

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 22-206**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
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Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## Statistical Review and Evaluation

### CLINICAL STUDIES

**NDA/Serial Number:** 22-206  
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## **1.0 EXECUTIVE SUMMARY**

### **1.1 Conclusion and Recommendations**

The results support the efficacy of Rapaflo 8 mg once daily in treating the signs and symptoms of benign prostatic hyperplasia (BPH) as measured by the International Prostate Symptom Score (IPSS) and maximum urine flow rate (Q<sub>max</sub>). In two US clinical trials, treatment with Rapaflo 8 mg resulted in statistically significant improvement in IPSS (P<0.01) and Q<sub>max</sub> (p<0.01) compared to placebo.

From a statistical perspective, this application provided adequate data to support the efficacy of Rapaflo 8 mg once a day for the treatment of BPH.

### **1.2 Brief Overview of Clinical Studies**

The applicant, Watson Laboratories, Inc. reports efficacy and safety data from two Phase 3 clinical studies (study SI04009 and study SI04010) to support Rapaflo 8 mg once a day for the treatment of signs and symptoms of BPH. Both studies were parallel-group, randomized, double-blind, double-dummy, placebo-controlled studies, conducted under identical but separate protocol.

Following a 4-week single-blind run-in phase, patients, aged ≥50 years who had BPH (with an International Prostate Symptom Score (IPSS) of ≥13 and maximum urinary flow rate of 4-14 mL/sec with a minimum voided volume of 125 mL) were randomized to receive either silodosin 8 mg (2 silodosin 4 mg capsules once daily) or matching placebo for a treatment period of 12 weeks. Efficacy was evaluated by IPSS questionnaire that consisted of 8-item questionnaire designed to quantify the symptoms experienced most frequently with BPH and urine flow rate measured by a calibrated device.

The primary and secondary efficacy endpoints were the change from baseline to week 12 in total IPSS score and Q<sub>max</sub>, respectively. The objective in both the studies was to demonstrate that Rapaflo 8 mg is superior to placebo with respect to the above endpoints. A total of 461 patients in study SI04009 and 462 patients in study SI04010 were randomized equally to Rapaflo and placebo, respectively.

### **1.3 Statistical Issues and Principal Findings**

There were no major statistical issues in the study conduct, however, the statistical analysis method (ANCOVA) used was not appropriate due to violation of normality assumption, a necessary condition for the method to be valid. We performed an alternative analysis method (ANCOVA based on rank) to perform the efficacy analysis. In addition, there were approximately 11.0% and 16.7% (study SI04009 and SI04010, respectively) of patients who had major protocol deviations. Compliance with the study medication was the major violation. The sponsor performed sensitivity analysis excluding major protocol violators from the efficacy analysis (evaluable population analysis) to evaluate the potential impact of protocol violations on the efficacy results.

Based on the applicant's data and confirmed by our independent analysis, the efficacy results can be summarized as follows:

- (1) In both studies, at 12 weeks of treatment, Rapaflo 8 mg once daily demonstrated statistically significant reductions ( $p < 0.01$ ) in IPSS total score compared to placebo.
- (2) Rapaflo 8 mg also demonstrated statistically significant ( $p < 0.05$ ) increase in  $Q_{max}$  (maximum urine flow rate) compared to placebo.
- (3) The efficacy conclusions based on sensitivity analysis using mITT, observed cases or evaluable analysis populations were same as above.

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## 2.0 INTRODUCTION

### 2.1 Overview

Silodosin was developed as once-a-day formulation to treat signs and symptoms of benign prostatic hyperplasia (BPH). It was approved in Japan in 2006 and currently being studied in the European Union. The applicant, Watson Laboratories, is seeking approval of Silodosin in the United States.

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To support the application, Watson submitted efficacy data from one Phase 2 (KMD3213-US021-99) and two Phase 3 (SI04009 and SI04010) studies conducted in the United States. Both Phase 3 studies were multicenter, double-blind, placebo-controlled studies conducted under two separate but identical protocols.

### 2.2 Data Sources

The submission was in hard copy and partially electronic. Submitted data were stored in folder \\C in FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limits.

### 2.3 Indication

*Silodosin capsule is indicated for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH).*

## 3.0 STATISTICAL EVALUATION

### 3.1 EVALUATION OF EFFICACY

#### 3.1.1 Overview of Studies: SI04009 and SI04010

Studies SI04009 and SI04010 were identical in design except that no plasma concentration data were collected in study SI04010. The methodologies in both studies were the same; therefore, unless otherwise indicated the study method described below are applicable to both studies.

