



Platinum Priority – Benign Prostatic Hyperplasia
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Silodosin Therapy for Lower Urinary Tract Symptoms in Men with Suspected Benign Prostatic Hyperplasia: Results of an International, Randomized, Double-Blind, Placebo- and Active-Controlled Clinical Trial Performed in Europe

Christopher R. Chapple^{a,*}, Francesco Montorsi^b, Teuvo L.J. Tammela^c, Manfred Wirth^d, Evert Koldewijn^e, Eldiberto Fernández Fernández^f,
on behalf of the European Silodosin Study Group¹

^a Department of Urology, Royal Hallamshire Hospital, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK

^b Department of Urology, Università Vita Salute San Raffaele, Milan, Italy

^c Department of Urology, Tampere University Hospital, Tampere, Finland

^d Department of Urology, University Hospital Carl Gustav Carus, Dresden, Germany

^e Department of Urology, Catharina Hospital, Eindhoven, The Netherlands

^f Department of Urology, University Hospital Ramón y Cajal, Madrid, Spain

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Abstract

Background: Silodosin is a new selective therapy with a high pharmacologic selectivity for the α_{1A} -adrenoreceptor.

Objective: Our aim was to test silodosin's superiority to placebo and noninferiority to tamsulosin and discuss the findings in the context of a comprehensive literature review of the new compound silodosin.

Design, setting, and participants: We conducted a multicenter double-blind, placebo- and active-controlled parallel group study. A total of 1228 men ≥ 50 yr of age with an International Prostate Symptom Score (IPSS) ≥ 13 and a urine maximum flow rate (Q_{max}) >4 and ≤ 15 ml/s were selected at 72 sites in 11 European countries. The patients were entered into a 2-wk wash-out and a 4-wk placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg ($n = 381$), tamsulosin 0.4 mg ($n = 384$), or placebo ($n = 190$) once daily for 12 wk.

Measurements: We calculated the change from baseline in IPSS total score (primary), storage and voiding subscores, quality of life (QoL) due to urinary symptoms, and Q_{max} . Responders were defined on the basis of IPSS and Q_{max} by a decrease of $\geq 25\%$ and an increase of $\geq 30\%$ from baseline, respectively.

Results and limitations: The change from baseline in the IPSS total score with silodosin and tamsulosin was significantly superior to that with placebo ($p < 0.001$): difference active placebo of -2.3 (95% confidence interval [CI], $-3.2, -1.4$) with

¹ A complete list of study participants is provided in the appendix.

* Corresponding author. The Royal Hallamshire Hospital, Sheffield Teaching Hospital NHS Foundation Trust, Glossop Road, Sheffield S10 2JF, United Kingdom. Tel. +44 74 271 2559; Fax: +44 74 279 7841.

E-mail address: c.r.chapple@shef.ac.uk (C.R. Chapple).

silodosin and -2.0 (95% CI, $-2.9, -1.1$) with tamsulosin. Responder rates according to total IPSS were significantly higher ($p < 0.001$) with silodosin (66.8%) and tamsulosin (65.4%) than with placebo (50.8%). Active treatments were also superior to placebo in the IPSS storage and voiding subscore analyses, as well as in QoL due to urinary symptoms. Of note, only silodosin significantly reduced nocturia versus placebo (the change from baseline was $-0.9, -0.8,$ and -0.7 for silodosin, tamsulosin, and placebo, respectively; $p = 0.013$ for silodosin vs placebo). An increase in Q_{\max} was observed in all groups. The adjusted mean change from baseline to end point was 3.77 ml/s for silodosin, 3.53 ml/s for tamsulosin, and 2.93 ml/s for placebo, but the change for silodosin and tamsulosin was not statistically significant versus placebo because of a particularly high placebo response (silodosin vs placebo: $p = 0.089$; tamsulosin vs placebo: $p = 0.221$). At end point, the percentage of responders by Q_{\max} was 46.6%, 46.5%, and 40.5% in the silodosin, tamsulosin, and placebo treatment groups, respectively. This difference was not statistically significantly ($p = 0.155$ silodosin vs placebo and $p = 0.141$ tamsulosin vs placebo).

Active treatments were well tolerated, and discontinuation rates due to adverse events were low in all groups (2.1%, 1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively). The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α_{1A} -adrenoreceptor antagonism of the drug. The incidence was higher than that observed with tamsulosin (2%); however, only 1.3% of silodosin-treated patients discontinued treatment due to this adverse event.

Conclusions: Silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in patients with lower urinary tract symptoms suggestive of bladder outlet obstruction thought to be associated with benign prostatic hyperplasia. Its overall efficacy is not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate caused by cellular hyperplasia of both glandular and stromal elements [1]. As the prostate increases in size, it may occlude the lumen of the prostatic urethra, obstructing urine flow [2]. However, studies have shown that prostate size and urinary flow rate usually do not correlate with the severity of lower urinary tract symptoms (LUTS), which may vary from subject to subject [3]. In clinical practice, patients are treated for LUTS suggestive of bladder outlet obstruction (BOO) due to BPH, often called “LUTS/BPH.”

Even if voiding symptoms are the most prevalent in cases of LUTS/BPH, patients usually perceive the storage symptoms as the most bothersome group of symptoms [4]. The objective of therapy for such patients is to improve LUTS/BPH and hence quality of life (QoL). In addition, treatment is aimed at preventing complications such as acute urinary retention or upper urinary tract dilation consequent to BOO. Existing medical therapy includes α -blockers, which are currently the preferred first-line therapy for all men with moderate or severe LUTS/BPH [5], and 5 α -reductase inhibitors (5-ARIs), which are a recommended treatment option for men with moderate or severe LUTS/BPH and an enlarged prostate. α -Blockers can be used regardless of prostate size because they act on the dynamic/neurally

mediated contraction of the muscular stroma that is increased in BPH; 5-ARIs act by shrinking the stromal component of the gland. Both components are thought to contribute to the symptoms and impairment of outflow in patients with LUTS/BPH [6].

Nonselective α_1 -adrenoceptor blockers increase urinary flow rate and improve symptoms in men with symptomatic BPH; however, they may be associated with side effects related to peripheral vasodilation, such as postural hypotension, dizziness, and headache [7–9]. Conversely, drugs with a high affinity for α_{1A} -adrenoceptors may be more prostate specific and may maintain the therapeutic response in the treatment of symptomatic BPH with less effect on blood pressure and fewer cardiovascular side effects [10,11].

Silodosin is a new agent with high selectivity for α_{1A} -receptors, which predominate in the male bladder outflow tract relative to α_{1B} -receptors. It has been demonstrated in vitro that silodosin's α_{1A} -to- α_{1B} binding ratio is extremely high (162:1), suggesting the potential to markedly reduce dynamic neurally mediated smooth muscle relaxation in the lower urinary tract while minimizing undesirable effects on blood pressure regulation [12]. In this context, the evaluation of the uroselectivity of silodosin versus that of tamsulosin and prazosin in vivo has shown good uroselectivity (determined from the ratio of the dose-reducing intraurethral pressure as contrasted to blood pressure) in rats and dogs [13,14].

