2. SYNOPSIS

NAME OF SPONSOR/COMPANY: Recordati S.p.A. Milan, Italy	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Urorec® NAME OF ACTIVE INGREDIENT(S): Silodosin	Volume: Page:	
Protocol No.: KMD 3213 IT-CL 0376 (EUDRACT No.: 2011-000045-20)		
Title of Study: Effectiveness and safety of silodosin in the treatment of LUTS in patients with benign prostatic hyperplasia: a European phase IV clinical study (the **S**ilodosin **i**n **R**eal-life **E**valuation study).		
Investigators: Investigators at 107 sites agreed to participate in this study, with scientific supervisors C. Chapple (UK), F. Cruz (Portugal), F. Desgrandchamps (France), C. Llorente (Spain), F. Montorsi (Italy).		
Study Centre(s): This study was performed in 107 sites located in France, Germany, Hungary, Ireland, Italy, Portugal, Romania, Spain, Turkey and UK.		
Publication (Reference): None to date.		
Studied Period (years): First Patient First Visit: 24 May 2011 Last Patient Last Visit (24 weeks of treatments, all centres): 11 March 2013. Last Patient Last Visit (additional 28 weeks of treatment, in Spain only): 17 July 2013		**Phase of development:** IV
Objectives: The objective of the study was to confirm in a larger and less selected population ("*real life conditions*") the positive risk-benefit balance observed with silodosin in previous double-blind, randomised clinical trials. The following aspects were evaluated: • The effects on lower urinary tract symptoms (LUTS), by means of the International Prostate Symptom Score (IPSS) questionnaire; • The effect on the most frequent and bothersome symptoms, by means of the International Continence Society (ICS)-male questionnaire; • The effects on quality of life (QoL) due to urinary symptoms by means of question 8 of the IPSS questionnaire; • The effects on No. of voids, urine volume and voided volume, as assessed by completing a Frequency-volume charts (FVCs) • The safety profile; • The adherence to therapy; • The patient satisfaction with treatment by means of the Patient Perception of Study Medication (PPSM) questionnaire. The effectiveness and safety of the drug were investigated also in different subgroups of patients according to age, severity of the disease, concomitant disease and medications.		
Methodology: International, multicentre, open-label, single-arm, phase IV clinical trial in patients with LUTS suggestive of a bladder outlet obstruction associated with benign prostatic hyperplasia (BPH) requiring a medical treatment. The study consisted of 2 periods: • A screening/wash-out period (from 3 days up to 4 weeks); • A 24-week active treatment period with silodosin 8 mg once daily. This period was prolonged for additional 28 weeks in Spanish centres only, according to a local amendment.		

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Number of Patients (planned and analysed): It was expected that 1000 patients would be enrolled.
A total of 95 sites screened 1111 patients, and enrolled 1036 patients in the study.
The analysis (March 2014) was conducted on the full set of patients;

- Number of patients enrolled: 1036;
- Number of patients analysed for safety: Safety (SAF) population = 1036;
- Number of patients analysed for efficacy: Full Analysis Set [FAS] population = 994; Per-Protocol [PP] population = 820.
- Number of patients treated for additional 28 weeks in Spanish centres only: 13

Diagnosis and Main Criteria for Inclusion: Men at least 60 years of age with a clinical diagnosis of BPH by the urologist and LUTS requiring a medical treatment (IPSS total score ≥ 12 at Screening and Baseline), able to comply with protocol procedures and with a written informed consent obtained before beginning any investigational procedures.

Test Product, Dose and Mode of Administration, Batch No.: One capsule (white, opaque, hard gelatin, size 0) of silodosin 8 mg taken orally once daily with food, preferably at the same time every day.
Marketed blisters of Silodosin 8 mg (Urorec®, Recordati Ireland Ltd., Cork, Ireland) were used in this study (batches No SF0L28, SF2C28 and SF1M98). Pierrel Research IMP, Cantù (CO) Italy, manufactured the final packaging of silodosin in accordance with current Good Manufacturing Practices (cGMP).

Duration of Treatment: After a screening/wash-out period (from 3 days up to 4 weeks), patients who met the selection criteria were treated with silodosin 8 mg for 24 weeks (52 weeks in Spanish centres only).

Reference Therapy, Dose and Mode of Administration, Batch No.:
Not applicable for this trial.

Criteria for Evaluation:

Efficacy:

Primary efficacy parameter

The primary efficacy parameter was the percentage of treatment responders at study end (defined as patients with a decrease ≥ 25% as compared to baseline in the IPSS total score).