**Design and Objectives:** Studies SI04009 and SI04010 were multi-center, randomized, placebo-controlled, and for a duration of 12-weeks with an open-label extension and conducted at 42 and 44 sites in the United States, respectively.

The objectives of the studies were to evaluate the safety and efficacy of once-a-day dosing of Silodosin relative to placebo, in reducing signs and symptoms of BPH as measured by the IPSS score and maximum urine flow (Q<sub>max</sub>).

Following a 4-week single-blind run-in phase, patients, aged  $\geq 50$  years who had BPH (with an International Prostate Symptom Score (IPSS) of  $\geq 13$  and maximum urinary flow rate of 4-14 mL/sec with a minimum voided volume of 125 mL) were randomized to receive either silodosin 8

mg (2 silodosin 4 mg capsules once daily) or matching placebo for a treatment period of 12 weeks.

**Outcomes:** Treatment outcomes were assessed by IPSS, urine flow, and quality of life due to urinary symptoms. Assessments were made at scheduled weeks -4, -2, 0, 0.5, 1, 2, 4, and 12 or discharge. IPSS consisted of 8-item questionnaire designed to quantify the symptoms experienced most frequently with BPH. Questions 1-6 were graded on a 6-point scale as 0='not at all' to 5='almost always', question 7 was graded as 0='none' to 5='5 or more times', and question 8 evaluated the patient's quality of life due to urinary symptoms. IPSS was the total score of question 1-7. Maximum urine flow was measured by a standard calibrated device. In addition, a voided volume of at least 125 mL, sub-scores of irritative (sum of questions 2, 4, 7) and obstructive (sum of questions 1, 3, 5, 6) symptoms were also obtained in all cases.

**Efficacy Endpoints:** As per protocol, the primary and secondary endpoints were change from baseline to week 12 in total IPSS score and Qmax, respectively.

**Sample Size:** The sample size for both studies was calculated based on testing the superiority hypothesis with respect to change in IPSS score. Using a difference in mean change of 1.54 between treatment groups and a common standard deviation of 5.2 (from Phase 2 study US021), a sample size of 240 patients (300 with a drop-out rate of 20%) per treatment group was required (to test the null hypothesis using a type-I error rate of .05 and 90% power).

**Definition of Analysis Population:** Efficacy analyses were planned using mITT and evaluable analysis population. The mITT population was defined as all randomized patients who received at least one dose of study drug and at a minimum, provided IPSS data at baseline, according to the actual treatment received. The evaluable population was defined as all patients who completed the study and provided data for primary efficacy variable at week 12.

For mITT population, last observation carried forward (LOCF) approach will be used for patients who fail to provide data at week 12 of the study.

**Statistical Analysis Method:** For comparison of treatment groups with respect to both primary and secondary endpoints, the statistical methods included an analysis of covariance (ANCOVA) model with respective baseline outcomes as covariate, and treatment effect as factor.

### 3.1.2 Reviewer's Comment

*The sample size was adequate for testing the superiority hypothesis for the primary efficacy endpoint in both studies and the use of ANCOVA as statistical analysis method was also appropriate, provided normality assumption is not violated.*

### 3.2 Results: Study SI04009

#### 3.2.1 Patient Disposition

A total of 461 patients were randomized equally to the treatment groups in study SI04009. Majority (90%) of the patients have completed 12 weeks of treatment. Forty five (9.8%) patient discontinued the study prematurely with 31 (13.3%) in the silodosin group and 14 (6%) in the placebo group. The predominant reasons for discontinuation were adverse event with a significantly higher number in the silodosin group than in the placebo group (8.6% versus 2.6%, respectively). Overall, 90% of the patients completed 12 weeks of treatment.

The final mITT analysis (LOCF) population included all 461 randomized patients and evaluable (observed cases) analysis population included 415 patients.

