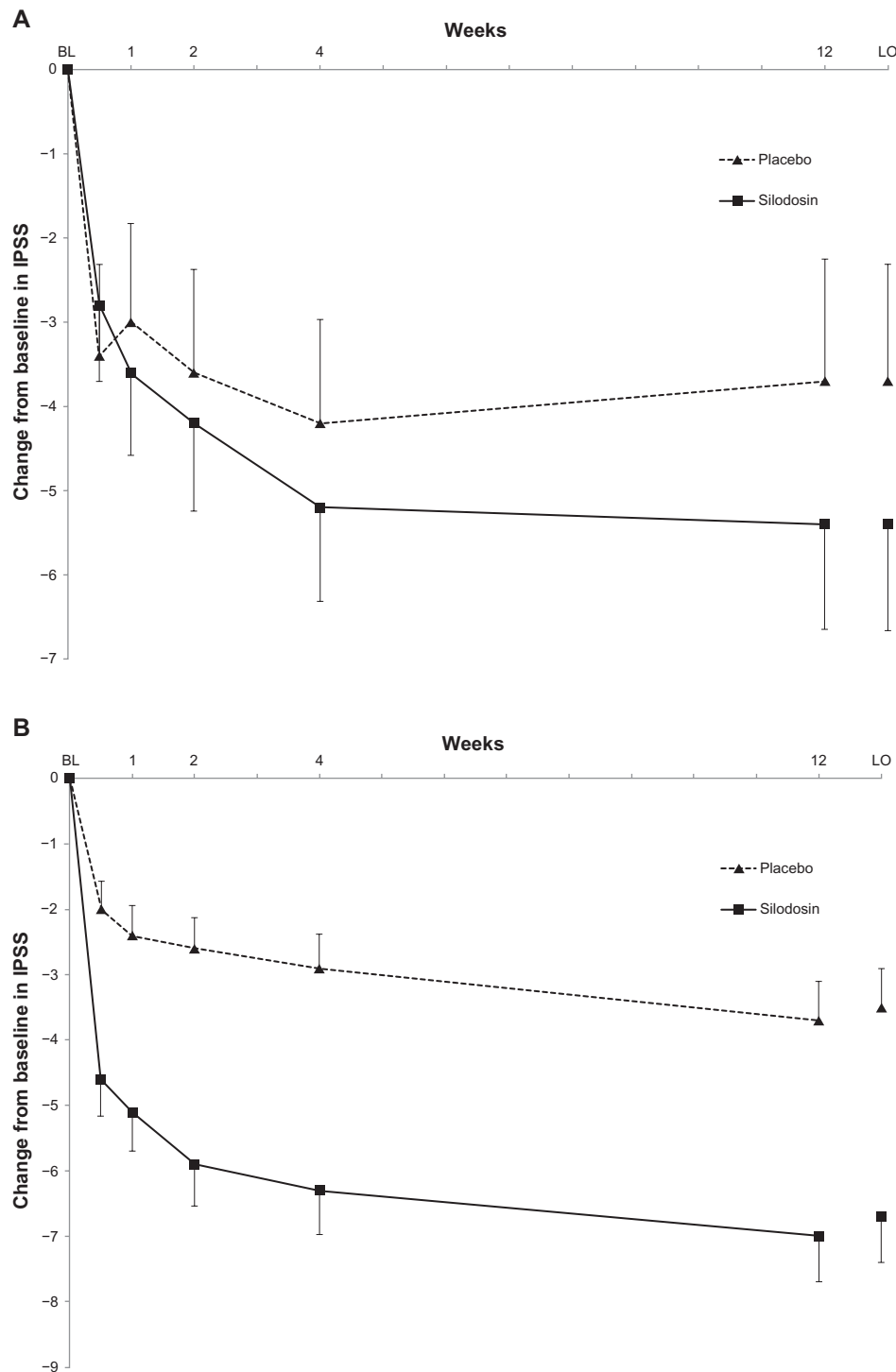
A histogram of the distribution of EPV for all patients with PSA data at baseline is shown in Figure 1. Of 890 patients