This paper reports the results of the first randomized placebo-controlled European study with silodosin in the treatment of patients with LUTS/BPH. The study compared silodosin with the effective and widely used drug tamsulosin [15].

2. Patients and methods

2.1. Study design

A multicenter double-blind, placebo- and active-controlled parallel group clinical study was conducted in 72 hospital clinics and inpatient units in 11 countries in Europe. After a wash-out phase of 14 d and a 4-wk single-blind placebo run-in period, subjects who met the selection criteria were randomly assigned (in a ratio of 2:2:1, with stratification by center, with blocks of five assigned to each center, produced and managed centrally by an international contract research organization) to a 12-wk treatment with silodosin 8 mg, tamsulosin 0.4 mg, or placebo, administered once daily. At the centers, all study personnel and participants were blinded to treatment assignment for the entire duration of the study. The ethics committee of each participating center approved the study protocol, and the study was conducted according to the Declaration of Helsinki. Each patient signed a written informed consent before beginning any investigational procedure.

Eight visits were foreseen: at day –42 (start of the wash-out period) and day –28 (start of the placebo run-in period); at baseline (pre- and postrandomization); and after 7, 14, 28, 56, and 84 d of treatment (or in the case of premature study termination).

Prerandomization procedures consisted of the collection of a medical history (including a urologic history), a check of concomitant medications, a physical examination (including a digital rectal examination), and a postvoid residual volume determination by ultrasound.

The International Prostate Symptom Score (IPSS) questionnaire (including question 8, BPH-related health status), a validated instrument widely used for the assessment of symptom severity in patients with BPH [14], was administered to the patients at screening, at baseline, and after 7, 14, 28, 56, and 84 d of treatment (or in the case of premature study termination). Because the study was performed in several European countries and involved patients speaking different languages, the questionnaire was linguistically validated by the MAPI Institute (an international company that specialized in linguistic validation for appropriate cross-cultural use and interpretation of patient-reported assessments) in the relevant languages.

Peak urine maximum flow rate (Q_{max}) was also measured once 2–6 h postdose at the same time periods as IPSS, using standard calibrated devices. A voided volume of at least 125 ml needed to be obtained for a valid assessment.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured at each visit, with the subject supine at rest for at least 5 min before measurements. A test for postural hypotension was performed at screening and pre- and postdose at baseline. Laboratory tests and a 12-lead electrocardiogram (ECG) were performed at screening, at baseline, and at study end (or in the case of premature discontinuation). Adverse events (AEs) were collected at each visit. The appearance of new unfavorable and unintended signs, symptoms, or diseases or worsening of conditions already present at baseline in the postrandomization period were considered as treatment-emergent adverse events (TEAEs).

2.2. Study population

Men ≥ 50 yr of age with LUTS (defined by a stable IPSS total score ≥ 13 points), BOO (defined by a Q_{max} between 4 and 15 ml/s, with a minimum

voided volume of ≥ 125 ml), and the evidence of satisfactory compliance with study medication (80–120% during the placebo run-in period) were eligible for inclusion in the study. Principal exclusion criteria were improvement in the IPSS total score $\geq 25\%$ in the run-in period, postvoid bladder residual volume ≥ 250 ml, intravesical obstruction from any cause other than BPH, history of any procedure considered an intervention for BPH, active urinary tract infection or history of recurrent urinary tract infections, current prostatitis or diagnosis of chronic prostatitis, history of prostate or invasive bladder cancer, significant postural hypotension, use of 5-ARIs within 6 mo, or use of an α -blocker or phytotherapy within 2 wk before entry.

2.3. Study end points and statistical analyses

The primary end point of the study was to demonstrate the superiority of silodosin to placebo and its noninferiority to tamsulosin for the relief of LUTS associated with BPH and suggestive of BOO. This was measured by a change from baseline in the total score (questions 1–7) of the IPSS questionnaire (primary efficacy parameter).

The total number of subjects to be randomized was set at 820 (328 for silodosin 8 mg, 328 for tamsulosin 0.4 mg, and 164 for placebo) to reject the null hypothesis that the two active treatments were not equivalent with the following assumptions: a standard deviation of 5.2, one sided, 90% of power, a noninferiority margin of a mean change of –1.5 IPSS points, and 20% of patients not valid for inclusion in the per-protocol (PP) population. This sample size was also adequate for a two-sided test at the 0.05 significance level, with 90% power, to detect a mean change in the IPSS total score [14] of –2 from baseline between each active group and placebo.

Secondary efficacy parameters were as follows: improvement in storage and voiding symptoms subscores, QoL due to urinary symptoms (question 8 of the IPSS), Q_{max} , and percentage of treatment responders by IPSS (decrease from baseline $\geq 25\%$) and by Q_{max} (increase from baseline $\geq 30\%$).

Statistical analyses were performed using the following procedures. For the analysis of the primary efficacy variable, the superiority of the active treatments (silodosin and tamsulosin) versus placebo was tested first in the intent-to-treat (ITT) population (all subjects who had a baseline IPSS assessment and at least one valid postbaseline IPSS assessment). Next, the noninferiority of silodosin versus tamsulosin was tested in the PP population (all subjects who completed the study without any major protocol violation). Last, because all the planned tests were satisfied, the superiority of silodosin versus tamsulosin was tested (ITT population). For the secondary efficacy variables, the superiority of the active treatments (silodosin and tamsulosin) versus placebo was tested first, followed by the comparison between silodosin and tamsulosin.

The overall treatment group comparisons of the change from baseline in the IPSS total score, by visit and at end point (in both ITT and PP populations), were estimated based on adjusted means obtained from the main analysis of the covariance model, which included terms for treatment, pooled center, and baseline value.

The percentage of responders to IPSS and the percentage of responders to Q_{max} were summarized at each visit and at end point by treatment group; comparisons between each of the active treatment groups and placebo and between silodosin and tamsulosin were made using the Cochran Mantel Haenszel test, stratified by pooled center, for both populations.

A post hoc analysis was conducted in the subgroup of patients with nocturia at baseline (defined as at least two voids per night), as assessed by question 7 of the IPSS.

In terms of safety, the safety population was defined as all subjects who were randomized and who received at least one dose of double-blind study medication. Safety was assessed primarily on the basis of

TEAEs occurring in the different groups postrandomization. In addition, the change from baseline was evaluated for the following safety parameters: DBP, SBP, and HR in a supine position and after standing (orthostatic test), laboratory determinations, ECG findings, and physical examination.