**Table 3.2.1: Disposition of Patients: Study SI04009**

	Placebo N (%)	Rapaflo N (%)	Total N (%)
Randomized	228 (49.0%)	233 (51.0%)	461 (100%)
Completed	214 (94.0%)	202 (86.7%)	416 (90.2%)
Discontinued	14 ( 6.0%)	31 (13.3%)	45 ( 9.8%)
Reasons for Discontinuation:			
Adverse Event	6 (2.6%)	20 (8.6%)	26 (5.6%)
Protocol deviation	3 (1.3%)	2 (0.9%)	5 (1.1%)
Withdrawal	4 (1.8%)	1 (0.4%)	5 (1.1%)
Lack of efficacy	0	2 (0.9%)	2 (0.4%)
Lost to follow-up	0	4 (1.7%)	4 (0.9%)
Other	1 (0.4%)	2 (0.8%)	3 (0.6%)
Analysis Population:			
mITT (LOCF) at week 12	228	233	461 (100%)
Evaluable (Observed) “	213 (93%)	202 (87%)	415 ( 90%)

Source: Table 10.1-1, Study Report

#### 3.2.2 Patient Demographics and Baseline Characteristics

The treatment groups were well balanced with regards to demographic and baseline characteristics such as age, race, gender, etc. Most of the patients were Caucasian (87%) with a mean age of 64 years and appeared to be representative of the patient population for BPH.

#### 3.2.3 Efficacy

**IPSS Total Score:** Per protocol, the primary efficacy endpoint was the change from baseline to week 12 in the total IPSS score. To evaluate treatment difference, an analysis of covariance ANCOVA model was used to assess the statistical significance of differences between the treatment groups. The

model included baseline values as covariate and treatment as factor in the model. We examined the data for testing the normality assumption of the ANCOVA model. The change from baseline data was slightly skewed and therefore a violation of normality assumption of ANOVA. Although not a gross violation, we performed analysis using both ANCOVA and non-parametric method. Results of our analyses using either parametric or non-parametric method were similar. However, we report the results based on ANCOVA in order to show the consistency with the sponsor's results, as shown in Table 3.2.3. Although demonstration of efficacy at the end of week 12 of treatment was the primary goal, the sponsor report results for all weeks. Our analysis also shows the results for all weeks (Appendix).

The baseline IPSS score was similar between Rapaflo and placebo patients. At 12 weeks of treatment, mean reduction was -6.5 for Rapaflo and -3.7 for placebo patients, respectively. The difference in reductions between the two groups were statistically significant ( $p < .01$ ). Results of analysis using observed cases (completers at 12 weeks of treatment) were similar. The results were also statistically significant starting at week 1 of treatment.

**Qmax:** Results of treatment difference in urine flow rates (Qmax) between two groups are shown in Table 3.2.3. Rapaflo had a moderate positive effect on the change from baseline in urine flow rates compared to placebo. At 12 weeks of treatment, the change (increase) in flow rates between two groups was statistically significant (2.2 versus 1.2,  $p < 0.01$ ).

**Table 3.2.3: Mean ( $\pm$ SD) Change from Baseline to Week 12 for IPSS Total Score and Maximum Urine Flow Rate (Qmax): ITT Population (LOCF), Study SI04009.**

Endpoint(s)	Statistics	Placebo N=228	Rapaflo 8 mg N=233	Treatment Difference <sup>+</sup>	P-value
IPSS Score	Baseline	21.4 (4.9)	21.5 (5.4)	--	<.0001
	Change	-3.7 (5.9)	-6.7 (6.8)	-3.0	
	n	228	233		
Qmax Values	Baseline	9.0 (2.8)	9.0 (2.6)	--	.0060
	Change	1.2 (3.8)	2.2 (4.3)	1.0	
	n	228	233		

<sup>+</sup> LS Mean change based on ANCOVA model with factors baseline value and treatment.  
Source: Table 3.2.3, Appendix.

### 3.2.4 Reviewer's Comment

*Results of our analysis confirmed the sponsor's conclusion that Rapaflo 8 mg was superior to placebo in the reduction of IPSS total score and in the improvement of Qmax, the urine flow rate.*

### 3.3 Results: Study SI04010

#### 3.3.1 Patient Disposition

A total of 462 patients were randomized equally to the treatment groups in study SI04010. Majority (90%) of the patients have completed 12 weeks of treatment. Forty six (10%) patient discontinued the study prematurely with 22 (9.4%) in the Rapaflo group and 24 (10.5%) in the placebo group. The predominant reasons for discontinuation were adverse event and voluntary withdrawal, with more Rapaflo patients discontinued due to adverse events than placebo patients (4.3% versus 1.7%). Overall, discontinuation did not appear to be related to study drug.

The final mITT analysis (LOCF) population included all 462 randomized patients and evaluable (observed cases) analysis population included 416 patients.

