1) Healthy male ≥45 years of age, including six subjects ≥65 years of age willing and able to comply with protocol requirements and able to provide a written informed consent;
2) Body mass index (BMI) of 18 to 35, inclusive.

Exclusion Criteria:

1) participation in a study involving the administration of an investigational compound within the past 30 days;
2) history of allergy to alpha-blockers, sildenafil, tadalafil, iodides, or to any of the inactive agents used in theses formulations;
3) any current medical condition which precluded the safe use of an alpha-blocker and maximum dose PDE-5 inhibitor, including, but not limited to
    - angina pectoris,
    - severe congestive heart failure,
    - significant cardiac dysrhythmias,
    - recurrent episodes of dizziness, vertigo, or loss of consciousness
    - renal insufficiency (serum creatinine >2.0 mg/dL)
    - left ventricular outflow obstruction
    - mild, moderate, or severe hepatic impairment;
4) history of or current significant postural hypotension, and or have experienced significant postural hypotension upon initiation of therapy with an alpha-blocker or PDE-5 inhibitor;
5) Consumption of any medication which precluded safe participation in the study (washed out by 10 days before Day 2 or five half-lives, whichever is greater), including nitrates, PDE5 inhibitors, alpha-blockers or potent CYP3A4 inhibitors
6) History of (within the last one year) or current evidence of alcohol or drug abuse;
7) Blood donation during the previous 4 weeks;
8) Positive test for Hepatitis B or HIV;
9) Current smoker or smoked within the past 6 months.

E.4 Study Population /Demographics

Twenty-four subjects were enrolled in the study. Subjects ranged in age from 45 to 78 years with a mean age of 59.5 years. All subjects were Caucasian. Of the 24 subjects, 7 were 65 years of age or older.

Subjects were generally healthy. Other than one subject with a history of hypertension and a second with sleep apnea, there were no significant medical problems reported among the volunteers recruited.

E.5 Subject Disposition and Protocol Violations

Twenty-two subjects completed the study and received both test doses of sildenafil and tadalafil. Two subjects voluntarily withdrew prior to completion, both for personal reasons. There were no major protocol violations.

E.6 Safety Analysis

E.6.1 Extent of Exposure

Twenty-two subjects were exposed to silodosin 8 mg daily for 21 days, and single doses of 100 mg sildenafil and 20 mg of tadalafil. Two subjects received one dose of silodosin of silodosin at the clinic on the first treatment day, and then failed to return for subsequent evaluation.

E.6.2 Serious Adverse Events
No deaths or serious adverse events occurred during the trial.

E.6.3 Premature discontinuation due to adverse events
None.

E.6.4 Common Treatment Emergent Adverse Events
Adverse events were not more common when silodosin was combined with a PDE-5 inhibitor than when combined with placebo (Table E.1). The most common treatment-emergent AEs are also shown in Table E.1.

Notably, no events of symptomatic orthostasis occurred. One event of dizziness occurred while the patient was receiving silodosin combined with placebo.

Table E.1 Number of Adverse Events by Treatment Group, Most Common Treatment Emergent Adverse Events

Adverse Event	Silodosin + Tadalafil (N=22)	Silodosin + sildenafil (N=22)	Silodosin + placebo (N=22)	Total (N=22)
Total # events	2	6	7	15
Headache	0	2	2	6
Nausea	0	1	0	3
Vomiting	1	1	0	3
Retrograde ejaculation	0	1	0	2

E.6.5 Orthostatic Test Results
E.6.5.1 Mean Change from Baseline
Orthostatic testing (blood pressure and pulse measured in the supine position and then at 1 and 3 minutes after standing upright) was performed at 0, 1, 2, 3, 4, 6, 8, and 12 hours after co-administration of silodosin with tadalfil/sildenafil/placebo. A positive orthostatic test was defined as any one of the following:

- decrease from baseline in systolic blood pressure of >30 mmHg
- diastolic blood pressure >20 mmHg
- increase in pulse of >20 bpm.

The maximum mean change from baseline (supine measurement) in orthostatic SBP, DBP and pulse measured during the twelve-hour observation period was similar among the three treatment groups, as shown in Table E.2.

Table E.2. Summary of Maximum Mean Change from baseline in orthostatic vital signs by treatment group (All Subjects)

	Silodosin + tadalafil	Silodosin + sildenafil	Silodosin + placebo
SBP (upright)	-10.2	-5.0	-10.7
DBP (upright)	-5.2	-1.6	-2.6
Heart Rate (upright)	+14.2	+15.6	+13.9

When results were stratified by age group (45-64 years and >65 years), there also was no significant difference in maximum mean change from baseline in SBP, DBP or heart rate among the three treatment groups (Tables E.3 and E.4). However, the maximum mean changes in orthostatic vital signs for all three treatments were greater in subjects ≥65 year than in younger subjects.

Table E.3. Summary of Maximum Mean Change from baseline in orthostatic vital signs by treatment group (Subjects 45-64 Years of Age)

	Silodosin + tadalafil	Silodosin + sildenafil	Silodosin + placebo
SBP	-9.1	-3.6	-10.1
DBP	-4.9	+0.3	-1.8
Heart Rate	+17.8	+16.3	+15.8

Table E.4. Summary of Maximum Mean Change from baseline in orthostatic vital signs by treatment group (Subjects >65 Years of Age)

	Silodosin + tadalafil	Silodosin + sildenafil	Silodosin + placebo
SBP	-15.2	-12.7	-13.3
DBP	-7.2	-7.3	-7.0
Heart Rate	+13.3	+17	+14.3

E.6.5.2 Positive Orthostatic Test Results

The percentage of subjects with a positive orthostatic test result at each post-dose time point is shown for the three treatment groups in Table 5. The greatest percentage of patients with a positive orthostatic test at any time point was seen in the silodosin+tadalfil group, followed by silodosin + sildenafil and then silodosin +placebo (see shaded cells in Table E.5).

Table E.5. Summary of Positive Orthostatic Test Results by Treatment Group (All Subjects)

Timepoint relative to dosing	Timepoint relative to standing upright	Sildenafil N=22	Tadalafil N=22	Placebo N=22
Pre-dose	1 minute	6 (27.3%)	4 (18.2%)	3 (13.6%)
	3 minutes	1 (4.5%)	3 (13.6%)	2 (9.1%)
Hour 1	1 minute	5 (22.7%)	5 (22.7%)	4 (18.2%)
	3 minutes	5 (22.7%)	6 (27.3%)	2 (9.1%)
Hour 2	1 minute	3 (13.6%)	4 (18.2%)	6 (27.3%)
	3 minutes	4 (18.2%)	4 (18.2%)	3 (13.6%)
Hour 3	1 minute	5 (22.7%)	5 (22.7%)	7 (31.8%)
	3 minutes	3 (13.6%)	2 (9.1%)	4 (18.2%)
Hour 4	1 minute	10 (45.5%)	8 (36.4%)	4 (18.2%)
	3 minutes	4 (18.2%)	6 (27.3%)	1 (4.5%)
Hour 6	1 minute	0	3 (13.6%)	6 (27.3%)
	3 minutes	1 (4.5%)	1 (4.5%)	3 (13.6%)
Hour 8	1 minute	5 (22.7%)	6 (27.3%)	2 (9.1%)
	3 minutes	1 (4.5%)	2 (9.1%)	2 (9.1%)
Hour 12	1 minute	6 (27.3%)	4 (18.2%)	5 (22.7%)
	3 minutes	5 (22.7%)	3 (13.6%)	4 (18.2%)

Reviewer's comment: It is notable that even in the silodosin+placebo group, up to a third of patients had a positive orthostatic test result during the 12 hour monitoring period.

In the twelve-hour monitoring period, the total number of positive orthostatic tests was greater in the silodosin + PDE-5 inhibitor groups than in placebo, for both middle-aged and older subjects (Table E.6).

Table E.6. Total number of positive orthostatic tests by age group and treatment

Age Group	Sildenafil	Tadalafil	Placebo
45-64 years	53	55	49
>64 years	12	11	9
All	65	66	58

E.6.5.3 Outliers

No subject had a SBP less than 90 mmHg or pulse greater than 100 bpm at any time point in the 12 hour period after combination dosing.

E.6.5.4 Laboratory Evaluation

There were no clinically significant changes in laboratory parameters during the study.

Summary:

1) The population studied was generally healthy and may not be representative of the patients likely to be prescribed a PDE-5 inhibitor in clinical practice (e.g.

diabetics, or patients with cardiovascular disease). Any synergistic effect of silodosin and a PDE-5 inhibitor on blood pressure may be enhanced in patients with other co-morbidities.

2) Although the maximum mean change in orthostatic vital sign parameters was similar among the three combination treatment groups, the number of positive orthostatic tests was greater when silodosin was combined with a PDE-5 inhibitor than with placebo. This was true both for subjects 45-64 years of age and those >65 years.
3) This study's small sample size limits the conclusions that can be drawn regarding the safety of silodosin combined with PDE-5 inhibitors, particularly in patients >65 years (N=6).

E.7 Conclusion:

This reviewer does not believe that this study supports the safety of the combination of silodosin and PDE-5 inhibitors for the reasons listed above.

Appendix F – SI04011, Phase 3 Open-label Safety Extension

"A multi-center open-label evaluation of the safety of silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia"

Trial start date: September 12, 2005 **Trial end date:** April 16, 2007

F.1 Objectives:
The objectives of the study were to evaluate the safety and sustained efficacy of silodosin 8 mg once daily for 40 weeks.

F.2 Design and Conduct of the Study:
This was a multi-center, 40-week, open-label extension for BPH patients who had previously completed study SI04009 or SI04010. Six-hundred and sixty-one men enrolled. The trial consisted of eight visits to the study clinic. Efficacy was assessed by the IPSS. Safety measurements included monitoring for adverse events, clinical laboratory evaluation and physical examination.

F.2.1 Schedule of Study Assessments
The schedule of events is shown in Table F.1.

F.1 Schedule of events, SI04011

Procedure	V1	V2	V3	V4	V5	V6	V7/ET
	W0	W2	W8	W16	W24	W32	W40
Informed Consent	X						
Demographics	[1]						
Medical History	[1]						
Medication History	[1]						
Physical Examination	[2]						X
ECG	[2]		X				X
Clinical Labs	[2]		X	X			X
Vital Signs	[2]		X	X			X
IPSS	[2]		X				X
Adverse Events		X	X	X	X	X	X
Concomitant Medication	[1]	X	X	X	X	X	X
Dispense Invest. Product	X	X	X	X	X	X	
Drug Account.		X	X	X	X	X	X

[1]Transferred data from double-blind study; ongoing therapies at the last visit of double-blind study will be transferred with their original start date.
[2]Transferred data from last visit of Study double-blind.

Copied from NDA 22-206, SI04011 study report, Table 9.5.1.4-1, p. 22.

Reviewer's comment: Orthostatic vital signs were not performed during this study.

Clinical laboratory evaluation included serum chemistries, hematology, and urinalysis at Visits 3, 4, and 7/discharge. PSA, TSH, T3and free and total T4 were obtained at Visit 7/discharge.

F.3 Entry Criteria:

Inclusion criteria:

Men aged 50 years or older who had successfully completed a previous silodosin double-blind study (SI04009 or SI04010).