**Figure 1** Histogram of estimated prostate volume. Estimated prostate volume mean  $\pm$  standard deviation (mL) was  $38.43 \pm 9.98$  (range 18.35–76.79);  $N = 890$ .

with PSA data at baseline, 192 had EPV < 30 mL, and 698 had EPV ≥ 30 mL. EPV values ranged from 18 to 77 mL, with a median of 37 mL. Of the 111 patients who had an EPV > 50 mL, 29 patients had an EPV > 60 mL. Observed changes in IPSS total score for silodosin versus placebo in

patients with EPV < 30 mL and in those with EPV ≥ 30 mL are shown in Figure 2. Silodosin-mediated decreases in IPSS (mean ± standard deviation) from baseline to week 12 (LOCF) tended to be slightly greater in patients with EPV ≥ 30 mL (−6.7 ± 6.7) than in those with EPV < 30 mL



**Figure 2** Observed changes from baseline in IPSS in patients with EPV < 30 mL (A) and in those with EPV ≥ 30 mL (B). Shown are mean values with 95% confidence intervals.

**Abbreviations:** BL, baseline; EPV, estimated prostate volume; IPSS, International Prostate Symptom Score; LO, last observation.

( $-5.4 \pm 6.4$ ), but the differences were not statistically significant ( $P=0.097$ ). In both analysis groups (EPV  $< 30$  mL, EPV  $\geq 30$  mL), silodosin was associated with significant symptom improvement compared with placebo (Table 1).

## Effect of EPV on symptom improvement at the end of OL extension (9 months)

Of the 662 patients who participated in the OL extension study, 639 had PSA data; of those, 122 had EPV  $< 30$  mL, and 517 had EPV  $\geq 30$  mL. Table 2 shows the effect of EPV on changes in IPSS from baseline (of the double-blind studies) to the end of OL extension. All participants of the OL extension received silodosin 8 mg/d; those who received silodosin as double-blind treatment and those who received placebo as double-blind treatment were analyzed separately. In both analysis groups, symptom improvement at the end of OL extension was numerically and statistically similar for patients with EPV  $< 30$  mL and those with EPV  $\geq 30$  mL (Table 2 and Figure 3).

## Discussion

The results of this post-hoc analysis of data from the two silodosin Phase III studies and the OL extension study show that silodosin provides statistically significant and clinically meaningful symptom relief in patients with BPH-related symptoms, irrespective of prostate size. Decreases in IPSS from baseline to week 12 in each silodosin subgroup (defined by EPV) were significantly greater than the IPSS decreases in the corresponding placebo subgroups. Mean change in IPSS in each silodosin subgroup was similar to that previously observed for the entire silodosin-treated population of the double-blind studies ( $-6.4$ ).<sup>10</sup> Most importantly, over the

**Table 2** Changes in IPSS in patients with EPV  $< 30$  mL and in those with EPV  $\geq 30$  mL at the end of OL extension

	EPV $< 30$ mL	EPV $\geq 30$ mL
<b>Silodosin as double-blind treatment</b>	<b>n = 60</b>	<b>n = 242</b>
BL (double-blind study), mean $\pm$ SD	20.8 $\pm$ 5.5	21.6 $\pm$ 5.2
Change from BL to end of OL extension, mean $\pm$ SD	-7.0 $\pm$ 6.8	-8.0 $\pm$ 7.1
Adjusted mean difference (95% CI)		-0.8 (-2.6 to 1.1)
<b>Placebo as double-blind treatment</b>	<b>n = 62</b>	<b>n = 275</b>
BL (double-blind study), mean $\pm$ SD	22.1 $\pm$ 4.9	21.3 $\pm$ 4.8
Change from BL to end of OL extension, mean $\pm$ SD	-6.2 $\pm$ 8.1	-6.7 $\pm$ 6.1
Adjusted mean difference (95% CI)		-0.8 (-2.6 to 0.9)

**Note:** Last observation carried forward for end of OL extension.

**Abbreviations:** BL, baseline; CI, confidence interval; EPV, estimated prostate volume; IPSS, International Prostate Symptom Score; OL, open-label; SD, standard deviation.