3. Results

3.1. Disposition of patients

A total of 1228 patients were screened, 955 of whom were randomized to receive silodosin 8 mg (381), tamsulosin 0.4 mg (384), or placebo (190), respectively. The first patient was enrolled on May 18, 2006, and the last patient completed the study on May 10, 2007. Fig. 1 shows the patient allocation. The main reasons for study discontinuation were protocol violation (2.5%) and voluntary withdrawal by the subject (2.4%). The discontinuation rate due to TEAE was low ($\leq 2.1\%$) in all groups.

3.2. Demographics and other baseline characteristics

Table 1 summarizes the demographic and baseline characteristics of the safety population. No statistically

significant differences were seen between the three treatment groups with respect to age, body mass index, IPSS total score, storage and voiding subscores, and QoL due to urinary symptoms. Of note, 424 patients (44.4%) were hypertensive, and many subjects were on concomitant antihypertensive medications. At baseline, many patients had a past or current history of erectile dysfunction (24.0%) or complained of ejaculation disorders. These included orgasm semen quantity reduced (8.3%), orgasm semen force reduced (6.9%), and orgasm with no semen (0.8%), with an overall 24.0% rate of pretreatment ejaculatory disorders.

3.3. Efficacy results

3.3.1. Change from baseline in International Prostate Symptom Score total score (primary efficacy parameter)

The change from baseline in the IPSS total score (questions 1–7) in the different groups and the differences from placebo and between active groups are shown in Table 2 and Fig. 2, respectively.

For all treatment groups, there was no plateau in response; however, the largest decreases in the total IPSS score occurred rapidly, within the first 2 wk of treatment.

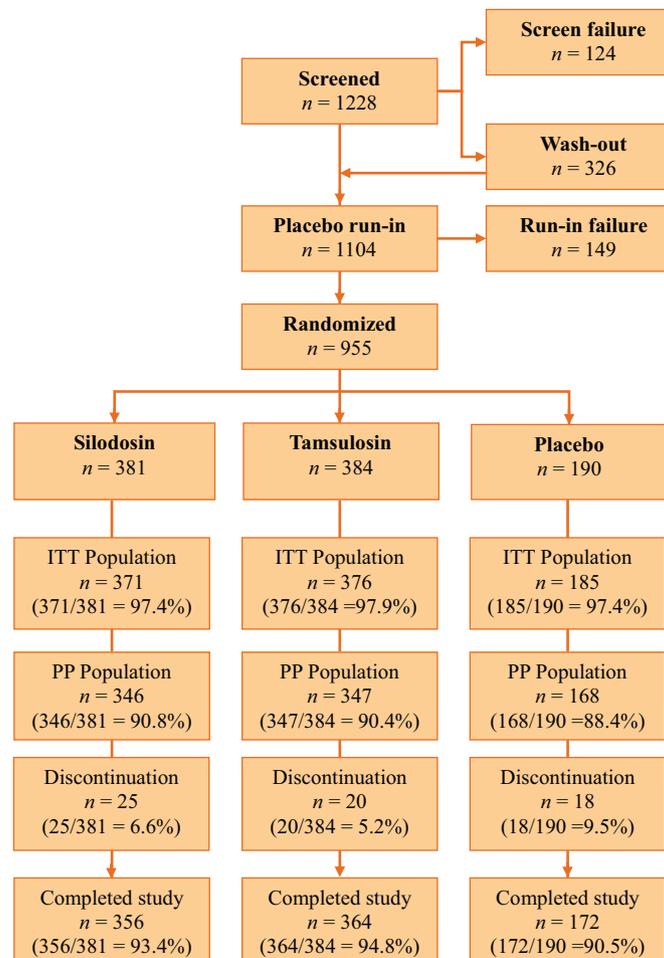


Fig. 1 – Disposition of subjects. ITT = intention to treat; PP = per protocol.

Table 1 – Demographic and baseline characteristics

	Silodosin 8 mg (n = 381)	Tamsulosin 0.4 mg (n = 384)	Placebo (n = 190)	Total (n = 955)	p value
Age, yr, n (%)					
50–64	158 (41.5)	157 (40.9)	75 (39.5)	390 (40.8)	
65–74	168 (44.1)	183 (47.7)	93 (48.9)	444 (46.5)	
≥75	55 (14.4)	44 (11.5)	22 (11.6)	121 (12.7)	
Mean ± SD	65.8 ± 7.70	65.9 ± 7.41	66.0 ± 7.37	65.8 ± 7.51	
Median	66.0	66.5	67.0	67.0	
Min–Max	50–87	50–85	50–81	50–87	0.957
Race, n (%)					
White	381 (100.0)	384 (100.0)	190 (100.0)	955 (100.0)	Not estimable
BMI, kg/m ² , n (%)					
<25	84 (22.0)	109 (28.4)	46 (24.2)	239 (25.0)	
25–29	238 (62.5)	214 (55.7)	118 (62.1)	570 (59.7)	
≥30	59 (15.5)	61 (15.9)	25 (13.2)	145 (15.2)	0.624
IPSS total score					
Mean ± SD	19.1 ± 4.23	18.9 ± 4.37	19.3 ± 4.33	19.1 ± 4.30	
Median	19.0	18.0	19.0	18.0	
Range	13–33	8–33	13–35	8–35	0.517
IPSS storage subscore					
Mean ± SD	7.9 ± 2.49	7.9 ± 2.51	8.0 ± 2.64	7.9 ± 2.53	
Median	8.0	8.0	8.0	8.0	
Range	1–15	0–15	1–15	0–15	0.836
IPSS voiding subscore					
Mean ± SD	11.3 ± 3.13	11.0 ± 3.27	11.3 ± 3.22	11.2 ± 3.20	
Median	11.0	11.0	11.0	11.0	
Range	2–20	3–20	4–20	2–20	0.481
QoL due to urinary symptoms, n (%)					
Delighted	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.3)	
Pleased	2 (0.5)	6 (1.6)	0 (0.0)	8 (0.8)	
Mostly satisfied	27 (7.1)	23 (6.0)	12 (6.3)	62 (6.5)	
Mixed	98 (25.7)	105 (27.3)	44 (23.2)	247 (25.9)	
Mostly dissatisfied	140 (36.7)	135 (35.2)	65 (34.2)	340 (35.6)	
Unhappy	98 (25.7)	95 (24.7)	57 (30.0)	250 (26.2)	
Terrible	16 (4.2)	17 (4.4)	10 (5.3)	43 (4.5)	
Missing	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.2)	
Mean ± SD	3.9 ± 1.01	3.9 ± 1.09	4.0 ± 1.00	3.9 ± 1.04	
Median	4.0	4.0	4.0	4.0	
Range	1–6	0–6	2–6	0–6	0.141
Urine Q _{max} , ml/s					
Mean	10.78 ± 2.726	10.27 ± 2.726	10.32 ± 2.816	10.49 ± 2.752	
Median	11.00	10.20	10.60	10.60	
Range	4.0–28.3	4.0–20.8	4.6–15.0	4.0–28.3	0.026

BMI = body mass index; IPSS = International Prostate Symptom Score; Q_{max} = maximum flow rate; QoL = quality of life; SD = standard deviation.