Exclusion Criteria:

1) Participation in a study other than double-blind trial SI04009 or SI04010 involving the administration of an investigational compound within the previous 30 days, or within 5 half-lives of the prior investigational drug.
2) Intravesical obstruction from any cause other than BPH
3) Bladder calculi
4) Neurogenic bladder and other conditions that could have affected bladder function
5) Any type of procedure during the study that was considered an intervention for BPH or bladder neck obstruction (e.g. prior TURP, TUNA therapy, etc)
6) An active urinary tract infection
7) Current prostatitis or a diagnosis of chronic prostatitis
8) Urinary retention from a cause other than BPH
9) Prostate cancer as suspected by TRUS, DRE or clinical acumen. Subjects with a PSA between 4.0 and 10.0 had prostate cancer ruled out to the satisfaction of the clinical investigator.
10) Invasive bladder cancer
11) Radiation to the pelvis
12) Bladder catheterization or bladder or prostate instrumentation
13) Any other current medical condition which precluded safe participation in the study, including angina pectoris, severe CHF, poorly controlled hypertension (SBP>160 mmHg, DBP>90 mmHg), poorly controlled diabetes (HgbA1C>10% ULN), renal insufficiency (serum creatinine>2.0 mg/dL), liver insufficiency (any LFT>2X ULN), abnormal chest x-ray within the last year, endocarditis, cardiac arrhythmias, recurrent episodes of dizziness, pelvic surgery for malignancy or bowel resection, and hematuria which has not been appropriately evaluated.
14) Currently receiving the following medications: alpha-blockers (other than silodosin); alpha-agonists; diuretics; antispasmodics; cholinomimetics; anticholinergics; tricyclic antidepressents; ketoconazole or other known potent CYP3A4 inhibitor; androgens or anti-androgens; and natural/herbal products for the treatment of prostate conditions.
15) Use of over-the-counter cough and cold remedies within 24 hours before Qmax measurements
16) Evidence of drug or alcohol abuse within the last 12 months
17) An allergy to any of the inactive agents used in the silodosin formulation
18) Uncontrolled hypo-or hyperthyroidism.

F.4 Primary and secondary endpoints:

The primary efficacy endpoint was the change from baseline in the IPSS total score at Visit 7/Week 40 (LOCF). Changes on the irritative and obstructive subscales of the IPSS and on the quality of life question were also described. Baseline was defined as the last visit of the double-blind study.

F.5 Study Population Demographics:
Six-hundred and sixty-one patients at 77 centers enrolled in the study. Of these, 91% were Caucasians, with a mean age of 65 years. Nearly half of patients (48.5%) were older than 65 years, and 11.9% were older than 75 years.

F.6 Patient Disposition
Of the 661 patients enrolled, 435 patients (65.8%) completed the trial. The most common reasons for early discontinuation was an adverse event (14.1%), followed by lack of efficacy (8.8%), and voluntary withdrawal (5.0%).

There were eighty major protocol deviations in 79 patients (77 for lack of compliance to study medication and three for eligibility criteria deviations).

Compliance was assessed by study medication count at each visit. Mean compliance in the study was 93.5%.

F.7 Efficacy Analysis
Efficacy analysis was performed only on the evaluable population – all patients who completed the study and who were without major protocol deviations.

During the 9-month treatment period, there was a mean decrease of 3.1 points in the IPSS total score. Patients who had previously received placebo during the double-blind treatment period had a larger response than those who had received silodosin (Table F.2). All subjects also experienced a decrease in irritative and obstructive symptom subscales at Week 40, also shown in Table F.2.

Table F.2. Mean (SD) Change from Baseline to Week 40 (LOCF) in IPSS Total and Subscale Scores

Assessment	Treatment Received During Double Blind Study		Overall N=429
	Placebo N=223	Silodosin N=206	
IPSS Total Score	-4.4 (6.71)	-1.6 (5.92)	-3.1 (6.49)
Irritative Symptom Subscale	-1.7 (3.23)	-0.7 (2.72)	-1.2 (3.04)
Obstructive Symptom Subscale	-2.7 (4.16)	-1.0 (3.87)	-1.9 (4.11)

At the conclusion of the nine-month treatment period (LOCF), 77.6% of patients were at least "mixed about equally satisfied and dissatisfied" regarding their quality of life due to urinary symptoms, compared to 56% of patients at baseline.

F.8 Safety analysis

F.8.1 Extent of Exposure
Mean exposure was 225.1 days. There were 519 patients exposed for at least 14 weeks, and 338 exposed for at least 40 weeks.

F.8.2 Serious Adverse Events

Deaths: There were two deaths during the study. Narratives are presented below.

Patient 259027 This patient was a 58 year old, markedly obese (164kg) Caucasian male who was randomized to placebo in the double-blind phase of study SI04010 from November 8, 2005, to March 13, 2006. He entered study SI04011 on March 14, 2006. His past medical history included abdominal hernia, obstructive sleep apnea and left carotid bruit. Baseline 12-lead ECG showed sinus arrhythmia with left bundle branch block. The patient was on no concomitant prescription medications.

On [redacted] the patient experienced a fatal myocardial infarction. According to the death certificate, the cause of death was listed as acute MI due to severe coronary atherosclerosis. The investigator assessed the event as not related to study drug. b(6)

Patient 133032 This patient was a 79-year-old Caucasian male who was randomized to silodosin in the double-blind phase of study SI04009 from October 25, 2005 to January 22, 2006. He entered study SI04011 on January 23, 2006. The patient had a past medical history of chronic bronchitis, bilateral knee arthritis and GERD. Concomitant medications were Naprosyn 500 mg bid and Nexium 40 mg daily.

Or [redacted] he patient was hospitalized for an elective left total knee replacement. Silodosin was discontinued on September 24, 2006 prior to surgery. The patient was discharted to a nursing home for physical rehabilitation on [redacted] On [redacted], the patient experienced acute shortness of breath with subsequent cardiopulmonary arrest and death. The diagnosis of probably pulmonary embolus was made at the time of death. The investigator assessed the adverse event as not related to study drug. b(6)

Reviewer's comment: There is no report that an autopsy was performed on the patient to confirm the clinical diagnosis of pulmonary embolism.

Serious Adverse Events (Other): Twenty-nine patients experienced 35 serious adverse events: diverticulitis (2 events), hip arthroplasty (2), atrial fibrillation (2), prostate cancer (2), aneurysm, deep vein thrombosis, osteoarthritis (4), back injury, lung neoplasm malignant (3), concussion, knee arthroplasty, pulmonary embolism (2), nerve root lesion, spinal laminectomy, arrhythmia, artharalgia, squamous cell carcinoma, acute myocardial infarction, myocardial infarction, gastritis, pain in extremity, femoral artery occlusion, transient ischemic attack, lobar pneumonia, and carotid artery stenosis). None of the SAEs was considered by the investigator to be related to silodosin.

Reviewer's comment: There is no commonality among the SAEs.

F.8.3 Premature discontinuation due to adverse events

Eighty-six patients (13.0%) discontinued prematurely due to an adverse event emerging during the open-label period. The most common AEs resulting in discontinuation were retrograde ejaculation (4.8%), diarrhea (0.8%), libido decreased (0.6%), dizziness (0.5%), and lung neoplasm malignant (0.5%). The events of retrograde ejaculation, diarrhea, libido decreased and dizziness were considered related to study drug, but lung neoplasm was considered unrelated.

F.8.4 Common Treatment Emergent Adverse Events

Treatment-emergent adverse events occurring in >2% of patients receiving silodosin are shown in Table F.3.

Table F.3. Summary of Most Common Treatment Emergent Adverse Events by MedDRA Preferred Term (Safety Population)

Adverse Event – MedDRA preferred term	Double-Blind Treatment Group		Overall N=661
	Placebo N=347 n (%)	Silodosin N=314 n (%)	
Retrograde ejaculation	108 (31.1)	30 (9.6)	138 (20.9)
Diarrhea	16 (4.6)	11 (3.5)	27 (4.1)
Nasopharyngitis	12 (2.5)	12 (3.8)	24 (3.6)
Dizziness	12 (3.5)	7 (2.2)	19 (2.9)
URI	9 (2.6)	9 (2.9)	18 (2.7)
Arthralgia	11 (3.2)	6 (1.9)	17 (2.6)
Orthostatic hypotension	10 (2.9)	7 (2.2)	17 (2.6)
PSA increased	8 (2.3)	6 (1.9)	14 (2.1)
Nasal congestion	8 (2.3)	5 (1.6)	13 (2.0)

Source: NDA 22-206 ser 000, SI04011 study report, Table 12.2.2-1

Reviewer's comment: Common AEs reported in this trial are consistent with those reported during the double-blind studies.

F.8.5 Other Notable Adverse Events

There was a single report of intraoperative floppy iris syndrome (IFIS).

F.8.6 Vital Signs

Subjects experienced a mean decrease in systolic and diastolic blood pressure and a mean increase in heart rate at all post-treatment time points relative to baseline (Table F.4).

Table F.4 Change from baseline in Vital Signs, SI04011

Vital Sign Parameter	Change from baseline (SD)
Systolic Blood Pressure (mm Hg)	
Week 8	-2.7 (13.41)
Week 16	-3.8 (13.89)
Week 40/ET	-2.7 (14.26)
Diastolic Blood Pressure (mm Hg)	
Week 8	-1.5 (8.33)
Week 16	-2.7 (8.80)
Week 40/ET	-1.5 (8.57)
Heart Rate (bpm)	
Week 8	0.6 (8.50)
Week 16	2.3 (10.07)
Week 40/ET	1.5 (9.74)

Reviewer's comment: Mean changes observed in vital signs are consistent with silodosin's mechanism of action. The small degree of change observed is not a significant safety concern..

F.9 Laboratory

There were no meaningful changes in mean serum chemistry, hematology or hormone parameters from baseline to up to 40 weeks.

F.9 Conclusion

Results of this trial suggest that efficacy of silodosin is maintained for up to 9 months of treatment. In addition, no safety concerns were identified in up to 9 months of treatment.

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Appendix G: SI05008, Maximum Tolerated Dose Study

"A Randomized, double-blind, placebo-controlled, dose escalation evaluation of the maximum tolerated dose of silodosin in healthy male subjects"

Trial Start date: October 4, 2005
Trial End date: December 13, 2005

G.1 Objectives

To determine the maximum tolerated dose of silodosin (16, 24, 32, 40, 48, 56, or 64 mg, administered once daily for 3 days) in healthy male subjects.

G.2 Design and Conduct of the Study

This study was a randomized, double-blind, placebo-controlled, sequential dose escalation trial in sequential cohorts of six healthy male subjects aged 18 to 45 years. Within each cohort, 5 subjects received active drug and one received placebo.

Each dose level was preceded by a variable titration period. Once at the target dose, that dose of study drug (or placebo) was administered once daily for three days. Throughout the dosing period, subjects remained in the study clinic and were monitored for safety via adverse event review, 12-lead ECG, Holter monitoring, vital signs and orthostatic testing. Plasma pharmacokinetic sampling was also performed. Escalation to the next higher dose occurred only when the safety of the previous dose was confirmed by review of all safety data.