Secondary efficacy parameters

LUTS - IPSS questionnaire

- IPSS response rate (decrease from baseline ≥ 25% in the IPSS total score) at each visit;
- Proportion of patients with a decrease in IPSS total score > 3 points from baseline (each visit and study end);
- Change from baseline in IPSS total score, storage and voiding subscores and QoL (each visit and study end).

LUTS – ICS-male questionnaire

- Change from baseline in the frequency and bothersomeness of each symptom at study end;
- Percentage of patients improving each symptom of the ICS-male questionnaire as compared to baseline;
- Percentage of patients showing an improvement in the symptoms perceived as most bothersome at baseline.

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Frequency-volume chart (FVC)

Change from baseline to study end in the following parameters:

- No. of voids (day/night/24 hours);
- Urine volume (day/night/24 hours);
- Min/max/mean voided volume.

PPSM questionnaire

- Percentage of patients satisfied with treatment according with PPSM questionnaire (study end).

Safety:

The following safety parameters were analysed:

- Treatment-emergent adverse events (TEAEs). Ejaculation disorders were reported according to the following terms: 1) orgasm no semen, 2) orgasm, semen quantity reduced, 3) orgasm, semen force reduced, 4) no orgasm;
- Change from baseline in sitting blood pressure (BP) and heart rate (HR) at study end;
- Laboratory tests: Red blood cell (RBC), white blood cell (WBC), platelet count, haemoglobin, haematocrit, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), glucose, serum creatinine and urinalysis;
- Electrocardiogram (ECG) parameters.

Adherence to therapy:

- Drug compliance;
- Discontinuations due to adverse reactions, lack of efficacy, other reasons.

Statistical Methods:

Descriptive statistics of the variables collected during the treatment phase are presented for each visit and endpoint including mean changes from baseline where required. Shift tables are used to describe changes at the end of the treatment with reference to baseline. Confidence intervals (95% CIs) are presented as well, and tests are applied where appropriate.

The effectiveness and safety of the drug are investigated also in different subgroups of patients according to age, severity of the disease, concomitant disease and medications, i.e.:

- Age (cut-off 65 and 75 years);
- Concomitant diseases (Cardiovascular disease, diabetes);
- Concomitant treatment with 5-ARI;
- Concomitant treatment with PDE-5 inhibitors;
- Concomitant treatment with anti-hypertensive drugs;
- Severity of symptoms at baseline.

Additionally, the subgroup analysis "Patients who are either naïve to therapy for LUTS or who were already on treatment at study entry (only in case of adequate subgroups size)" is performed.

Data collected in the additional 28 week treatment period foreseen in the Spanish sites only are presented separately.

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SUMMARY – CONCLUSIONS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Most patients (99.6%) of the SAF population were Caucasians. The mean (standard deviation [SD]) age was 67.8 (5.7) years, with 540 patients (52.1%) aged between 65 and 74 years, and 150 (14.5%) aged ≥ 75 years. The mean (SD) body mass index (BMI) at screening was 27.6 (4.0) kg/m^2.

Overall, mean (SD) time since diagnosis of BPH was 3.6 (4.0) years and the mean PSA value was 2.6 (2.8) ng/mL. In total, 209 patients (20.2%) had already taken a medication for LUTS, mostly alpha-blockers (16.5%), followed by 5-ARI (4.7%), herbals products (1.6%) and urinary antispasmodics (0.5%).

The mean (SD) IPSS total score at baseline was 18.9 (5.0), with 397 patients (38.3%) complaining severe symptoms (IPSS total score ≥ 20). A total of 689 patients felt mostly dissatisfied, unhappy or terrible if they had to spend the rest of their life with their current urinary condition, as assessed by Question 8 of the IPSS questionnaire. Nocturia, defined as at least 2 voids per night was reported by 876 patients (84.6%) (Question 7 of the IPSS questionnaire).

In the ICS-male questionnaire completed at baseline, the most frequent symptom was a decreased stream, while the most bothersome was considered nocturia.

The mean (SD) number of voids reported in the FVC in the 24 hour period was overall 10.3 (2.9) at baseline, of which 2.4 (1.1) in the nocturnal period. In total, the mean (SD) daily urine volume was 1753.2 (558.0) mL, 460.8 (255.9) in the nocturnal period)

The most frequently recorded urological/sexual dysfunction reported in the medical history was erectile dysfunction (15.5%), while ejaculation failure was reported by 3.8% of patients. A previous prostate biopsy was performed by 4.2% of patients.