Table 2 – Change in International Prostate Symptom Score total score

	Silodosin 8 mg	Tamsulosin 0.4 mg	Placebo
ITT population	n = 371	n = 376	n = 185
Baseline, mean ± SD	19 ± 4	19 ± 4	19 ± 4
Change from baseline to end point, adjusted means	–7.0	–6.7	–4.7
Difference active vs placebo (95% CI)	–2.3 (–3.2, –1.4) [*]	–2.0 (–2.9, –1.1) [*]	–
Difference tamsulosin vs silodosin (95% CI)	0.3 (–0.4, 1.0) [†]	–	–
PP population	n = 346	n = 347	n = 168
Baseline, mean ± SD	19 ± 4	19 ± 4	19 ± 4
Change from baseline to week 12, adjusted means	–7.0	–6.7	–4.8
Difference active vs placebo (95% CI)	–2.2 (–3.2, –1.3) [*]	–1.9 (–2.8, –0.9) [*]	–
Difference tamsulosin vs silodosin (95% CI)	0.4 (–0.4, 1.1) [†]	–	–

CI = confidence interval; ITT = intention to treat; PP = per protocol; SD = standard deviation.
^{*} p < 0.001 versus placebo.
[†] Noninferiority.

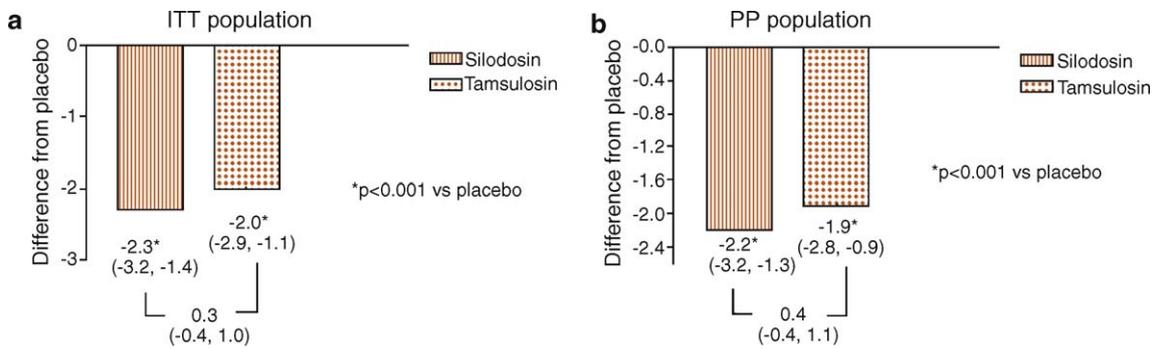


Fig. 2 – Differences from placebo in International Prostate Symptom Score total score.
ITT = intention to treat; PP = per protocol.

Superiority of active treatments versus placebo was observed with highly statistically significant differences at all weeks ($p < 0.001$) both in the ITT and PP population.

3.3.2. Responder rates according to International Prostate Symptom Score total score

In all three treatment groups, the percentage of IPSS responders progressively increased from baseline to week 12. At study end, 66.8% and 65.4% of the patients receiving silodosin or tamsulosin were responders (respectively), compared with 50.8% in the placebo group.

The differences versus placebo were highly significant ($p < 0.001$) for both active compounds, whereas the comparison between silodosin and tamsulosin did not show a statistically significant difference.

3.3.3. Voiding and storage subscores

Table 3 shows the mean change from baseline to end point in the IPSS subscore of voiding symptoms (questions 1, 3, 5, and 6) and of storage symptoms (questions 2, 4, and 7). The statistically significant superiority of both active treatments versus placebo on voiding and storage subscores was observed at all weeks of treatment. The comparison between silodosin and tamsulosin did not show a statistically significant difference, even if a numerical difference in favor of silodosin was observed in the voiding subscore. Of note, in the subgroup of patients with nocturia at baseline ($n = 764$), only silodosin significantly reduced nocturia versus placebo (change from baseline -0.9 , -0.8 , and -0.7 for silodosin, tamsulosin,

and placebo, respectively; $p = 0.013$ for silodosin vs placebo, $p = 0.095$ for tamsulosin vs placebo, and $p = 0.314$ for silodosin vs tamsulosin).

3.3.4. Quality of life

An improvement in the change from baseline in QoL due to urinary symptoms (question 8 of the IPSS) was reported for all treatment groups (-1.1 for silodosin, -1.1 for tamsulosin, and -0.8 for placebo). Once again, highly statistically significant differences were observed between active treatments and placebo at all weeks (at end point $p = 0.002$). At end point, the percentage of patients negatively affected by urinary symptoms (feeling mostly dissatisfied, unhappy, and terrible) was reduced $>50\%$ in the silodosin and tamsulosin groups (from 66.9% to 34.0% and from 64.1% to 29.0%, respectively), and about a third in the placebo group (from 69.7% to 45.4%) (Table 4).

3.3.5. Maximum flow rate

A larger increase from baseline in Q_{max} (milliliters per second) was observed for both active treatment groups compared with placebo but was not statistically significant. The adjusted mean change from baseline to end point was 3.77 ml/s for silodosin ($p = 0.089$ vs placebo), 3.53 ml/s for tamsulosin ($p = 0.221$ vs placebo), and 2.93 ml/s for placebo. The percentage of Q_{max} responders was larger for the silodosin and the tamsulosin treatment groups compared with the placebo group; however, only sporadic statistically significant differences versus placebo were found for either active treatment group during the various

Table 3 – Change in International Prostate Symptom Score storage and voiding subscore

Treatment arm	IPSS storage symptoms		IPSS voiding symptoms	
	Change from baseline	Difference (95% CI) vs placebo	Change from baseline	Difference (95% CI) vs placebo
Silodosin	-2.5	-0.7 [†] (-1.1, -0.2)	-4.5	-1.7 [*] (-2.2, -1.1)
Tamsulosin	-2.4	-0.6 [†] (-1.1, -0.2)	-4.2	-1.4 [*] (-2.0, -0.8)
Placebo	-1.8		-2.9	

CI = confidence interval; IPSS = International Prostate Symptom Score.

^{*} $p < 0.001$ versus placebo.

[†] $p = 0.002$ versus placebo.