G.3 Entry Criteria:

Inclusion Criteria:

Healthy males aged 18 to 45 years with a BMI of 18 to 33 and a body weight $\leq$120kg who are willing and able to comply with the protocol requirements.

Exclusion Criteria:

1. participation in a study involving the administration of an investigational compound within the past 30 days;
2. history of allergy to alpha-blockers;
3. any current medical condition which precluded the safe use of an alpha-blocker (e.g. angina pectoris, severe congestive heart failure, significant cardiac dysrhythmias, recurrent episodes of syncope/dizziness/vertigo, renal or hepatic insufficiency);
4. history of or current significant postural hypotension and/or experienced postural hypotension upon initiation of an an alpha-blocker;
5. consumption of any medication or herbal product, with the exception of occasional acetaminophen or aspirin, from 7 days before Day 1 to study exit;
6. History within the last year or current evidence of alcohol or substance abuse;
7. blood donation during the previous 4 weeks;
8. positive serology for Hepatitis B, C, or HIV;
9. clinically significant abnormalities on screening Holter monitoring;

10. current smokers or patients who had smoked within the past 6 months;

G.4. Study Population /Demographics

Thirty male subjects, aged 19 to 45 years, were enrolled in the study. Two subjects were African-American while the remaining subjects were Caucasian. There was no significant difference among treatment groups in demographic characteristics. Subjects were generally healthy with no significant past medical history reported. Two subjects had a history of Gilbert's syndrome.

G.5. Subject Disposition and Protocol Violations

Twenty-nine of the thirty enrolled subjects completed the study. One subject discontinued due to an adverse event. There were no major protocol deviations identified during the trial.

G.6 Safety Evaluations

G.6.1 Extent of Exposure

The extent of exposure experienced by the 25 subjects receiving silodosin in the study is summarized in Figure G.1.

Figure 1. Summary of Extent of Exposure for Silodosin Subjects

Cohort	N	Days
16 mg	5	4
24 mg	5	5
32 mg	5	6
40 mg	5	7
48 mg	4	8
48 mg	1	4

Source: NDA 22-2-6, Study SI05008 report, Table 12.1-1, page 34.

The maximum tolerated dose was found to be 48 mg as a result of postural hypotension, so escalation above 48 mg was not possible.

G.6.2 Adverse Events

G.6.2.1 Serious adverse events

No deaths or serious adverse events occurred during the study.

G.6.2.2 Other Significant Adverse Events

One subject in the 48 mg dose group discontinued prematurely due to the adverse event of severe postural hypotension. The narrative of this event follows:

> *Subject 130* was a 40-year-old male with no significant past medical history. He developed symptomatic orthostatic hypotension on Day 4 of dosing (still during the titration phase; he had not reached the 48 mg dose level). At the seven hour post-dose orthostatic test, the subject complained of significant lightheadedness, weakness, double vision, and a cold and numb feeling below his waist. Vital signs showed a supine BP of 102/61 mmHg and pulse of 64 bpm. At 1 minute after standing, BP of 65/43 and pulse 77. The 3 minute BP could not be obtained due to severe symptoms. The subject was

placed in the supine position with gradual resolution of symptoms. He was discharged early from the study and evaluation the following day showed no further episodes though he continued to have asymptomatic increase in his heart rate with standing. Vital signs for this patient are shown in Table G.1.

Table G.1. Vital Signs, Subject 130

Dosing Day	Silodosin dose	Time point relative to silodosin dose	Position	Blood Pressure	Pulse	Symptoms
1	8 mg bid	Pre-dose	Supine	109/65	55	
			Upright (1 min)	105/68	64	
			Upright (3 min.)	100/65	66	
1	8 mg bid	3 hour	Supine	---	57	
			Upright (3 min)	---	78	None
2	16 mg AM, 8 mg PM	7 hours	Supine	108/65	61	lightheadedness
			Upright (1 min)	119/68	86	Lightheaded
			Upright (3 min)	Not obtained due to symptoms		
4	32 mg AM, 8 mg PM	7 hours	Supine	102/61	64	
			Upright (1 min)	65/43	77	
			Upright (3 min)	Not obtained due to symptoms		
		10 hours	Supine	115/70	71	
			Upright (1 min)	119/68	88	
			Upright (3 min)	106/72	91	

G.6.2.3 Common Treatment Emergent Adverse Events

Overall, there were 98 adverse events reported by subjects receiving silodosin compared to 22 by those receiving placebo. The most common AE experienced by subjects on silodosin was postural hypotension, the frequency of which was directly proportional to dose (shown in Table G.2). Tachycardia and headache were other commonly reported AEs.

Table G.2. Summary of most common treatment emergent adverse events by dose group

Adverse Event	16 mg N=5		24 mg N=5		32 mg N=5		40 mg N=5		48 mg N=5	
	N	# events	N	# events	N	# events	N	# events	N	# event
Symptomatic postural hypotension	5	5	4	8	5	9	5	11	5	12
Tachycardia	2	2	3	3	4	4	5	5	5	5
Headache	3	3	0	0	1	1	5	5	1	1

G.6.2.4 Orthostatic Test Results

Orthostatic testing was performed daily at three hour intervals for 12 hours after silodosin (or placebo) dosing. One or more of the following observations defined a positive test:

- Decrease in SBP >30 mmHg
- Decrease in DBP >20 mmHg
- Increase in heart rate >20 bpm.

This reviewer defined a positive orthostatic test by a decrease in SBP ≥20 mmHg, a criterion typically used in clinical practice. Number of subjects and events by dose group meeting this reviewer's orthostatic criteria are shown in Table G.3.

Table G.3. Positive Orthostatic Tests (number of subjects and events by dose group)

	Orthostatic Criterion					
	SBP ≥20 mmHg		DBP≥20 mmHg		HR +20 bpm	
Dose	N	#	N	#	N	#
16 mg	0	0	0	0	5/5	82
24 mg	0	0	0	0	5/5	120
32 mg	2/5	6	2/5	3	5/5	163
40 mg	3/5	2	0	0	5/5	256
48 mg	2/5	2	0	0	5/5	209

In addition, a trend toward larger changes in orthostatic SBP, DBP and heart rate were observed at higher doses (Figure G.2).

Figure 2. Maximum Observed Change from Baseline in Orthostatic Measurements

Cohort	Systolic Blood Pressure mmHg	Diastolic Blood Pressure mmHg	Heart Rate BPM
16 mg	-13.0	-4.0	51.0
24 mg	-16.0	-7.0	73.0
32 mg	-31.0	-24.0	75.0
40 mg	-25.0	-9.0	76.0
48 mg	-37.0	-18.0	51.0

Source: NDA 22-206, Study SI05008 report, Table 12.4-1, page 37.

G.6.2.4.1 Orthostatic Outliers

The incidence of extreme orthostatic vital signs (SBP<90 mmHg or HR>120 bpm while standing) increased in a dose-proportional manner (Table G.4).

Table G.4 Number of Events meeting extreme orthostatic criteria by dose group, SI05008

Cohort	SBP <90 while upright	HR>100 while upright	HR >120 while upright
16 mg	0	12	0
24 mg	0	33	2
32 mg	0	64	1
40 mg	4	193	4
48 mg	2	54	1

G.6.3 Laboratory Evaluation

There were no clinically significant changes in laboratory parameters during the study.

G.6.4 Summary

- The most common adverse event experienced by silodosin subjects was symptomatic postural hypotension.
- A general dose-response relationship was apparent for both symptomatic postural hypotension and maximum change from baseline in orthostatic blood pressure.
- All subjects at the lowest dose studied (16 mg) met orthostatic pulse criteria ($\Delta \geq 20$ bpm) at several time points during the study.

G.6.5 Conclusion

Although the sponsor concluded that 48 mg was the maximum tolerated dose of silodosin, results of this study suggest that even a 16 mg dose may be unsafe.

Olivia Easley, MD
Medical Officer
Division of Reproductive and Urologic Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Olivia Easley
10/7/2008 04:13:47 PM
MEDICAL OFFICER

George Benson
10/7/2008 04:39:14 PM
MEDICAL OFFICER
Second MO review. Includes addendum regarding manufacturing site inspection

Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review

NDA	22-206
Brand Name	RAPAFLO ™
Generic Name	Silodosin
Sponsor	Watson Laboratories
Indication	Treatment of the Signs and Symptoms of Benign Prosthetic Hyperplasia
Dosage Form	Tablets
Drug Class	α-adrenergic antagonist
Therapeutic Dose	8 mg once daily with food
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	24 mg per DRUP
Application Submission Date	12/13/07
Review Classification	Standard NDA
Date Consult Received	1/24/08
Clinical Division	Division of Reproductive and Urologic Products
PDUFA Date	4/1/08 (Desired Completion Date)

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant effect of silodosin was detected in this 'thorough QT' study. The largest upper limits of the two-sided 90% CI for the placebo-corrected mean change in QTcF from baseline between the two doses of silodosin (8 mg and 24 mg) and placebo were both below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

The study was a double-blind, randomized, placebo- and moxifloxacin- (open label), four-arm parallel study in which 186 healthy male subjects were administered silodosin 8 mg, silodosin 24 mg or placebo once daily for 5 days. Moxifloxacin 400 mg was administered as a single dose on day 5 to establish assay sensitivity. Overall findings are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Silodosin (8 mg and 24 mg) and the Largest Lower Bound for Moxifloxacin

Treatment	Time (hour)	ΔΔ QTcF (ms)	90% CI (ms)
Silodosin 8 mg	6	3.95	(0.03, 7.87)
Silodosin 24 mg	6	4.80	(0.28, 9.31)
Moxifloxacin *	3	9.63	(6.18, 13.09)

*Multiple endpoint adjustment was not performed here. Using Bonferroni adjustment for 9 time points, the largest lower bound is 4.2 ms.

At the supratherapeutic dose (24 mg), mean silodosin plasma concentrations were approximately 3-fold higher than the concentrations following the highest therapeutic dose (8 mg). The plasma concentrations attained do not cover the increases due to CYP3A inhibition with ketoconazole (3.7-fold increase in C_{max}). Given the lack of dose-response in the primary statistical endpoint and the lack of an exposure-response relationship for silodosin, the increase in silodosin exposures due to metabolic inhibition is not expected to prolong the QT interval. Furthermore, there were no reports of clinically important adverse events related to QT prolongation (seizure, TdP, ventricular tachycardia or sudden death) reported by the sponsor in the clinical summary.

2 PROPOSED LABEL

The sponsor has proposed describing study results in the clinical pharmacology section of the label. We defer all final labeling decisions to the Clinical Review Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

b(4)

Reviewer's Comments: Acceptable.

3 BACKGROUND

Silodosin (KMD-3213) is a selective α_{1A}-AR antagonist created by Kissei Pharmaceutical Co., Ltd. of Japan in 1993, and developed for the treatment of the signs and symptoms of benign prostatic hyperplasia. According to the sponsor, Phase 3 clinical studies in the United States and Japan have demonstrated that silodosin is effective in improving the lower urinary tract symptoms (LUTS) associated with BPH, and has a favorable cardiovascular side effect profile. The Sponsor is seeking approval of silodosin in the United States for the "treatment of the signs and symptoms of BPH."