The most frequent concomitant diseases were cardiovascular disease (including hypertension) (60.6%), dyslipidemia (19.5%) and diabetes (17.4%). Overall, 727 patients (70.2%) took at least one concomitant medication at baseline, including agents acting on the renin angiotensin system (41.9%), lipid modifying agents (23.2%), beta-blockers (21.8%), antithrombotics (20.1%), antidiabetics (15.7%), diuretics (13.4%) and calcium channel blockers (13.5%).

EFFICACY RESULTS:

Primary efficacy parameter

The primary efficacy variable of this study was the percentage of treatment responders at study end (defined as patients with a decrease ≥ 25% in the IPSS total score as compared to baseline).

A total of 766 patients (77.1%; Wilson Confidence Limits 95% [WCL]: 74.3-79.6%) of the FAS population and 655 patients (79.9%, WCL: 77.0-82.5%) of the PP population were treatment responders at study end.

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Secondary efficacy parameters (FAS analysis)

IPSS questionnaire

A significant improvement in LUTS and QoL due to urinary symptoms was observed after silodosin treatment, as evaluated by the change from baseline in the IPSS total score, storage and voiding subscores and Question 8 of the IPSS questionnaire:

	Baseline value	Change from baseline at endpoint	95% CI
IPSS total score	18.9 (4.9)	−8.3 (6.1)	(−8.7 ; −8.0)
IPSS storage subscore	8.1 (2.7)	−3.2 (3.0)	(−3.4 ; −3.1)
IPSS voiding subscore	10.8 (3.6)	−5.1 (4.1)	(−5.4 ; −4.9)
IPSS QoL (Q8)	4.0 (1.2)	−1.8 (1.5)	(−1.9 ; −1.7)

A total of 803 patients (80.8%, WCL 78.2-83.1%) reported a decrease from baseline > 3 points in the IPSS total score. Nocturia, as assessed by Question 7 of the IPSS questionnaire, was reported by 85.7% of patients at baseline (WCL 83.4-87.8%) and by 52.4% (49.3-55.5%) at the end of treatment.

ICS-male questionnaire

Half of the patients had an improvement in the symptoms reported as most frequent and most bothersome at baseline:

Most bothersome symptoms at baseline	Baseline value (SD)	Change in bother from baseline (SD) p value	% patients improved in bother	Most frequent symptoms at baseline	Baseline value (SD)	Change in frequency from baseline (SD) (p value	% patients improved in frequency
Nocturia	2.6 (0.9)	−0.7 (0.9) p <.001	52.6%	Decreased stream	3.6 (1.0)	−0.9 (1.2) p <.001	56.9%
Frequency	2.6 (0.8)	−0.7 (0.9) p <.001	54.7%	Terminal dribbling	3.1 (1.1)	−0.6 (1.2) p <.001	49.4%
Decreased stream	2.5 (0.9)	−0.6 (0.9) p <.001	49.4%	Incomplete emptying	2.9 (1.0)	−0.7 (1.1) p <.001	53.0%
Urgency	2.4 (0.9)	−0.6 (0.9) p <.001	48.9%	Intermittency	2.7 (1.0)	−0.6 (1.1) p <.001	47.5%
Terminal dribbling	2.3 (0.9)	−0.5 (0.9) p <.001	43.8%	Urgency	2.7 (1.0)	−0.7 (1.0) p <.001	49.4%
Incomplete emptying	2.3 (0.9)	−0.6 (0.9) p <.001	47.3%	Hesitancy	2.6 (1.0)	−0.6 (1.0) p <.001	47.8%

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Frequency Volume Chart (FVC)

The FVC analysis revealed for overall, daytime and nocturnal voids that the number of voids and urine volume decreased, while mean voided volumes increased during the study:

Parameter	Period	Baseline	End of study	Change from baseline	
		Mean (SD)	Mean (SD)	Mean (SD)	95% CI
No. of voids	24 h	10.7 (3.1)	9.3 (2.9)	-1.3 (2.7)	-1.6; -1.1
	Day	8.4 (2.6)	7.5 (2.4)	-0.9 (2.3)	-1.1; -0.7
	Night	2.4 (1.1)	2.0 (1.0)	-0.4 (1.1)	-0.5; -0.3
Urine volume (mL)	24 h	1793 (567)	1666 (581)	-127 (509)	-170; -84.0
	Day	1352 (440)	1282 (443)	-70.3 (403)	-105; -36.0
	Night	482 (261)	418 (249)	-64.0 (241)	-84.4; -43.6
Mean voided volume (mL)	24 h	173 (51)	183 (55)	10.0 (44.6)	6.2; 13.8
	Day	166 (48)	177 (56)	11.4 (44.7)	7.6; 15.2
	Night	206 (85)	212 (84)	6.7 (76.0)	0.2; 13.2

PPSM questionnaire

The 74.2% of patients reported to be satisfied with the study medication and its effect on their urinary problems treatment at study end.