Table 4 – Summary of quality of life related to urinary symptoms

	Silodosin No. (%)	Tamsulosin No. (%)	Placebo No. (%)
Baseline			
Delighted, pleased, or mostly satisfied	29 (7.8)	32 (8.5)	12 (6.5)
Mixed: about equally satisfied and dissatisfied	94 (25.3)	103 (27.4)	43 (23.2)
Mostly dissatisfied, unhappy, or terrible	248 (66.9)	241 (64.1)	129 (69.7)
Week 12*			
Delighted, pleased, or mostly satisfied	163 (44.0)	168 (44.7)	63 (34.0)
Mixed: about equally satisfied and dissatisfied	82 (22.1)	99 (26.3)	38 (20.5)
Mostly dissatisfied, unhappy, or terrible	126 (34.0)	109 (29.0)	84 (45.4)

* Data analysis for week 12 was based on last observation carried forward.

follow-up visits due to a particularly high placebo response. At end point, the percentage of responders was 46.6% ($p = 0.155$ vs placebo) and 46.5% ($p = 0.141$ vs placebo) in the silodosin and the tamsulosin treatment groups, respectively, and 40.5% in the placebo group. This difference was not statistically significant.

3.4. Safety results

3.4.1. Treatment-emergent adverse events

Overall, the percentage of subjects who reported at least one TEAE was 34.9% (133 of 381) for subjects in the silodosin group, 28.9% (111 of 384) in the tamsulosin group, and 24.2% (46 of 190) in the placebo group (silodosin vs placebo: $p = 0.0094$; silodosin vs tamsulosin: $p = 0.0749$). The most frequently reported TEAEs (>2%) were a reduced or absent ejaculation during orgasm (coded by the Medical Dictionary for Regulatory Activities preferred term as “retrograde ejaculation”) and headache. The percentage of subjects reporting AEs coded as “retrograde ejaculation”

was 14.2% (54 of 381) in the silodosin treatment group, which was significantly higher compared with 2.1% (8 of 384) and 1.1% (2 of 190) of subjects in the tamsulosin and placebo treatment groups, respectively. The verbatim terms reported by the investigators in the silodosin group and coded as retrograde ejaculation were *orgasm with no semen*, *orgasm semen quantity reduced*, and *retrograde ejaculation*. Headache was reported by a higher percentage of subjects in the tamsulosin group (5.5%; 21 of 384) compared with the silodosin group (2.9%; 11 of 381) but was similar and not significantly different than headaches reported in the placebo group (4.7%; 9 of 190).

The percentage of subjects who discontinued the study due to a TEAE was small and not statistically different in all treatment groups (silodosin 2.1%, eight subjects; tamsulosin 1.0%, four subjects; placebo 1.6%, three subjects). The most common TEAE leading to discontinuation was failure of ejaculation (five subjects in the silodosin group and one in the tamsulosin group). This TEAE was reversible after study discontinuation.

Table 5 – Supine blood pressure

	Silodosin 8 mg (n = 381)	Tamsulosin 0.4 mg (n = 384)	Placebo (n = 190)
Supine systolic BP			
Baseline (mean ± SD)	133.8 (12.61)	133.0 (13.29)	132.8 (13.57)
CFB at end point (adjusted means)	−1.8	−2.2	−0.4
Difference active vs placebo (95% CI)	−1.4 (−3.0, 0.1)	−1.8 (−3.4, −0.3)	−
p value vs placebo	0.075	0.022	−
Difference tamsulosin vs silodosin (95% CI)	−0.4 (−1.7, 0.9)	−	−
p value vs tamsulosin	0.536	−	−
Supine diastolic BP			
Baseline (mean ± SD)	80.6 (7.47)	80.5 (7.99)	80.6 (7.70)
CFB at end point (adjusted means)	−1.0	−1.6	−0.6
Difference active vs placebo (95% CI)	−0.3 (−1.4, 0.7)	−1.0 (−2.1, 0.0)	−
p value vs placebo	0.515	0.060	−
Difference tamsulosin vs silodosin (95% CI)	−0.7 (−1.5, 0.2)	−	−
p value vs tamsulosin	0.132	−	−
Supine heart rate			
Baseline (mean ± SD)	67.4 (8.83)	67.8 (9.10)	67.3 (8.43)
CFB at end point (adjusted means)	0.8	1.3	1.1
Difference active vs placebo (95% CI)	−0.3 (−1.6, 1.0)	0.2 (−1.1, 1.5)	−
p value vs placebo	0.643	0.753	−
Difference tamsulosin vs silodosin (95% CI)	0.5 (−0.5, 1.5)	−	−
p value vs tamsulosin	0.340	−	−

BP = blood pressure; CFB = change from baseline; CI = confidence interval; SD = standard deviation.

Nine subjects of 955 (0.9%) experienced a serious TEAE; of these, three were considered possibly related to the study drug by the treating investigator: prostate cancer and supraventricular arrhythmia (silodosin) and anxiety (tamsulosin). Two subjects died during the study; both deaths were unrelated to the drugs used in the study.

3.4.2. Other safety parameters

No clinically meaningful changes were recorded for any of the laboratory parameters, vital signs, or ECGs observed during the study in any of the treatment groups. Table 5 presents the supine DBP, SBP, and HR and the change from baseline in DBP, SBP, and HR observed with the silodosin, tamsulosin, and placebo groups. No clinically relevant or statistically significant differences versus placebo were observed with silodosin. An important characteristic of silodosin is the lack of clinically relevant or statistically significant changes in blood pressure or heart rate versus placebo. However, a minor but statistically significant difference versus placebo was observed with tamsulosin.

No subject experienced a marked decrease in blood pressure when performing the postrandomization orthostatic test after the first dosing of the drug. Only a few subjects in both active treatment groups reported an increase in HR >20 beats per minute without any clinically important change in SBP or DBP.

4. Discussion

This prospective statistically well-powered study evaluated the efficacy and safety of the new highly selective agent silodosin, an α_{1A} -receptor, for the treatment of moderate to severe LUTS due to BPH. A population of patients with LUTS/BPH who were representative of those seen in clinical practice in terms of age, concomitant diseases, and medication was selected. In the patient group, approximately 60% were elderly, and about 57% were on concomitant antihypertensive medication.

In this study, silodosin proved to be an effective drug for the treatment of both storage and voiding LUTS associated with BPH because a statistically significant and potentially clinically relevant difference versus placebo was observed in the IPSS total score, in the storage and voiding subscores, and in QoL due to urinary symptoms. The improvement became evident soon after the initiation of therapy. The treatment effect with silodosin appeared to be at least equivalent to and numerically consistently greater than that seen with tamsulosin when considering the change from baseline in the IPSS total score, in the voiding subscore, and in the responder rates, even if the differences were not statistically significant. There was also a greater benefit seen when considering the QoL on active therapy with either silodosin or tamsulosin as compared with placebo.

It is noteworthy that the selective effect of α_{1A} -receptor antagonism seemed to offer a clinically relevant benefit not only on voiding but also on storage symptoms. Of note, only the effect of silodosin (and not of tamsulosin) on nocturia was significantly better than that of placebo. The mechanism of this action remains to be clarified.

In this study, treatment with silodosin also showed an early and sustained increase in Q_{max} ; however, the difference versus placebo was not statistically significant. A similar order of magnitude for the flow rate was seen with the active comparator tamsulosin, which has been clearly documented in the past to produce significant changes when compared with placebo.