3.1 MARKET APPROVAL STATUS

Silodosin was approved in Japan in January 2006. The product is currently in Phase 3 development in the European Union under Recordati, S.p.A.,

b(4)

3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary

"The hERG tail current using HEK293 cells was determined after administration of silodosin at concentrations of 1×10-7, 3×10-7, 1×10-6, 3×10-6 and 1×10-5 mol/L. The hERG tail current was inhibited in a concentration-dependent manner at 1×10-6 mol/L and higher concentrations, with an IC50 value of 8.91×10-6 mol/L. In the evaluation of myocardial action potential waveform in the papillary muscle isolated from male Hartley guinea pigs to which silodosin was administered at concentrations of 1×10-7, 1×10-6 and 1×10-5 mol/L. APD90 was prolonged by 6.4% and 17.1% at concentrations of 1×10-6 and 1×10-5 mol/L, respectively.

"In the determination of hERG tail current in HEK293 cells and of myocardial action potential waveform in the papillary muscle isolated from male Hartley guinea pigs to which KMD-3213G was administered at concentrations of 1×10-7, 1×10-6 and 1×10-5 mol/L, KMD-3213G did not show any effect up to 1×10-5 mol/L.

"Conscious male beagle dogs (n=7) were used to evaluate blood pressure, heart rate and ECG after a single oral administration of silodosin at doses of 0.2, 2 and 20 mg/kg (washout period of 7 days between dosages). Silodosin did not show any effect on heart rate and ECG, even at the highest dose of 20 mg/kg. A decreasing effect on blood pressure was observed, which was attributable to α1-AR antagonistic effect, a pharmacological action of silodosin. Transient decreases in mean blood pressure and diastolic blood pressure (by 12% and 16%, respectively) were observed only at 1 hour after administration of 0.2 mg/kg. After administration of 2 mg/kg, transient decreases in mean blood pressure and diastolic blood pressure (by 13% and 12%, respectively) were observed at 1 hour, and a decrease in systolic blood pressure (by up to 18%) was observed at 1 to 6 hours. After administration of 20 mg/kg a decrease in systolic blood pressure (by up to 24%) at 0.5 to 8 hours, a decrease in diastolic blood pressure (by up to 22%) at 1, 3, 4, 6 and 8 hours, and a decrease in mean blood pressure (by up to 23%) at 0.5 to 8 hours were observed. These effects were resolved by 24 hours after administration.

"After intravenous injection of KMD-3213G at doses of 0.3, 1 and 3 mg/kg in conscious male beagle dogs, the metabolite did not show any effect on blood pressure, heart rate or ECG up to 3 mg/kg."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety

"Twenty-five clinical studies have been performed with silodosin in 1,774 subjects or patients that contribute data describing its safety. Data from all US Phase 2/3 studies were combined for the ISS. Studies within the integrated database were grouped for analysis in three groups:

- All US Controlled Studies (KMD3213-US021-99, SI04009, SI04010)

- US Phase 3 Controlled Studies (SI04009, SI04010)
- All US Controlled and Uncontrolled Studies (KMD3213-US021-99, SI04009, SI04010, SI04011)

"From the two US Phase 3 Controlled Studies, related adverse events occurring in ≥ 1% of silodosin patients were retrograde ejaculation (28.1%), dizziness (2.4%), orthostatic hypotension (1.9%), nasal congestion (1.5%), headache (1.3%), and diarrhea (1.1%).

"Three deaths occurred in the four US Phase 2/3 studies as follows: acute myocardial infarction in a silodosin patient, pulmonary embolism in a silodosin patient, cerebral hemorrhage in a placebo patient.

"No consistent meaningful effects of silodosin on the QTC interval were noted during the clinical pharmacology studies. Additionally, a pilot investigation was performed on ECG data during a maximum tolerated dose study (Study SI05008). There appears to be no significant effect of Silodosin upon heart rate, PR, QRS or QT. There is a suggestion of QTc shortening early after dosing with no evidence of QT prolongation. There were no outliers identified when the heart rate was appropriately corrected with the Fridericia formula.

"Foreign post-marketing experience -In summary, patient exposure was estimated at —— patients having received silodosin in Japan during the first year and a half of postmarket experience. During this time period 2,559 adverse cases were reported in Japan. Based upon Kissei's reference safety information, their Core Safety Information (CSI), they assessed 62 cases as serious, unlisted and 36 cases as serious, listed. In this time period Kissei updated their CSI with syncope, unconsciousness (unknown duration), and a class statement on intra-operative floppy iris syndrome (IFIS). In these PSURs, all safety information on silodosin received and assessed by Kissei in the period of 23 January 2006 to 30 July 2007 has been reviewed by Watson. No specific areas of concern have been identified in this year and a half of safety information. The safety profile of silodosin emerging from postmarket use in Japan appears congruent with the Watson clinical experience."

b(4)

Reviewer's Comment: There are no reports of clinically important adverse events related to QT prolongation (seizure, TdP, ventricular tachycardia or sudden death) in the clinical summary. Syncope is expected with α-adrenergic receptor blockade.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of silodosin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

4.2 TQT STUDY

The sponsor submitted the study report for SI05014, including electronic datasets and digital waveforms to the ECG warehouse.

4.2.1 Title

A Double-Blind, Randomized, Parallel Group Trial to Define the Electrocardiographic Effects of Silodosin, Using a Therapeutic and a Supra-therapeutic Dose, Compared with Placebo and Moxifloxacin (a Single Blinded Positive Control) in Healthy Male Subjects: A Thorough QT ECG Trial

4.2.2 Protocol Number

SI05014

4.2.3 Study Dates

21 April 06 to 02 June 06

4.2.4 Objectives

4.2.4.1 Primary

The primary objective of this study was to evaluate the effect of silodosin on the time-matched changes from baseline in the corrected QT interval of the electrocardiogram using an individual correction method.

4.2.4.2 Secondary

The secondary objectives were to evaluate the change from baseline in selected electrocardiogram parameters (Fridericia and Bazett corrected QT interval, heart rate, PR interval, QRS interval, uncorrected QT interval, and morphological patterns) following silodosin treatment. The correlation between individually corrected QT interval change from baseline and plasma concentrations of silodosin and main metabolites were also evaluated.

Other secondary objectives were to assess general safety and tolerability of treatments through the monitoring of adverse events, clinical laboratory measurements, and physical examinations.

4.2.5 Study Description

4.2.5.1 Design

This study was a double-blind (except for the use of moxifloxacin), randomized, placebo controlled, four-arm parallel group investigation in healthy male subjects.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomized to receive one of the following four treatment regimens:

- silodosin 8 mg (total daily dose) for 5 days
- silodosin 24 mg (total daily dose) for 5 days
- placebo for 5 days
- moxifloxacin 400 mg once, on Day 5.

Subjects randomized to silodosin or placebo treatments ingested a divided dose of the assigned study drug twice daily, from Days 1 to 3, and then only in the morning on Days 4 and 5. The moxifloxacin group was used as a positive control to determine the "assay sensitivity" of this trial. One moxifloxacin 400 mg tablet was ingested by assigned subjects in the morning on Day 5.

4.2.6.2 Sponsor's Justification for Doses

> "The therapeutic dose of silodosin is 8 mg once daily. The drug is predominantly (54.9%) metabolized by liver. The worst case scenario predicted from ketoconazole 400mg study is a increase in C_{max} by 3.7 fold and AUC by 3.2 fold increase. Hence, the supratherapeutic dose selected is 24 mg."

The dose of moxifloxacin is 400 mg given as a single dose.

Reviewer's Comments: Although the maximum tolerated dose as per sponsor is 48mg, the clinical division recommended that 24mg be selected as supratherapeutic dose for TQT study due to effects on blood pressure. The reviewer agrees with the choice of 8mg as therapeutic dose and 24mg as supratherapeutic dose. The reviewer also agrees with the dose of moxifloxacin.

4.2.6.3 Instructions with Regard to Meals

Silodosin was administered with food.

4.2.6.4 ECG and PK Assessments

Table 1: Sampling Schedule

Study Day	-1	5
Intervention	No treatment (Baseline)	Multiple dose (Silodosin), Single dose (Moxifloxacin)
12-Lead ECGs (5 ECGs for each time point)	-0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, and 23.5 hours	-0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, and 23.5 hours
PK Samples for Silodosin and metabolite (KMD-3213G, KMD-3293)	None collected	-0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 23.5 hours

Reviewer's Comments: The sampling schedule for ECGs and PK is acceptable to capture peak concentrations of silodosin and its metabolites.

4.2.6.5 Baseline

Time-matched baseline adjustment was used in the study.

4.2.7 ECG Collection

ECGs were obtained digitally using a ——— ECG continuous 12-lead digital recorder on Day –1 (baseline) and on Day 5 of therapy at the time points specified above. b(4)

The 12-lead ECG signal was stored continuously and was not available for review until the flash card was received by the central ECG laboratory and analyzed. ECGs to be used in the primary analysis were selected by predetermined time points and were read centrally. Five 12-lead ECGs were extracted from the — flash card within 1-3 minutes (providing five ECGs for each time point) b(4)

The ECG vendor utilized a semi-automated approach to the ECG reads. All ECG reads were performed by a very limited number of cardiologists on an ongoing basis. Readers were blinded to subject demographics, treatment, study time, and study day.

A minimum of three complexes on Lead II (primary) were used for QT assessment. If QT assessment could not be completed on Lead II, then V5, V2 or any other available ECG lead was used. The lead used for assessment was documented.

A quality assurance plan was prepared by the ECG vendor that documented: a) a statement of minimum reliability standards expected for trial as expected by the FDA, b) plans to perform 10% QA on initial 500 ECGs and 5% on each subsequent 1000 ECGs, c) processes to ensure the same reader reads all ECGs for the same subject, and d) the method for documenting deviations from this quality assurance plan, and e) a remediation plan in the event minimum reliability standards were not met. Inter- and intra-reader variability were assessed through re-read of a subset of ECGs and reported.

Standard digital 12-lead ECGs with 1 minute tracings were recorded at screening, baseline, at exit, and at approximately 2 hours (± 30 minutes) after morning dosing on Days 1 through 5 of treatment to detect any immediate ECG effects that could have suggested risk for subject safety. An ECG on therapy with a QTc >500 ms at the site at any time point and confirmed on a second ECG taken within 1 hour as defined by automatically measured intervals was used as a criterion for the discontinuation of subjects from the study.

Reviewer's Comments: Independent review of the ECG waveforms was performed and presented in section 5.3.2.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

188 healthy male subjects between 18 to 45 years of age with a normal baseline ECG and BMI between 18 to 32 kg/m^2. Two subjects were not treated and 2 subjects in the silodosin 8mg and 24 mg group withdrew consent prior to study completion for personal reasons.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the time-matched changes from baseline in the corrected QT interval of the electrocardiogram using an individual correction method (QTcI). For each dose of silodosin, the two-sided 90% CI (equivalent to a one-sided 95% CI) at each time point showing the placebo and baseline corrected (delta–delta analysis) at steady state on Day 5 was presented in Table 2.