**Table 3.3.1: Disposition of Patients: Study SI04010**

	Placebo N (%)	Rapaflo N (%)	Total N (%)
Randomized	229 (49.0%)	233 (51.0%)	462 (100%)
Completed	205 (89.5%)	211 (90.6%)	416 (90.0%)
Discontinued	24 (10.5%)	22 (9.4%)	46 (10.0%)
Reasons for Discontinuation:			
Adverse Event	4 (1.7%)	10 (4.3%)	14 (3.0%)
Protocol deviation	0 (0.0%)	1 (0.4%)	1 (0.2%)
Withdrawal	10 (4.4%)	5 (2.1%)	15 (3.2%)
Lack of efficacy	2 (0.9%)	0 (0.0%)	2 (0.4%)
Lost to follow-up	3 (1.3%)	2 (0.9%)	5 (1.1%)
Other	5 (2.2%)	4 (1.7%)	3 (1.9%)
Analysis Population:			
mITT (LOCF) at week 12	229	233	462 (100%)
Evaluable (Observed) "	207 (90%)	210 (90%)	417 (90%)

Source: Table 10.1-1, Study Report

#### 3.3.2 Patient Demographics and Baseline Characteristics

The baseline characteristics such as age, race, gender, and body mass index were similar across treatment groups. Concomitant medication use and prior drug treatment for OAB were also similar between treatment groups.

#### 3.3.3 Efficacy

**IPSS Total Score:** As shown in Table 3.3.3, the baseline IPSS score was similar between Rapaflo and placebo patients. At 12 weeks of treatment, mean reduction was -6.4 for Rapaflo and -3.4 for

placebo patients, respectively. Similarly, the results were also statistically significant starting at week 1 of treatment, the average reductions (improvement) from baseline in the IPSS score was greater for Rapaflo treated patients, compared to placebo patients. Results of analysis using observed cases (completers at 12 weeks of treatment) were similar.

**Qmax:** Results of treatment difference in urine flow rates (Q<sub>max</sub>) between two groups are shown in Table 3.3.3. Rapaflo had a moderate positive effect on the change from baseline in urine flow rates compared to placebo. At 12 weeks of treatment, the change (increase) in flow rates between two groups was statistically significant (1.9 versus 2.9, p<0.01).

**Table 3.3.3 Change (Baseline to Week 12) for IPSS Total Score and Maximum Urine Flow rate: ITT (LOCF) Population, Study SI04010.**

Endpoint(s)	Statistics	Placebo N=229	Rapaflo 8 mg N=233	Treatment Difference	P-value
IPSS Score	Baseline	21.2 (4.9)	21.2 (4.9)	--	<.0001
	Change n	-3.4 (5.8) 229	-6.4 (6.7) 233	-3.0	
Q <sub>max</sub> Values	Baseline	8.7 (2.7)	8.4 (2.5)	--	0.0431
	Change n	1.9 (4.8) 229	2.9 (4.5) 233	1.0	

+ LS Mean change based on ANCOVA model with factors baseline value and treatment.  
Source: Table 3.2.3, Appendix.

**3.3.4 Reviewer’s Comment**

*In study SI04010, the results of our independent analysis confirmed that compared to placebo, Rapaflo 8 mg once daily treatment resulted in statistically significant improvements in both IPSS total score and maximum urine flow rates.*

**4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

In both studies, change from baseline in IPSS score were also examined by race, and geriatric status (ages <65, ≥65, and ≥75years). Although most (90%) patients randomized in both studies were Caucasian, there appear to be no clinically meaningful differences in effect size between treatments by different races. Similarly, no statistically significant differences were noted between age groups (<65, ≥65), except that in small subpopulations of geriatric (≥75 years) patients the results were not statistically significantly different between Rapaflo and placebo treatment. The sponsor concluded however that the magnitude of change was comparable to mITT population.

## 5.0 SUMMARY AND CONCLUSIONS

We performed statistical analyses to evaluate the protocol-specified primary and secondary endpoints. Our statistical analysis method included ANCOVA based on ranks, since the normality assumption for parametric ANCOVA was not met. Results of our analysis support the efficacy of Rapaflo 8mg once daily for the treatment of signs and symptoms of BPH, as measured by IPSS total score and Qmax (maximum urine flow rate). The difference in treatment effect (change from baseline to week 12 in IPSS score) was approximately -3 in both studies and statistically significant ( $p < .01$ ) between Rapaflo and placebo. Similarly, the treatment effect in Qmax was statistically significantly superior for Rapaflo, compared to placebo, although the magnitude of difference is approximately 1.