SAFETY RESULTS:

The mean (SD) exposure to the study drug in the SAF population was 164.9 (37.1) days

TEAEs

Overall 587 TEAEs were reported from 366 patients (35.3%). The intensity of TEAEs was mild in 273 patients (26.4%), moderate in 115 patients (11.1%) and severe in 30 patients (2.9%). There were 77 patients (7.4%) with a TEAE that led to withdrawal from the study. Two patients (0.2%) experienced a fatal AE. Serious TEAEs were reported by 32 subjects (3.1%). TEAEs that occurred in ≥1% of the patients were "Ejaculation failure" (18.1%), "Dizziness" (2.1%), "Erectile dysfunction" (1.8%), "Diarrhoea" (1.6%), "Headache" (1.4%) .

Treatment-related TEAEs

Overall 278 patients (26.8%) reported any TEAE considered treatment-related.

The most frequently reported treatment-related TEAE was "Ejaculation failure" reported in 185 patients (17.9%). This MedDRA PT codes mainly the verbatim "Orgasm, no semen" (n=141) and "Orgasm, semen quantity reduced" (n=41). Other treatment-related TEAEs that occurred at a frequency of ≥ 3 patients were: "Dizziness" reported in 20 patients (1.9%), "Erectile dysfunction" in 16 patients (1.5%), "Diarrhoea" in 13 patients (1.3%), "Headache" in 10 patients (1.0%), "Vertigo" in 7 patients (0.7%), "Anorgasmia" in 7 patients (0.7%), "Hypotension" in 7 patients (0.7%), "Dry mouth" in 6 patients (0.6%), "Nasal congestion" in 6 patients (0.6%), "Libido decrease" in 5 patients (0.5%), "Abdominal pain upper" in 3 patients (0.3%), "Nausea" in 3 patients (0.3%), "Fatigue" in 3 patients (0.3%), and "Testicular pain" reported in 3 patients (0.3%).

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Serious Adverse Events (SAEs)

TEAEs considered serious occurred in 32 patients (3.1%), including two patients who died in the course of the study. One patient (ID No. FR12−002) died due to a Road traffic accident associated with his job, and another patient (ID No. HU06−007) died due to a Cardiac failure associated with a concomitant disease (extensive coronary arteriosclerosis and previous old myocardial infarction). Both fatal AEs were not related to the study medication. The only expected SAE considered possibly related to silodosin was a case of Dizziness in a 70 years old male patient with a medical history of diabetes mellitus, hypertension and dyslipidemia, which resolved after treatment discontinuation (ID No. PT06-001). Four unexpected SAEs were considered at least possibly related to silodosin (SUSARs), even if concomitant diseases or medications may also have played a causative role:

Patient No.	Country Age (yr)	Medical history	Dates of treatment	Serious adverse drug reactions	Date of onset	Outcome
IT18-009	Italy 72	Hypertension and cardiac arrhythmia.	22-Dec-11 22-Jan-12	Syncope Sudden hearing loss	20-Jan-12	Recovered Not Recovered
FR02-014	France 70	Sinus node disease (pacemaker), gout, hypercholesterolemia, left renal cancer with bone metastasis	8-Feb-12	Cerebral ischaemia	28-Mar-12	Recovered with sequelae
DE03-004	Germany 75	Hypertension, heart rhythm disorder, hypercholesterolemia. Concomitant treatment with doxazosin (protocol violator).	13-Dec-11 10-May-12	Bradycardia	11-May-12	Recovered
DE04-020	Germany 64	Hypertension, diabetes mellitus, syncope, cardiac pacemaker, old cerebral infarction, obesity	5-Apr-12 8-Jun-12	Transient ischaemic attack	9-Jun-12	Recovered

TEAE leading to treatment discontinuation

A total of 77 patients (7.4%) reported TEAEs leading to treatment discontinuation. Although "Ejaculation failure" was the most common TEAE leading to treatment discontinuation, this occurred in only a minority of patients (25 patients, 2.4%). No other TEAE lead to treatment discontinuation in more than 1% of the patients.

Other safety parameters

No clinically relevant changes were observed in mean sitting BP and HR during treatment: the mean change from baseline (SD) was of -1.2 (13.3) mmHg for systolic BP, -0.4 (8.7) for diastolic BP and + 1.0 (9.8) bpm for HR. No patient discontinued due to clinically significant abnormalities in laboratory parameters.