Table 2: QTcI Placebo- and Baseline-Adjusted CI by Treatment Group and Time Point

Time Point Post-Dose (Hour)	Treatment Group	Least Squares Mean Change in QTcI Interval	Least Squares Mean Difference of Change from Placebo in QTcI Interval (90% Confidence Interval)
-0.25 hr	Silodosin - 8 mg	2.41	1.53 (-4.83, 7.88)
	Silodosin - 24 mg	2.25	1.36 (-5.01, 7.79)
	Placebo	0.89	
1 hr	Silodosin - 8 mg	-3.96	-0.04 (-6.39, 6.32)
	Silodosin - 24 mg	-4.45	-0.53 (-6.95, 5.90)
	Placebo	-3.92	
1.5 hr	Silodosin - 8 mg	-3.05	2.20 (-4.17, 8.56)
	Silodosin - 24 mg	-3.65	1.60 (-4.83, 8.03)
	Placebo	-5.25	
2 hr	Silodosin - 8 mg	-1.71	2.03 (-4.34, 8.39)
	Silodosin - 24 mg	-5.97	-2.23 (-8.66, 4.20)
	Placebo	-3.74	
3 hr	Silodosin - 8 mg	-1.17	-0.18 (-6.56, 6.19)
	Silodosin - 24 mg	-1.19	-0.20 (-6.64, 6.23)
	Placebo	-0.98	
4 hr	Silodosin - 8 mg	1.46	0.94 (-3.42, 7.31)
	Silodosin - 24 mg	0.15	-0.37 (-6.79, 6.06)
	Placebo	0.52	
6 hr	Silodosin - 8 mg	3.24	3.42 (-2.94, 9.78)
	Silodosin - 24 mg	1.21	1.39 (-5.00, 7.82)
	Placebo	-0.18	
8 hr	Silodosin - 8 mg	-2.50	0.27 (-6.10, 6.65)
	Silodosin - 24 mg	-5.63	-2.86 (-9.30, 3.58)
	Placebo	-2.78	
10 hr	Silodosin - 8 mg	-0.12	0.20 (-6.17, 6.58)
	Silodosin - 24 mg	-0.60	-0.27 (-6.71, 6.16)
	Placebo	-0.33	
23.5 hr	Silodosin - 8 mg	3.30	1.28 (-5.09, 7.65)
	Silodosin - 24 mg	1.44	-0.58 (-7.03, 5.87)
	Placebo	2.02	

(Source: Clinical Study Report: Study SI05014; Table 11.3.2-1., page 44)

To evaluate assay sensitivity, a positive control (400 mg moxifloxacin) was compared to placebo using baseline-adjusted QTcI at all time points.

Table 3: Assay Sensitivity by Treatment Group and Time Point

Time Point Post-Dose (Hour)	Treatment Group	Least Squares Mean Change in QTcI Interval	Least Squares Mean Difference of Change from Placebo in QTcI Interval (99% Confidence Interval)
-0.25 hr	Moxifloxacin	1.15	0.26 (-9.68, 10.20)
	Placebo	0.89	
1 hr	Moxifloxacin	-3.02	0.90 (-9.04, 10.84)
	Placebo	-3.92	
1.5 hr	Moxifloxacin	-0.75	4.50 (-5.46, 14.45)
	Placebo	-5.25	
2 hr	Moxifloxacin	0.90	4.64 (-5.32, 14.60)
	Placebo	-3.74	
3 hr	Moxifloxacin	5.30	6.29 (-3.68, 16.25)
	Placebo	-0.98	
4 hr	Moxifloxacin	8.61	8.09 (-1.87, 18.05)
	Placebo	0.52	
6 hr	Moxifloxacin	9.41	9.59 (-0.36, 19.55)
	Placebo	-0.18	
8 hr	Moxifloxacin	4.13	6.91 (-3.05, 16.87)
	Placebo	-2.78	
10 hr	Moxifloxacin	5.50	5.82 (-4.15, 15.80)
	Placebo	-0.33	
23.5 hr	Moxifloxacin	3.83	1.81 (-8.15, 11.78)
	Placebo	2.02	

(Source: Clinical Study Report: Study SI05014: Table 11.3.2-2., page 45).

Reviewer's Comments: The sponsor provided 99% CI for the baseline adjusted mean difference of moxifloxacin and placebo in order to preserve the overall 0.10 two-sided alpha level. We calculated the largest lower bound of the one-sided 95 % CI with/without multiple endpoint adjustment. According to our analysis, the study has assay sensitivity (section 5.1).

4.2.8.2.2 Categorical Analysis

A categorical analysis was done summarize QTc intervals of >450, >480 and >500 ms as well as QTc changes from time-matched baseline of ≥30 and ≥60 ms. All categorical summaries were based on the average of replicates within a time point. The results are summarized in Table 4.

Only one subject in each silodosin group had postdose QTcI intervals above 450 ms. The nonspecific outlier criterion (a 30-60 ms change from baseline) showed 22% of subjects had this criterion on placebo, while 20% and 34% in the clinical and supratherapeutic dose groups of silodosin demonstrated this results. While no subject had > 60 ms change from baseline on placebo, 1 and 2 subjects on silodosin had this finding in the clinical and supratherapeutic dose groups, respectively. Categorical assessments using QT intervals, and QTc values based on Fridericia's correction and Bazett's correction were consistent with that using the QTcI intervals.

Table 4: Summary of Categorical ECG Interval Data by Treatment Group

	Placebo	Silodosin - 8 mg	Silodosin - 24 mg	Moxifloxacin
Evaluable Population [1]	46	46	44	47
Maximum QTcI (Post Drug), msec				
≤450 msec	46 (100.0%)	45 (97.8%)	43 (97.7%)	46 (97.9%)
> 450 msec	0	1 (2.2%)	1 (2.3%)	1 (2.1%)
> 480 msec	0	0	0	0
> 500 msec	0	0	0	0
Maximum QTcI Change from Baseline, msec				
No increase	1 (2.2%)	3 (6.5%)	0	0
1-29 msec increase	35 (76.1%)	33 (71.7%)	27 (61.4%)	29 (61.7%)
30-60 msec increase	10 (21.7%)	9 (19.6%)	15 (34.1%)	17 (36.2%)
> 60 msec increase	0	1 (2.2%)	2 (4.5%)	1 (2.1%)

(Source: Clinical Study Report: Study SI05014; Table 14.2.1-12.. page 158)

4.2.8.2.3 Additional Analyses

The average change from baseline in QT interval corrected by Fridericia's formula was analyzed as a secondary endpoint. The results of QTcF interval analysis was presented in Table 5. Time-averaged and morphology analysis were also conducted by sponsor.

Table 5: QTcF Placebo- and Baseline-Adjusted CI by Treatment Group and Time Point

Time Point Post-Dose (Hour)	Treatment Group	Least Squares Mean Change in QTcF Interval	Least-Squares Mean Difference of Change from Placebo in QTcF Interval (90% Confidence Interval)
-0.25 hr	Silodosin - 8 mg	1.26	2.32 (-3.20, 7.83)
	Silodosin - 24 mg	0.56	1.61 (-3.97, 7.19)
	Placebo	-1.05	
1 hr	Silodosin - 8 mg	-1.94	2.03 (-3.49, 7.55)
	Silodosin - 24 mg	-2.32	1.65 (-3.93, 7.23)
	Placebo	-3.97	
1.5 hr	Silodosin - 8 mg	-1.49	3.45 (-2.08, 8.97)
	Silodosin - 24 mg	-1.95	2.99 (-2.60, 8.57)
	Placebo	-4.94	
2 hr	Silodosin - 8 mg	-0.62	2.73 (-2.79, 8.26)
	Silodosin - 24 mg	-3.72	-0.37 (-5.96, 5.21)
	Placebo	-3.35	
3 hr	Silodosin - 8 mg	-1.03	2.70 (-2.84, 8.24)
	Silodosin - 24 mg	-1.61	2.13 (-3.46, 7.71)
	Placebo	-3.73	

4 hr	Silodosin - 8 mg	0.86	3.66 (-1.87, 9.18)
	Silodosin - 24 mg	-0.62	2.18 (-3.40, 7.76)
	Placebo	-2.80	
6 hr	Silodosin - 8 mg	4.67	4.49 (-1.03, 10.02)
	Silodosin - 24 mg	4.80	4.63 (-0.95, 10.21)
	Placebo	0.18	
8 hr	Silodosin - 8 mg	-1.48	1.31 (-4.23, 6.85)
	Silodosin - 24 mg	-2.79	0.00 (-5.59, 5.60)
	Placebo	-2.79	
10 hr	Silodosin - 8 mg	-1.21	1.08 (-4.47, 6.62)
	Silodosin - 24 mg	-0.22	2.06 (-3.52, 7.65)
	Placebo	-2.29	
23.5 hr	Silodosin - 8 mg	1.35	2.46 (-3.07, 7.99)
	Silodosin - 24 mg	-0.34	0.76 (-4.84, 6.37)
	Placebo	-1.10	

Note: Evaluable population is all randomized subjects who receive at least one dose of study drug and have time-matched ECG data on Day -1 and Day 5. QTcF=Fridericia's QT Correction.
(Source: Clinical Study Report: Study SI05014; Table 14.2.1-12., page 65)

Reviewer's Comments: Although none of the upper bound of the 2-sided 90% CIs for QTcI was below 10 ms submitted by sponsor, the upper bound of the 2-sided 90% CIs for QTcF was above 10 ms for both treatment groups of Silodosin at 6 hr post-treatment according to the sponsor's analysis. The statistical reviewer re-analyzed the data as described in section 5.1. The FDA results are summarized in Table 8.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study. There were no discontinuations due to AEs. The most common related treatment emergent adverse events in patients receiving 8 mg of silodosin were retrograde ejaculation (16.7%), nasal congestion (10.4%), headache (8.3%), fatigue (6.3%), and dizziness, nausea, orthostatic hypotension, and palpitation (all 4.2%). The most common related adverse events in patients receiving 24 mg of silodosin were headache (13.3%), retrograde ejaculation (11.1%), orthostatic hypotension and fatigue (both 8.9%), diarrhea and dyspepsia (both 4.4%).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The sponsor analyzed the plasma concentration data of silodosin and its two metabolites (KMD-3213G and KMD-3293) using non-compartmental analysis. The summary of the important PK parameters (Mean±Standard deviation) is shown in Table 6.