The first randomized double-blind, placebo-controlled study that was conducted with silodosin in Japan recruited men ≥ 50 yr of age with an IPSS of ≥ 8 and a QoL score of ≥ 3 . Patients were randomized to receive silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily (the Japanese dosage, lower than the European dosage), or placebo for 12 wk [15]. The primary end point was the change in IPSS from baseline. In all, 457 patients were randomized (176 to silodosin, 192 to tamsulosin, and 89 to placebo). The change in the total IPSS from baseline in the silodosin, tamsulosin, and placebo groups was -8.3 , -6.8 , and -5.3 , respectively. There was a significant decrease in the IPSS versus placebo in the silodosin group from 1 wk, and silodosin showed a significant decrease in IPSS versus tamsulosin at 2 wk. In the subgroup of patients with severe symptoms (IPSS ≥ 20), silodosin also offered a significantly better improvement than placebo (-12.4 vs -8.7). The incidence rates of AEs were 88.6%, 82.3%, and 71.6%, respectively; for drug-related AEs they were 69.7%, 47.4%, and 36.4%, respectively. The most common AE in the silodosin group was abnormal ejaculation, which occurred more often in the silodosin than in the tamsulosin group (22.3% vs 1.6%). However, only five men (2.9%) discontinued treatment because of abnormal ejaculation.

Marks and colleagues assessed the efficacy and safety of silodosin 8 mg for the treatment of BPH in two randomized placebo-controlled phase 3 studies done in the United States [16]. Of 923 patients with a mean age of 65 yr, 466 received silodosin (8 mg/d) and 457 were given placebo with breakfast for 12 wk. After 0.5 wk (3–4 d) of treatment, patients receiving silodosin showed significant improvement in IPSS subscores (difference -1.9 ; $p < 0.0001$), storage (-0.5 ; $p = 0.0002$), and voiding (-1.4 ; $p < 0.0001$) compared with the placebo group. The mean change from baseline in total IPSS was -4.2 for silodosin versus -2.3 for placebo, and differences between treatments in total IPSS and subscores increased by week 12 ($p < 0.0001$). Mean change from baseline in Q_{max} (ml/s) 2–6 h after initial dose was greater ($p < 0.0001$) with silodosin (2.8 ± 3.4) than placebo (1.5 ± 3.8). These differences remained significant ($p < 0.001$) for the 12 wk. The lack of significant difference as compared with placebo in our study could be explained by a higher than expected placebo response, supported by the similar efficacy to tamsulosin, which was also not significantly different from placebo and was at variance with the published literature [17].

A long-term open-label extension study of patients from these two studies was conducted over 40 wk, with all patients receiving silodosin 8 mg once daily with breakfast [18]. The primary objective of this study was to assess safety. Of the 661 participants, 435 (65.8%) completed the study and 431 (65.2%) experienced 924 AEs. No serious AEs that the investigators considered to be drug related

occurred. AEs reported most often (percentage of patients) included retrograde ejaculation (20.9%), diarrhea (4.1%), and nasopharyngitis (3.6%). Orthostatic hypotension and dizziness occurred in 2.6% and 2.9% of patients, respectively. The percentage of patients with TEAEs, stratified by preceding double-blind treatment (placebo or silodosin), was higher for de novo (previous treatment with placebo: 71.5%) than for continuing silodosin treatment (58.3%). More patients receiving de novo (7.5%) versus continuing treatment (1.9%) discontinued study participation because of retrograde ejaculation. The mean IPSS change (standard deviation) from baseline (after 12 wk of previous double-blind therapy) to week 40 (observed cases) was -4.5 (6.7) for de novo treatment ($p < 0.0001$) and -1.6 (6.0) for continuing treatment ($p < 0.01$). Silodosin was well tolerated and in particular was associated with low incidences of dizziness and orthostatic hypotension.

Because the efficacy of both tamsulosin and silodosin appear to be very similar, the question has to be posed regarding the potential additional advantage of silodosin. Studies conducted recently have suggested that silodosin as a consequence of its high subtype selectivity is less likely than tamsulosin to have significant cardiovascular side effects either when used alone or in combination with other agents, which may affect blood pressure. This is particularly important and relevant in more elderly patients.

Kobayashi et al. [19] provided evidence for this suggestion. They evaluated the efficacy on the urethra (intraurethral pressure) and cardiovascular system (hypotension) of silodosin (α_{1A} -adrenoceptor antagonist) and tamsulosin (α_{1A+1D} -adrenoceptor antagonist) in dogs with BPH altered with age. Under anesthesia, the increase in intraurethral pressure evoked by hypogastric nerve stimulation was measured, together with the level of systemic mean blood pressure. Each drug was administered intravenously in progressively increasing doses. Silodosin (0.3–300 $\mu\text{g}/\text{kg}$) dose-dependently inhibited the hypogastric nerve stimulation-induced increase in intraurethral pressure (without significant hypotensive effects) in both young and old dogs with BPH. Tamsulosin (0.3–300 $\mu\text{g}/\text{kg}$) also dose-dependently inhibited the intraurethral pressure increase in both groups, but it had a hypotensive effect that was significantly greater in old than in young dogs with BPH. The potency of silodosin on intraurethral pressure was similar between young and old dogs with BPH and was without significant hypotensive effects. The authors concluded that if one extrapolated these data to man, silodosin should be a safe and effective medication for LUTS in patients of all age groups.

In a placebo-controlled open-label clinical crossover study evaluating potential interaction with a phosphodiesterase inhibitor [20], 22 healthy men 45–78 yr of age received 8 mg silodosin for 21 d. On days 7, 14, and 21, subjects also received a single dose of sildenafil 100 mg, tadalafil 20 mg, or placebo in random sequence. Orthostatic tests were performed before (baseline) and 1–12 h after single-dose treatment. Coadministration of silodosin and maximum therapeutic doses of sildenafil or tadalafil in healthy men caused no clinically important orthostatic changes in blood

pressure or HR and no orthostatic symptoms. The most frequent TEAE observed during silodosin therapy was ejaculatory dysfunction (EjD) consisting of one of the following group of symptoms: orgasm, semen quantity reduced; orgasm, semen force reduced; or orgasm, no semen.

Although it is a widely held view among clinicians that EjD is a consequence of an effect on the bladder neck, it is in fact not true retrograde ejaculation but rather “anejaculation” caused by an effect on the ejaculatory apparatus (prostate, seminal vesicles, and vasa) and indeed has been coded incorrectly as retrograde ejaculation in several clinical studies [21]. It has been recognized for many years that the vas is an excellent pharmacologic model for the α_{1A} -receptor [22]. Although it is possible that the clinical differences between silodosin and tamsulosin as compared with other α_1 -adrenoceptor antagonists do not exclusively relate to their subtype selectivity [23], additional properties of these drugs such as a proposed insurmountable antagonism in the vas deferens [24] or additional effects on other receptor systems (eg, dopamine and/or serotonin [25]) should be considered. Finally, it has been proposed that abnormal ejaculation is not primarily regulated at the level of the vas deferens but rather at central nervous sites that control its function [26].