Adherence to therapy

The overall mean (SD) compliance to the study medication was high: 96.8 (11.1). A total of 154 patients (14.9%) prematurely discontinued the 24-week treatment period. This was due to TEAEs (7.4%), patient's decision (4.5%), patient lost to follow-up (1.2%), lack of efficacy (0.9%), protocol violation (0.6%) and other reasons (0.3%).

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Subgroup analysis

Efficacy (FAS population): responders were 80.8% in the age group < 65 years, 75.8% in patients aged 65-74 years and 73.0% in patients aged ≥ 75 years (p value of Chi-Square Test = 0.115, p-value of Cochran Armitage Trend Test = 0.041). Naïve patients (n = 791) had a higher response rate (79.3%) in comparison to patients on previous treatment for BPH (68.5%) (p-value of Chi-Square Test = 0.001). No significant change was instead observed according to the severity of the disease at baseline or the presence of concomitant disease.

Safety (Safety population): The subgroup analysis on different age classes revealed that there was an association between the age class and the occurrence of any treatment-related TEAE, since their percentage decreased with increasing age class, due to a lower occurrence of ejaculation failure in the elderly. No significant difference was observed according to concomitant diseases or antihypertensive medications. The subgroup of patients with concomitant treatment with PDE-5 and 5-ARI is too low to draw some conclusion.

Parameter	**Subgroup**	**No. of patients**	**% of patients with any treatment-related TEAE**	**% of patients with any TEAEs leading to discontinuation**
Age (years)	<65 65-74 ≥ 75	N=346 N=540 N=150	33.8 % 23.5 % 22.7 % Chi square: p 0.002	8.1 % 6.5 % 9.3 % Chi square: p 0.424
Cardiovascular disease	Yes No	N=628 N=408	25.3% 29.2% Chi square: p 0.172	7.2% 7.8% Chi square: p 0.685
Diabetes	Yes No	N=181 N=855	24.9% 27.3% Chi square: p 0.510	6.1% 7.7% Chi square: p 0.444
Previous treatment for BPH	Naïve Treated	N=827 N=209	26.5 % 28.2% Chi square: p 0.610	7.1 % 8.6% Chi square: p 0.467
Severity of symptoms	IPSS < 20 IPSS ≥ 20	N=632 N=397	28.3 % 23.9% Chi square: p 0.121	6.3 % 9.1% Chi square: p 0.102
Antihypertensive medications	Yes No	N=580 N=456	25.3 % 28.7% Chi square: p 0.223	7.2 % 7.7% Chi square: p 0.792
PDE-5 inhibitors	Yes No	N=18 N=1018	61.1 % 26.2% Chi square: p < 0.001	16.7 % 7.3% Chi square: p 0. 132
5-ARI	Yes No	N=42 N=994	21.4 % 27.1% Chi square: p 0.420	7.1 % 7.4% Chi square: p 0.942

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Additional 28 week treatment period: no safety issue was identified in the 13 patients included in the additional 28 week-treatment period according to a local amendment in Spain.

CONCLUSION:

This large phase IV clinical trial, conducted in various European Countries with inclusion of patients with LUTS/BPH of all age-groups, with frequent concomitant diseases and taking various concomitant medications, was performed to confirm in a larger and less selected population the positive risk-benefit balance observed with silodosin in previous randomized, double blind clinical trials.

In this study population silodosin, at a dose of 8 mg once daily, has significantly improved the LUTS complained by the patients at baseline, with 77.1% resulting treatment responders, as assessed by the IPSS questionnaire. This data favorably compares with the efficacy data observed in previous phase III clinical trials. In fact, in the active-controlled phase III clinical study conducted in Europe the responder rate (i.e. improvement in the IPSS total score by at least 25%) was significantly higher in the silodosin (68%) and tamsulosin group (65%), as compared to placebo (53%).

In the present study it was also possible to demonstrate a significant improvement in the symptoms that were considered as most bothersome by the patients at baseline, as assessed by the ICS-male questionnaire. Approximately half of the patients reported an improvement in nocturia, frequency, decreased stream. urgency, terminal dribbling and incomplete emptying at study end.

As expected, the most frequently reported treatment-related TEAE was ejaculation failure (17.9%), that however lead to treatment discontinuation in only a minority of patients (25/1,036, 2.4%). Despite the high number of patients with concomitant cardiovascular disease or antihypertensive medications, only a few cases of hypotension have been reported.

Overall, the adherence to therapy was good, with only few patients discontinuing the treatment due to any type of AEs or lack of efficacy. In addition, 74.2% of patients at study end reported to be satisfied with the study medication and its effect on their urinary problems.

Date of the report: 21 March 2014