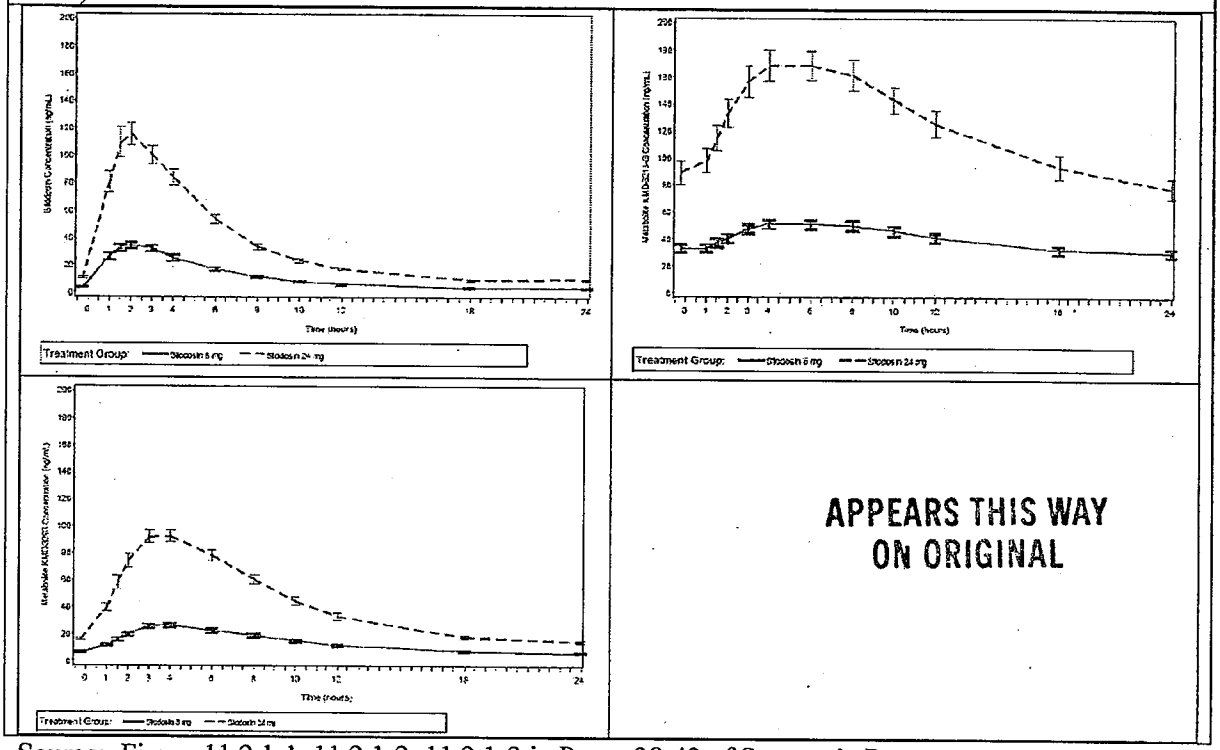
Table 6. Summary of PK parameters of Silodosin and its metabolites (KMD-3213G, KMD-3293)

Compound	C_{max}		T_{max}		$T_{1/2}$	
	8 mg	24 mg	8 mg	24 mg	8 mg	24 mg
Silodosin	42.5±19.4	143.9±64.3	2.3±0.8	2.4±1.3	7.6±3.4	6.6±3.0
KMD-3213G	56.2±23.7	185.3±77.1	4.9±2.1	5.2±1.9	18.5±11.6	14.9±5.9
KMD-3293	28.9±11.0	104.1±31.4	3.7±1.5	3.8±1.4	8.8±2.9	7.0±1.8

Source Data: Table 11.2.1-1, 11.2.2-1, 11.2.3-1 from Page 37-41 of Sponsor's Report

The time course of plasma concentration data of Silodosin and its two metabolites (KMD-3213G and KMD-3293) is shown in Figure 1.

Figure 1. Mean (±SEM) plasma time course of Silodosin and its metabolites (KMD-3213G, KMD-3293).



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Source: Figure 11.2.1-1, 11.2.1-2, 11.2.1-3 in Pages 38-42 of Sponsor's Report

4.2.8.4.2 Exposure-Response Analysis

A linear mixed effects model was used to estimate the slope (β) and slope standard error (SEβ) of the plasma concentration relative to ΔΔQTcI (placebo- and baseline-adjusted QTcI) interval for silodosin and its metabolites (KMD-3213G, KMD-3293). The expected maximum QTcI effect for each dose was estimated as a function of the slope and average maximum plasma concentration (C_{max}) for each analyte and Silodosin dose with 90% confidence intervals as shown in Table 7.

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Table 7. Estimate of slope and predicted Maximum QTcI effect along with 90% confidence intervals for Silodosin, KMD-3213G and KMD-3293.

Silodosin

Treatment Group	Slope (S.E.) Relative to Plasma Concentration and QTcI	90% Confidence Interval for Slope	Expected Max QTcI Effect	90% Confidence Interval for Max QTcI Effect	P-value
Silodosin 8 mg	-0.057 (0.031)	-0.108, -0.006	-2.425	-4.613, -0.236	0.068
Silodosin 24 mg	0.002 (0.010)	-0.014, 0.018	0.263	-2.061, 2.588	0.852

KMD-3213G

Treatment Group	Slope (S.E.) Relative to Plasma Concentration and QTcI	90% Confidence Interval for Slope	Expected Maximum QTcI Effect	90% Confidence Interval for Maximum QTcI Effect	P-value
Silodosin 8 mg	-0.036 (0.028)	-0.083, 0.011	-2.050	-4.696, 0.596	0.202
Silodosin 24 mg	-0.001 (0.008)	-0.014, 0.012	-0.133	-2.557, 2.292	0.928

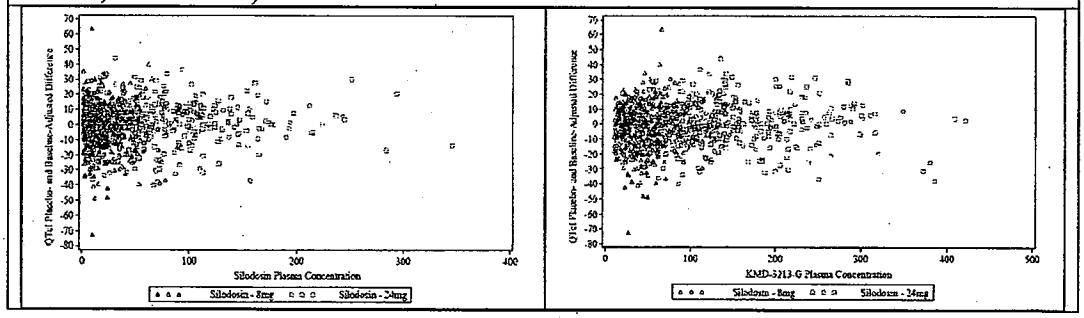
KMD-3293

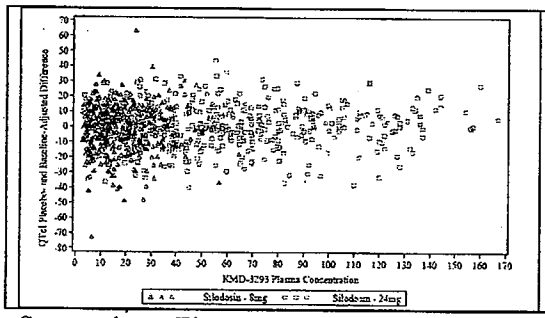
Treatment Group	Slope (S.E.) Relative to Plasma Concentration and QTcI	90% Confidence Interval for Slope	Expected Maximum QTcI Effect	90% Confidence Interval for Maximum QTcI Effect	P-value
Silodosin 8 mg	-0.045 (0.049)	-0.125, 0.036	-1.300	-3.647, 1.048	0.362
Silodosin 24 mg	0.004 (0.014)	-0.019, 0.027	0.405	-1.956, 2.767	0.777

Source data: Table 11.3.3-1, 11.3.3-2, 11.3.3-3 in Page 49 from sponsor's report

The relationship between ΔΔQTcI and plasma concentrations of silodosin and its metabolites (KMD-3213G, KMD-3293) is shown in Figure 2.

Figure 2. Mean (±SEM) plasma time course of Silodosin and its metabolites (KMD-3213G, KMD-3293).





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Source data: Figure 14.2.1-19, 14.2.1-20, 14.2.1-21 in Pages 170, 182, 193 from sponsor's report

Reveiwer's Comments: The analysis conducted by the sponsor is acceptable. Overall, there is no relationship between ΔΔQTcI and plasma concentrations of Silodosin, KMD-3213G and KMD-3293. The upper 90% CI for the maximum ΔΔQTcI changes at C_{max} of Silodosin, KMD-3213G and KMD-3293 is less than 10 ms.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

This statistical reviewer performed an independent analysis based on the electronically submitted ECG data using QTcF.

The ANCOVA model was used to compare the change from baseline between placebo and treatment groups with treatment as fixed effect and baseline QTc as covariate. As showed in Table 8 and Figure 3, the upper bounds of the 2-sided 90% CIs for the mean differences between Silodosin and placebo in the time-matched QTcF change from baseline at 6 hour post dosing are both below 10 ms for both 8 mg and 24 mg treatment groups.

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Table 8: 90% ANOVA model based CI for the placebo and time-matched baseline corrected values (delta delta analysis) of QTcF

Treatment	Time (hr)	ΔQTcF		Δ Placebo		ΔΔQTcF	
		n	mean	n	mean	Diff.	90% CI
Silodosin 8 mg	–0.25hr	46	-6.19	46	-7.42	1.22	(-3.36, 5.81)
	1 hr	46	-4.38	46	-5.12	0.74	(-4.02, 5.51)
	1.5 hr	46	-3.76	45	-5.06	1.31	(-2.94, 5.55)
	2 hr	46	-1.89	45	-2.52	0.64	(-3.46, 4.73)
	3 hr	44	-2.47	45	-3.08	0.61	(-3.65, 4.87)
	4 hr	45	-2.71	46	-5.61	2.90	(-1.73, 7.53)
	6 hr	45	5.51	46	1.56	3.95	(0.03, 7.87)
	8 hr	44	1.01	45	0.02	0.99	(-4.08, 6.06)
	10 hr	44	-1.65	45	-1.54	-0.11	(-4.18, 3.97)
	23.5 hr	45	7.72	45	5.41	2.31	(-2.41, 7.03)
Silodosin 24 mg	–0.25hr	44	-4.48	46	-6.82	2.34	(-2.01, 6.69)
	1 hr	44	-3.57	46	-4.73	1.16	(-2.74, 5.07)
	1.5 hr	44	-1.77	45	-4.64	2.87	(-1.13, 6.86)
	2 hr	44	-2.53	45	-2.13	-0.40	(-4.68, 3.89)
	3 hr	44	0.39	45	-2.76	3.14	(-1.20, 7.39)
	4 hr	44	-3.36	46	-5.39	2.03	(-2.48, 6.54)
	6 hr	44	6.56	46	1.77	4.80	(0.28, 9.31)
	8 hr	43	-0.91	45	0.22	-1.13	(-5.91, 3.65)
	10 hr	44	1.78	45	-0.84	2.62	(-1.84, 7.07)
	23.5 hr	42	8.22	45	5.90	2.32	(-1.83, 6.46)