This is clearly a typical side effect of α_1 -adrenoceptor antagonists, particularly those with selectivity for α_{1A} -adrenoceptors, because this subtype is distributed throughout the organs participating in the emission phase of ejaculation [27]. Nonclinical studies have shown that α -adrenoceptors, particularly α_{1A} -adrenoceptors, are essential for the physiologic contraction of the vas deferens and hence for sperm delivery from the testes to the urethra [28]. Reduced ejaculation is caused by an impaired function of the vas deferens rather than by alterations in sperm formation, number, or function [29]. This effect does not represent a safety concern because it indicates only a reduction in semen volume that is reversible (within a few days) upon discontinuation of treatment [30,31], and it is not perceived as particularly bothersome (in this study, the discontinuation rates were very low in all groups and were comparable with placebo).

It is now well established that EjD is commonly associated with both increasing age and the presence of LUTS [32–35]. The Multinational Survey of the Aging Male-7 results confirmed the significant relationship between LUTS and EjD in aging men.

A post hoc analysis of the North American studies on silodosin [16] suggested that EjD may be a predictor of the efficacy of the α_1 -adrenoceptor blockade. Roehrborn and colleagues found that 28.1% of patients in these studies experienced EjD and reported that these patients experienced a greater improvement in symptoms and a clinically meaningful greater improvement in flow rate than those who did not experience EjD [36]. Homma et al. [37] carried out a similar analysis evaluating improvements in symptoms in the Japanese study [15]. The silodosin subgroup with failure of ejaculation experienced a greater reduction in total IPSS than the silodosin subgroup without impairment of ejaculation and the placebo subgroup (-11.8 vs -7.2 vs -5.3 ,

respectively). Interestingly, the dropout rates in both of the silodosin groups were very similar.

As expected for a highly uroselective drug, silodosin appears to be a safe drug that is at least equivalent to tamsulosin in efficacy. A major advantage of this drug is its lack of cardiovascular side effects. It has no clinically relevant effect on blood pressure when measured either in the supine position or during orthostatic testing. This is important because most patients treated for LUTS associated with BPH are elderly and often on concomitant antihypertensive therapy or taking agents such as phosphodiesterase inhibitors. No unfavorable effect has been observed on ECG or laboratory tests, including liver function tests and tests of creatinine and glucose levels.

5. Conclusions

This large multinational study has confirmed the results of previous studies, demonstrating silodosin to be an effective and safe treatment for the relief of both voiding and storage symptoms in patients with benign prostatic enlargement consequent upon BOO due to BPH. It may be particularly useful in more elderly patients where there is the potential for drug–drug interactions and where potential cardiovascular side effects need to be minimized.

Author contributions: Christopher R. Chapple 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: Chapple, Montorsi.

Acquisition of data: Chapple, Montorsi, Tammela, Wirth, Koldewijn, Fernández Fernández.

Analysis and interpretation of data: Chapple, Montorsi, Tammela, Wirth, Koldewijn, Fernández Fernández.

Drafting of the manuscript: Chapple, Montorsi, Tammela, Wirth, Koldewijn, Fernández Fernández.

Critical revision of the manuscript for important intellectual content: Chapple, Montorsi, Wirth, Koldewijn, Fernández Fernández.

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Supervision: None.

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Appendix A. Complete List of Study Participants

Finland: T. Forsell (Kotka); P. Hellström (Oys); M. Multanen (Kouvola); T.L.J. Tammela (Tampere)

France: H. Botto (Suresnes); D. Chevallier (Nice)

Germany: F. König (Berlin); M. Schulze (Markkleeberg); J. Willgerodt (Leipzig); M. Wirth (Dresden); A. Von Keitz (Marburg)

Italy: F. Gaboardi (Milan); V. Gentile (Rome); M. Motta (Catania); P. Rigatti (Milano); R.M. Scarpa (Orbassano); O. Risi (Treviglio)

The Netherlands: E. Koldewijn (Eindhoven); E. Meuleman (Amsterdam); V. Van de Walle (Geleen)

Poland: P. Chlosta (Kielce); B. Darewicz (Bialystok); A. Dobrowolski (Myslowice); W. Dudziak (Srem); A. Gajda (Warszawa); P. Wedzikowski (Lodz); R. Jarema (Warszawa); R. Szwedowski (Opole); J. Szyperki (Bydgoszcz); P. Trypens (Warszawa); M. Wyczółkowski (Krakow)

Romania: F. Bajan (Pitesti); N. Calomfirescu (Bucharest); M. Dinu (Bucharest); C. Gingu (Bucharest); V. Jinga (Bucharest); C. Nitoiu (Bucharest)

Russia: S. Al-Shukri (St. Petersburg); V.P. Avdoshin (Moscow); I.A. Gorelov (St. Petersburg); I.S. Gorelov (St. Petersburg); V.K. Kheifets (St. Petersburg); B.V. Kunin (St. Petersburg); V.I. Kuzmin (St. Petersburg); O.B. Loran (Moscow); E.B. Mazo (Moscow); L.S. Mikhailov (St. Petersburg); I. Sedavnykh (St. Petersburg); A.V. Shanava (St. Petersburg); V.N. Shirshov (Moscow); V.N. Surikov (Moscow); A. Zhivov (St. Petersburg); M. Forkampf-Laue (St. Petersburg)

Spain: J. Caballero Alcántara (Marbella); E. Leon Dueñas (Sevilla); E. Fernández Fernández (Madrid); J.M. Fernández Gómez (Oviedo); F. Jiménez Cruz (Valencia); J.A. Portillo Martín (Santander)

Ukraine: A.A. Lyulko (Zaporizhzhya); A.V. Lyulko (Dnipropetrovsk); I. Gorpynchenko (Kyiv); F. Kostyev (Odesa); V. Lesovoy (Kharkiv); S. Pasiechnikov (Kyiv); V. Pirogov (Kyiv); V. Zaytsev (Chernivtsi)

United Kingdom: C.R. Chapple (Sheffield); S. Natale (Plymouth); R. Persad (Bristol); M. Speakman (Taunton, Somerset); A. Thorpe (Newcastle upon Tyne)

References

- [1] Chapple C. Medical treatment for benign prostatic hyperplasia. *BMJ* 1992;304:1198–9.
- [2] Clifford GM, Farmer RDT. Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol* 2000;38:2–19.
- [3] Barry MJ, Cockett AT, Holtgrewe HL, et al. Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. *J Urol* 1993;150:351–8.
- [4] Peters TJ, Donovan JL, Kay HE, et al. The International Continence Society “Benign Prostatic Hyperplasia” Study: the bothersomeness of urinary symptoms. *J Urol* 1997;157:885–9.
- [5] Madersbacher S, Alivizatos G, Nordling J, Rioja Sans C, Emberton M, de la Rosette JJMCH. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004;46:547–54.