9-month period of the OL extension, differences in silodosin-mediated symptom improvement between patients with EPV  $< 30$  mL and those with EPV  $\geq 30$  mL were small and not statistically significant. Together, these observations suggest that silodosin can be expected to be effective regardless of prostate size, including in patients with enlarged prostates. The analysis of the OL extension data also indicates that prostate size is not a meaningful predictor of the extent of silodosin-mediated symptom improvement. Overall, the findings of our analyses are consistent with the results of placebo-controlled studies of other  $\alpha$ -blockers in patients with BPH symptoms that showed a lack of association between efficacy in symptom relief and prostate size.<sup>14,15</sup>

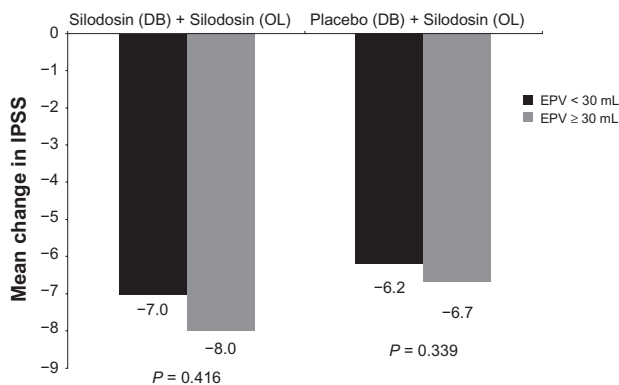
The original silodosin Phase III studies were not designed to evaluate the effect of PV on the efficacy of silodosin. Consequently, this retrospective analysis has some

**Table 1** Changes in IPSS in patients with EPV  $< 30$  mL and in those with EPV  $\geq 30$  mL at the end of double-blind treatment

	Silodosin	Placebo
<b>EPV <math>&lt; 30</math> mL</b>	<b>n = 100</b>	<b>n = 92</b>
BL, mean $\pm$ SD	21.0 $\pm$ 5.2	22.0 $\pm$ 5.2
Change from BL to week 12, mean $\pm$ SD	-5.4 $\pm$ 6.4	-3.7 $\pm$ 6.8
Adjusted mean difference (95% CI) and P-value silodosin versus placebo		-2.0 (-3.8 to -0.1) $P = 0.038$
<b>EPV <math>\geq 30</math> mL</b>	<b>n = 350</b>	<b>n = 348</b>
BL, mean $\pm$ SD	21.4 $\pm$ 5.1	21.0 $\pm$ 4.8
Change from BL to week 12, mean $\pm$ SD	-6.7 $\pm$ 6.7	-3.5 $\pm$ 5.6
Adjusted mean difference (95% CI) and P-value silodosin versus placebo		-3.0 (-3.9 to -2.1) $P < 0.0001$

**Note:** Last observation carried forward for week 12.

**Abbreviations:** BL, baseline; CI, confidence interval; EPV, estimated prostate volume; IPSS, International Prostate Symptom Score; SD, standard deviation.



**Figure 3** Effect of EPV on symptom improvement from baseline to the end of OL treatment.

**Abbreviations:** DB, double-blind; EPV, estimated prostate volume; IPSS, International Prostate Symptom Score; OL, open-label.

limitations. Because determination of actual PV was not mandated by the protocol, values for PV were estimated from serum PSA and age using a published algorithm.<sup>12</sup> Although data stratification reduced the power of our treatment group comparisons, both EPV subgroups were large enough to demonstrate the significance of the treatment effects of silodosin versus placebo. Therefore, we believe that the lack of significant differences in symptom improvement between EPV groups during the OL extension is a meaningful result, suggesting that prostate size has no major effect on the extent of silodosin-mediated symptom relief.

## Conclusion

This retrospective analysis of data from two placebo-controlled Phase III studies and the OL extension study of silodosin in patients with BPH-related symptoms provides evidence that silodosin is effective irrespective of PV. Our findings further suggest that PV is not a clinically meaningful predictor of the extent of silodosin-mediated symptom improvement.

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## Disclosure

SA Kaplan and CG Roehrborn have served on advisory boards for Watson Pharmaceuticals. LA Hill and W Volinn are employees of Watson Laboratories.

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