Figure 3: Time Course of Mean Changes in ΔΔ QTcF by treatment

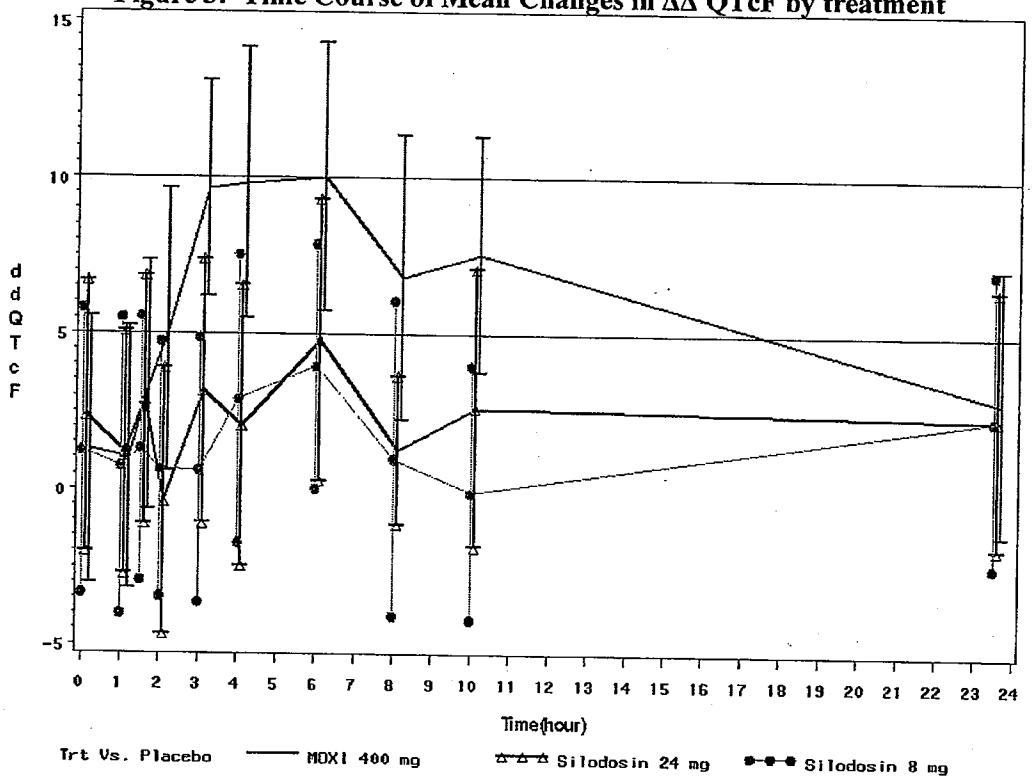

Table 9 summarizes the results of the mean difference between moxifloxacin and placebo in QTcF without multiple adjustments. Without multiple endpoint adjustment, the largest lower bound is 6.18 ms at 3 hour; if multiple endpoints were adjusted using the most conservative Bonferroni method with 9 time points, the largest lower bound is 4.16 ms at 3 hour.

Table 9: Assay Sensitivity Analysis of time-matched and baseline corrected of QTcF (ms) by Time Point

Timepoint (hr)	# of Obs	QTcF Mean (ms)	QTcN 90% CI (ms) Lower Bound	Upper Bound
–0.25hr	47	1.26	-3.03	5.54
1 hr	47	1.02	-3.19	5.23
1.5 hr	47	3.32	-0.67	7.32
2 hr	46	5.08	0.55	9.61
3 hr	46	9.63	6.18	13.09
4 hr	45	9.80	5.47	14.13
6 hr	46	10.02	5.72	14.32
8 hr	46	6.80	2.23	11.36
10 hr	45	7.54	3.78	11.31
23.5 hr	46	2.87	-1.39	7.13

Table of Study Assessments

	Inpatient Period							
Procedure	**Scr**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**6/ET**
Informed Consent	X							
Demographics	X							
Medical History	X	X						
Concurrent Illness	X	X						
Concomitant Med	X	X	X	X	X	X	X	X
Physical Exam	X							X
Clinical Labs (1)	X	X						X
Safety ECG	X	X	X	X	X	X	X	X
Vital Signs (2)	X	X	X	X	X	X	X	X
Randomization		X						
H-12 ECG (3)		X					X	
PK Plasma sample (4)							X	
Administer Study Med (5)			X	X	X	X	X	
Adverse Events			X	X	X	X	X	X

(1) Includes screen for drugs of abuse, cotinine, hepatitis B & C, and HIV at screening, and drugs of abuse, cotinine on Day -1
(2) At pre-dose and approximately 2.5, 8, 16 hours post-dose on Days 1-5
(3) Subject at rest for 15 minutes at approx. -0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 23.5 relative to dosing
(4) At approximately -0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 23.5 relative to dosing
(5) Moxifloxacin administered on Day 5 only

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/s/

Christine Garnett
4/14/2008 10:40:30 AM
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Atul Bhattaram
4/14/2008 10:43:07 AM
BIOPHARMACEUTICS

Joanne Zhang
4/14/2008 12:16:17 PM
BIOMETRICS
Dr. Kate Dwyer was the primary statistical reviewer for this QT NDA.

Suchitra Balakrishnan
4/15/2008 09:29:12 AM
MEDICAL OFFICER

Norman Stockbridge
4/16/2008 12:38:50 PM
MEDICAL OFFICER

NDA 22-206

Medical Officer's 45-Day Filing Memorandum

Application Letter Date:	December 12, 2007
45-Day Filing Review Date:	February 8, 2008
Prescription Drug User Fee Act (PDUFA) Goal Date:	October 13, 2008
Related Submission:	IND 56,605
Product, route, and dose:	Silodosin (RAPAFLO™) Capsules, 4 mg and 8 mg
Indication:	Treatment of signs and symptoms of benign prostatic hyperplasia (BPH)

I. Objective:
This review assesses whether NDA 22-206 is suitable for filing under 21 CFR 314.50 (Content and format of an application) and 21 CFR 314.71 (Procedures for submission of a supplement to an approved application). This document also serves as the basis for communicating to the sponsor potential clinical review issues identified during this initial review period.

Conclusion: From a clinical perspective, the NDA may be filed.

II. Background
Silodosin (also referred to as KMD-3213) is a selective α_{1A}–adrenergic receptor antagonist created by Kissei Pharmaceutical Co, Ltd. of Japan in 1993, and developed as a once-daily formulation for the treatment of signs and symptoms of benign prostatic hyperplasia.

Watson Laboratories, Inc., which owns the North American licensing rights to the compound, is seeking approval of silodosin in the United States for the **"treatment of the signs and symptoms of BPH."** The proposed dosage is 8 mg once daily, with the 4 mg dose limited to use in [redacted] renal [redacted] b(4)

Silodosin was approved in Japan in January, 2006, at a recommended dose of 8 mg daily given in two divided doses. The product is currently in Phase 3 development in the European Union under Recordati, S.P.A., [redacted] b(4)

III. Brief U.S. Regulatory History:

The IND for silodosin (IND 56,605) was opened on August 13, 1998, by Watson Laboratories, Inc. An End-of-Phase 2 meeting was held with the sponsor on February 10, 2005.

The sponsor submitted protocols for two double-blind, placebo-controlled, Phase 3 clinical trials (Protocols #SI04009 and #SI04010) and a protocol for open-label safety extension (Protocol #SI4011) for review on March 15, 2005. DRUP reviewed the two Phase 3 protocols and responded with the following comments in a May 2, 2005, letter:

1) We do not currently agree with evaluating only the 8 mg dose in the phase 3 trials. It is not clear whether 4 or 8 mg is the lowest effective dose. Any safety concerns identified with the 8 mg dose may require evaluation of lower doses. In addition, further efficacy and safety data on lower doses may be needed, as lower doses may be recommended in patients taking concomitant medications and in "special populations." If only the 8 mg dose is studied, significantly restrictive labeling may be required, which could become a review issue for drug approval.
2) The primary endpoint is the IPSS. We consider the quality of life question and the IPSS sub-scores of irritative and obstructive voiding symptoms secondary exploratory endpoints.

The DRUP statistical reviewer agreed with the statistical analysis plan contained in the two phase 3 protocols.

The following agreements were reached regarding serum prolactin and thyroid monitoring in Phase 3 during two separate teleconferences, on July 22, 2005, and August 12, 2005, respectively:

1) The sponsor's proposals to amend ongoing protocols SI04009 and SI04010 to include prolactin assays and breast exams is acceptable to the Division. The Division understands that approximately 400 patients (200 silodosin and 200 placebo) will have baseline and end-of-study prolactin levels and breast examinations. All patients will have an end-of-study assessment.
2) The sponsor's proposal to amend protocols SI04009 and SI04010 to include a free T4 assay at visit 1 and at the end of the study is acceptable.
3) The sponsor's proposal to amend protocols SI04009, SI04010 and SI04011 to include a thyroid examination is acceptable to the Division.
4) The exclusion of thyroid ultrasound and an age-matched control group as part of thyroid monitoring in phase 3.

A pre-NDA meeting was held on July 23, 2007. DRUP stated that

1) the summarized efficacy data from the two U.S., Phase 3 studies appears to be adequate to support an NDA for the proposed indication.
2) The number of patients exposed and the duration of exposure appear to be adequate.
3) [redacted] b(4)

4) The safety data from the Japanese and European studies should be submitted as either final study reports, or as abbreviated or interim clinical study reports, if they are still ongoing at the time of NDA submission.

IV. NDA Filing Review:

The review is based on three criteria proposed in the FDA guidance for conducting a filing review, based on the Agency's interpretation of 21 CFR 314.101 (d) (3) and 21 CFR 314.50.

1. Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner.
2. Failure to include evidence of effectiveness compatible with the statute and regulations.
3. Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

REVIEW RESULTS

1. ***Does this application omit a section required under CFR 314.50, or was a particular section presented in such a manner as to render it incomplete for the clinical review?***

No.

This application contains the critical sections in sufficient detail (Table 1.1).

Table 1. 1 Checklist for critical sections

Comprehensive Table of contents	Yes
Summary of the application (314.50 (c))	Yes
Technical sections (CMC, non-clinical pharm/tox, human pK, clinical data)	Yes (statistical section not included; as per pre-NDA meeting minutes, DRUP agreed that the SAP for clinical studies, ISE or ISS did not need to be submitted)
Case report forms and tabulations (21 CFR 314.50 (f))	Yes

2. ***Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:***
    a. ***Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints***
    b. ***Presentation or what appears to be only a single adequate and well controlled trial without adequate explanation***
    c. ***Use of a study design clearly inappropriate***

No.

2.1 Efficacy Data

The sponsor has submitted efficacy data from one Phase 2 study (KMD3213-US021-99) and two Phase 3 trials (#SI04009 and #SI04010) with a subsequent open-label extension study (#SI04011), all conducted in the U.S. The trials were randomized, double-blind, placebo-controlled, parallel-group studies in patients with BPH, defined as an International Prostate Symptom Score (IPSS)≥13 and maximum urinary flow rate (Qmax) of 4-15 mL/sec with a minimum voided volume of 125 mL.

Study KMD3213-US021-99

This Phase 2 study was comprised of three periods: a 4-week placebo run-in period, a 2-week dose adjustment period and a 6-week stable dosing period. Following the placebo run-in period, 264 eligible patients, aged 45-75 years, were randomized as follows:

- 8 mg silodosin (n=90)
- 4 mg silodosin (n=88)
- Placebo (n=86).

Studies SI04009 and SI04010:

These studies consisted of two periods -- a 4-week single-blind placebo run-in period and a 12-week dosing period. Four-hundred and sixty-one eligible patients, aged ≥50 years, were randomized to either 8 mg silodosin (N=233 in each study) or placebo (N=228 in each study) administered once daily.

The design of these Phase 3 trials was identical except that plasma concentration data were not collected in study SI04010.

The primary endpoint in all three double-blind, placebo-controlled trials was change from baseline (CFB) to last observation carried forward (LOCF) in the IPSS total score. Change from baseline in Qmax was a co-primary endpoint in Phase 2 study, KMD3213-US021-99, only.