- [6] Lepor H. Alpha blockers for the treatment of benign prostatic hyperplasia. *Rev Urol* 2007;9:181–90.
- [7] Chapple CR. Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: an overview for the practicing clinician. *BJU Int* 2004;94:738–44.
- [8] Lepor H, Auerbach S, Puras-Baez A, et al. A randomised, placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. *J Urol* 1992;148:1467–74.
- [9] Chapple CR, Carter P, Christmas TJ, et al. A three-month double-blind study of doxazosin as treatment for benign prostatic bladder outlet obstruction. *J Urol* 1994;74:50–6.
- [10] Michel MC, Grubbel B, Möllhoff S, et al. 1-Adrenoceptor affinities of drugs for the treatment of benign prostatic hyperplasia in human prostate, rat tissues and at cloned subtypes. Abstract presented at: 23rd Congress of the Société Internationale d'Urologie; September 18–24, 1994; Sydney, Australia. Abstract 649.
- [11] Hatano A, Takahashi H, Tamaki M, Komeyama T, Koizumi T, Takeda M. Pharmacological evidence of distinct α_1 -adrenoceptors subtypes mediating the contraction of human urethra and peripheral artery. *Br J Pharmacol* 1994;113:723–8.
- [12] Tatemichi S, Kobayashi K, Maezawa A, et al. α_1 -Adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213). *Yakugaku Zasshi* 2006;126:209–16.
- [13] Akiyama K, Hora M, Tatemichi S, et al. KMD-3213, a uroselective and long-acting alpha(1a)-adrenoceptor antagonist, tested in a novel rat model. *J Pharmacol Exp Ther* 1999;291:81–91.
- [14] Akiyama K, Noto H, Nishizawa O, et al. Effect of KMD-3213, an alpha1A-adrenoceptor antagonist, on the prostatic urethral pressure and blood pressure in male decerebrate dogs. *Int J Urol* 2001;8:177–83.
- [15] Kawabe K, Yoshida M, Homma Y, Silodosin Clinical Study Group. Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. *BJU Int* 2006;98:1019–24.
- [16] Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective alpha1A-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. *J Urol* 2009;181:2634–40.
- [17] Chapple C, Andersson KE. Tamsulosin: an overview. *World J Urol* 2002;19:397–404.
- [18] Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. *Urology* 2009;74:1318–22.
- [19] Kobayashi S, Tomiyama Y, Tatemichi S, Hoyano Y, Kobayashi M, Yamazaki Y. Effects of silodosin and tamsulosin on the urethra and cardiovascular system in young and old dogs with benign prostatic hyperplasia. *Eur J Pharmacol* 2009;613:135–40.
- [20] MacDiarmid SA, Hill LA, Volinn W, Hoel G. Lack of pharmacodynamic interaction of silodosin, a highly selective alpha1a-adrenoceptor antagonist, with the phosphodiesterase-5 inhibitors sildenafil and tadalafil in healthy men. *Urology* 2010;75:520–5.
- [21] van Dijk MM, de la Rosette JJMCH, Michel MC. Effects of alpha-1 adrenoceptor antagonists on male sexual function. *Drugs* 2006;66:287–301.
- [22] Furukawa K, Rosario DJ, Smith DJ, Chapple CR, Uchiyama T, Chess-Williams R. Alpha 1A-adrenoceptor-mediated contractile responses of the human vas deferens. *Br J Pharmacol* 1995;116:1605–10.
- [23] Michel MC, Hanft G, Groß G. Functional studies on alpha-1-adrenoceptor subtypes mediating inotropic effects in rat right ventricle. *Br J Pharmacol* 1994;111:539–46.
- [24] Noble AJ, Chess-Williams R, Couldwell C, et al. The effects of tamsulosin, a high affinity antagonist at functional α_{1A} - and α_{1D} -adrenoceptor subtypes. *Br J Pharmacol* 1997;120:231–8.
- [25] Leonardi A, Hieble JP, Guarneri L, et al. Pharmacological characterization of the uroselective alpha-1 antagonist Rec 15/2739 (SB 216469): role of the alpha-1L adrenoceptor in tissue selectivity, part I. *J Pharmacol Exp Ther* 1997;281:1272–83.
- [26] Giuliano FA, Clement P, Denys P, Alexandre L, Bernabe J. Comparison between tamsulosin and alfuzosin on the expulsion phase of ejaculation in rats. *BJU Int* 2006;98:876–9.
- [27] Miller J, Carson CC. Alpha blockers and ejaculatory function: a state of the art review. *Curr Sex Health Rep* 2007;4:141–4.
- [28] Sanbe A, Tanaka Y, Fujiwara Y, et al. α_1 -Adrenoceptors are required for normal male sexual function. *Br J Pharmacol* 2007;152:332–40.
- [29] Michel MC. α_1 -Adrenoceptors and ejaculatory function. *Br J Pharmacol* 2007;152:289–90.
- [30] Hisasue S, Furuya R, Itoh N, Kobayashi K, Furuya S, Tsukamoto T. Ejaculatory disorder caused by alpha-1 adrenoceptor antagonists is not retrograde ejaculation but a loss of seminal emission. *Int J Urol* 2006;13:1311–6.
- [31] Kobayashi K, Masumori N, Hisasue SI, et al. Inhibition of seminal emission is the main cause of anejaculation induced by a new highly selective α_1A -blocker in normal volunteers. *J Sex Med* 2008;5:2185–90.
- [32] Hellstrom WJ, Giuliano F, Rosen RC. Ejaculatory dysfunction and its association with lower urinary tract symptoms of benign prostatic hyperplasia and BPH treatment. *Urology* 2009;74:15–21.
- [33] Blanker MH, Bosch JL, Groeneveld FP, et al. Erectile and ejaculatory dysfunction in a community-based sample of men 50–78 years old: prevalence, concern, and relation to sexual activity. *Urology* 2001;57:763–8.
- [34] Blanker MH, Bohnen AM, Groeneveld FP, et al. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. *J Am Geriatr Soc* 2001;49:436–42.
- [35] Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). *Eur Urol* 2003;44:637–49.
- [36] Roehrborn CG, Lepor H, Kaplan SA. Retrograde ejaculation induced by silodosin is the result of relaxation of smooth musculature in the male urogenital tract and is associated with greater urodynamic and symptomatic improvement in male LUTS secondary to BPH. *J Urol* 2009;181. Abstract 1922.
- [37] Homma Y, Kawabe K, Takeda M, Yoshida M. Ejaculation disorder is associated with increased efficacy of silodosin for benign prostatic hyperplasia. *Urology* 2010;76:1446–50.