From a statistical perspective, the data provided in this application demonstrated the efficacy of Rapaflo 8 mg once daily in the treatment of signs and symptoms of BPH.

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APPENDIX

Table 3.2.3 Change from Baseline in IPSS Total Score by Weeks: Study SI04009.

Visit	Statistics	Placebo N=233	Rapaflo N=228	Treatment Difference <sup>+</sup>	P-value
Week 0 (Baseline)	Mean (SD) n	21.4 (4.9) 228	21.5 (5.4) 233	-	
Week 1 (OC)	Mean (SD) n	-2.1 (4.6) 226	-4.4 (5.7) 226	-2.3	<.0001
Week 2 (OC)	Mean (SD) n	-2.5 (4.6) 221	-5.3 (6.4) 222	-2.8	<.0001
Week 4 (OC)	Mean (SD) n	-2.9 (5.4) 218	-5.9 (6.6) 214	-3.0	<.0001
Week 12 (OC)	Mean (SD) n	-3.7 (5.9) 213	-6.7 (6.8) 202	-3.0	<.0001
Week 12 (LOCF)	Mean (SD) n	-3.6 (5.8) 228	-6.5 (6.7) 233	-2.9	<.0001

<sup>+</sup> LS mean change based on ANCOVA model with factors baseline value and treatment.

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Table 3.2.3 Change from Baseline in Qmax by Weeks: Study SI04009.

Visit	Statistics	Placebo N=233	Rapaflo N=228	Treatment Difference <sup>+</sup>	P-value
Week 0 (Baseline)	Mean (SD) n	9.0 (2.8) 228	9.0 (2.6) 233	-	
Week 1 (OC)	Mean (SD) n	1.1 (3.3) 224	2.2 (3.5) 224	1.1	.0005
Week 2 (OC)	Mean (SD) n	1.4 (3.5) 222	2.6 (3.9) 219	1.2	.0009
Week 4 (OC)	Mean (SD) n	1.4 (3.6) 220	2.4 (4.2) 214	1.0	.0075
Week 12 (OC)	Mean (SD) n	1.1 (3.7) 213	2.1 (4.3) 203	1.0	.0098
Week 12 (LOCF)	Mean (SD) n	1.2 (3.8) 228	2.2 (4.3) 233	1.0	.0060

<sup>+</sup> LS mean change based on ANCOVA model with factors baseline value and treatment.

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Table 3.3.3 Change from Baseline in IPSS Total Score by Weeks: Study SI04010

Visit	Statistics	Placebo N=229	Rapaflo N=233	Treatment Difference <sup>+</sup>	P-value
Week 0 (Baseline)	Mean (SD) n	21.2 (4.9) 229	21.2 (4.9) 233	-	
Week 1	Mean (SD) n	-2.8 (4.7) 222	-4.9 (5.4) 228	-2.1	<.0001
Week 2	Mean (SD) n	-3.1 (4.9) 220	-5.6 (5.5) 228	-2.5	<.0001
Week 4	Mean (SD) n	-3.4 (4.8) 216	-6.2 (5.9) 225	-2.8	<.0001
Week 12	Mean (SD) n	-3.6 (6.0) 207	-6.6 (6.5) 210	-3.0	<.0001
Week 12 (LOCF)	Mean (SD) n	-3.4 (5.8) 229	-6.4 (6.4) 233	-2.9	<.0001

<sup>+</sup> LS mean change based on ANCOVA model with baseline value and treatment as factors.

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Table 3.3.4 Change from Baseline in Qmax by Weeks: Study SI04009.

Visit	Statistics	Placebo N=229	Rapaflo N=233	Treatment Difference <sup>+</sup>	P-value
Week 0 (Baseline)	Mean (SD) n	8.7 (2.7) 228	8.4 (2.5) 233	-	
Week 1 (OC)	Mean (SD) n	2.2 (3.7) 223	2.9 (3.7) 227	1.1	0.0583
Week 2 (OC)	Mean (SD) n	2.2 (4.6) 219	2.9 (4.1) 227	1.2	0.2090
Week 4 (OC)	Mean (SD) n	2.0 (4.4) 213	2.7 (3.9) 223	1.0	0.1892
Week 12 (OC)	Mean (SD) n	2.0 (5.0) 207	3.1 (4.7) 210	1.0	0.0554
Week 12 (LOCF)	Mean (SD) n	1.9 (4.8) 229	2.9 (4.5) 233	1.0	0.0431

<sup>+</sup> LS mean change based on ANCOVA model with factors baseline value and treatment.

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