The secondary efficacy endpoint in both pivotal Phase 3 trials was CFB to LOCF in Qmax.

Reviewer's comment: The study design and endpoints for both Phase 3 trials were acceptable and agreed upon by the Division.

Reviewer's comment: The Division agreed to the statistical analysis plans (including primary endpoints and imputation method) for both phase 3 studies in a letter dated March 16, 2007.

Change from baseline in scores on two subscales of the IPSS instrument (irritative and obstructive) and on the quality of life question were also described in both Phase 3 trials.

Reviewer's comment: In the May 2, 2005, letter to the sponsor regarding the Phase 3 protocols, the Division wrote, "The primary endpoint is the IPSS. We consider the

quality of life question and the IPSS sub-scores of irritative and obstructive voiding symptoms secondary exploratory endpoints."

Study SI04011

Six-hundred and sixty-one (N=661) men who successfully completed study SI04009 or SI04010 enrolled in this 40-week open-label extension study. The primary objective was to evaluate the safety of silodosin 8 mg once daily. Evaluation of the sustained efficacy of silodosin as measured by change in the IPSS total score from baseline to week 40 (LOCF) was a secondary objective.

Overall Efficacy Results

Efficacy data from the Phase 2 study and the Phase 3 pivotal studies were integrated for combined summary and analysis. As the Phase 2 study included both a 4 mg and 8 mg dose group, only data from the 8 mg and placebo dose groups were integrated into the efficacy summary.

For all US controlled studies, silodosin's effect on symptoms of BPH as measured by a change from baseline in the IPSS total score exceeded that of placebo in a statistically significant manner ($p<0.0001$) (Table 2.1).

Table 2. 1 Summary of Change from Baseline to LOCF in Total IPSS Score – All US Controlled Studies (Phase 2 Study and 2 Phase 3 studies) (mITT population)[1]

Study	Visit	Statistic	Placebo	Silodosin	p-value
			N=540	N=556	
Overall	Endpoint (LOCF)	Mean (SD)	-3.6 (5.79)	-6.4 (6.5)	<0.001

1 – For the Phase 3 studies, the modified intent-to-treat (mITT) population consisted of all randomized patients who provided data for the primary efficacy variable at baseline. If a patient was mis-randomized, then the actual treatment given was used in all summary statistics and analyses.
For the Phase 2 study, the mITT population included all randomized patients with a baseline evaluation and at least one post-baseline AUA symptom score or Qmax measurement.

For all US controlled studies, silodosin's effect on symptoms of BPH as measured by a change from baseline in Qmax exceeded that of placebo in a statistically significant manner ($p<0.0002$) (Table 2.2).

Table 2.2. Summary of Change from Baseline to LOCF in Qmax – All US Controlled Studies (Phase 2 Study and 2 Phase 3 studies) (mITT population)

Study	Visit	Statistic	Placebo	Silodosin	p-value
			N=540	N=556	
Overall	Endpoint (LOCF)	Mean (SD)	+1.6 (4.39)	2.7 (4.68)	0.0002

Reviewer's Comment: A preliminary review of the efficacy data appears to support efficacy of silodosin in the treatment of signs and symptoms of BPH.

Question 3: Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:

a) ***Total patient exposure at relevant doses that is clearly inadequate to evaluate safety***
b) ***Clearly inadequate evaluation for safety and/or effectiveness of the population intended of use the drug, including pertinent subsets, such as gender, age and racial subsets;***
c) ***Absence of a comprehensive analysis of safety data***
d) ***Absence of an analysis of data supporting the proposed dose and dose interval***

3.1 Exposure
A total of 1,371 subjects or patients were exposed to silodosin in the studies summarized in the NDA. In the clinical pharmacology studies conducted for the NDA, there were 474 patients exposed to daily doses of silodosin of 0.1 to 48 mg, for 1 to 21 days. In the US Phase 2/3 studies, 897 patients were exposed to daily doses of 8 mg silodosin (the proposed therapeutic dose), of which 486 patients were exposed for 26 weeks or more, and 168 patients were exposed for 52 weeks or more.

Reviewer's comment: Data from the one Phase 2 double-blind study (KMD3213-US021-99), two Phase 3 double-blind studies (SI04009 and SI04010), and one Phase 3 open-label safety study (SI04011) were combined for the integrated summary of safety. Phase 1 studies were not integrated because of highly dissimilar study designs and dose regimens.

Additional safety data for silodosin are available from foreign sources. Nine-hundred and fifty BPH patients were exposed to silodosin (doses 0.1 mg bid to 4 mg bid) in six Phase 2/3 Japanese studies. A double-blind Phase 3 European study included 390 patients randomized to silodosin 8 mg daily for 12 weeks. Finally, an estimated ——— patients have received silodosin in Japan during the first eighteen months of post-marketing experience. b(4)

Reviewer's comment: The quantity and duration of patient exposure is adequate.

3.2 Patient Demographics
Demographic characteristics of patients exposed to silodosin in all US controlled and uncontrolled studies (double blind Phase 2 study, two pivotal Phase 3 trials and open-label Phase 3 safety extension) is shown in Table 3.1.

Table 3.1 Summary of Patient Demographics --
All US Controlled and Uncontrolled Studies (Safety Population)

Demographic Characteristic	N (%)
Overall	897 (100)
By Race	
Asian	7 (0.8)
Black	29 (3.2)
Caucasian	811 (90.4)
Hispanic	45 (5.0)
Other	45 (0.6)
By Age	
<65 years	513 (57.2)
≥65 years	384 (42.8)
<75 years	801 (89.3)
≥75 years	96 (10.7)

Reviewer's comment: Age range exposed is acceptable. Dearth of minority patients is noted.

3.3 Dose Rationale

An analysis of data supporting the proposed 8 mg once daily dose is provided:

- According to the sponsor, in the Phase 2 dose-finding study, the 4 mg dose did not demonstrate efficacy as measured by IPSS or Qmax. The safety profile was similar to the 8 mg dose.
- The long terminal elimination half-life of silodosin and the extended pharmacokinetic profile of silodosin's active metabolite KMD-3213G provided the rationale for once a day dosing.

Reviewer's comment: At the EOP2 meeting on February 10, 2005, the Division stated that it believes "it would be prudent to study the 4 mg dose [in Phase 3]. The Division agreed, however, that the sponsor is not required to examine the 4 mg dose in Phase 3. The sponsor assumes risk if there are safety issues [with the 8 mg dose] identified at the time of review."

3.4 Special Populations

3.4.1 Race – No clinical pharmacology investigations of the effects of race were performed. The sponsor conducted a qualitative review of the pharmacokinetic data obtained in Caucasians and non-Caucasians and found no meaningful differences between races in the pharmacokinetics of silodosin or its main metabolites.

The sponsor also assessed the incidence of adverse events by race for all U.S. Phase 2/3 studies and identified no differences.

3.4.2 Age – A clinical pharmacology study investigating the effects of age on silodosin metabolism and safety was performed in 21 Japanese subjects (Study KMD-105). In the elderly, no statistically significant differences were noted between healthy and elderly subjects for AUC or C_{max}.

The sponsor also reviewed the incidence of adverse events by age for all U.S. Phase 2/3 and observed no differences.

3.4.3 Renal Insufficiency -- A clinical pharmacology study investigating the effects of kidney dysfunction was performed in 13 Japanese subjects (Study KMD-309). Renal dysfunction had a significant impact on the pharmacokinetics of silodosin, with the ratio of the geometric least squared means of renal impaired to normals being 3.11 for C_{max} and 3.22 for AUC.

According to the sponsor's analysis, no increased incidence of adverse events was observed for patients with low estimated creatinine clearance in the four US Phase 2/3 studies.

3.4.4 Hepatic Insufficiency -- A clinical pharmacology study investigating the effects of hepatic dysfunction was performed in 18 U.S. subjects with moderate liver dysfunction (Child-Pugh 7-9) (Study SI05010). Pharmacokinetics of silodosin and its main metabolites were slightly altered – C_{max} and AUC values for total concentrations were slightly lower for the liver dysfunction subjects compared with the healthy controls (ratios of means 0.8 and 0.8).

3.4.5 Drug-Drug Interactions:
3.4.5.1 CYP3A4 inhibitors: As silodosin is a CYP3A4 substrate, a ketoconazole drug interaction study was performed (Study SI06008). When silodosin was administered on the second day of a four-day, 400 mg ketoconazole once daily regimen, silodosin AUC increased 3.1 fold and Cmax increased 3.7-fold.

Reviewer's comments:

1) *The effects of race, age and renal insufficiency on safety and tolerability of silodosin will be a review issue.*
2) *The sponsor proposes a 4 mg dose of silodosin to be used in patients* [redacted] b(4)

   [redacted] *will be a review issue.*

3.4.5.2 PDE-5 inhibitors: The sponsor conducted a pharmacodynamic interaction study of silodosin with sildenafil, tadalafil, and placebo in 24 healthy male subjects (Study SI06002). [redacted] b(4)

[redacted] b(4)

3.4.6 Electrophysiology

The NDA contains results from a "thorough" QT study (SI05014). This study was a double-blind, randomized, parallel group trial in 45 healthy male subjects. Subjects received silodosin 8 mg for 5 days, silodosin 24 mg for 5 days, placebo for 5 days, or moxifloxacin 400 mg once on Day 5. Time-matched change from baseline in the corrected QT interval (using individual correction method) was the primary endpoint. ECGs were obtained on Day -1 (baseline) and on Day 5 of therapy at the following time points relative to dosing: -0.25, 1, 1.5, 2, 3, 4, 6, 8, 10 and 23.5 hours.

Reviewer's comment: A preliminary review of the thorough QT study reveals no obvious QT prolonging effect.

3.5 Integrated Summary of Safety

The integrated summary of safety contains data from one Phase 2 double blind study (KMD3213-US021-99), two Phase 3 double blind studies (SI04009 and SI04010) and one Phase 3 open-label safety study (SI04011). Phase 1 studies were not integrated because of highly dissimilar study designs and dose regimens.

3.5.1 Common Treatment-Emergent Adverse Events

From all four US Phase 2/3 studies, treatment-emergent adverse events occurring in ≥1% of patients are shown in Table 3.5.1.

Table 3.5.1 Summary of Treatment-Emergent Adverse Events Occurring in >1% of Patients (All U.S. Controlled and Uncontrolled Trials)

Adverse Event	Percentage
retrograde ejaculation	31.9
diarrhea	4.8
dizziness	3.8
nasopharyngitis	3.8
orthostatic hypotension	3.2
headache	2.7
nasal congestion	2.7
URI	2.5
PSA increased	2.3
arthralgia	2.2
hypertension	2.0
Sinusitis	1.8
Back pain	1.6
Cough	1.4
Erectile dysfunction	1.4
Libido decreased	1.4
Urinary tract infection	1.4
Influenza	1.3
Abdominal pain	1.2
Bronchitis	1.1
Sinusitis	1.1
Blood urine present	1.0
GGT increased	1.0
Nausea	1.0
Pharyngolaryngeal pain	1.0

Treatment-emergent adverse events that occurred in >2% of patients receiving silodosin in Phase 3 controlled trials, and at an incidence numerically higher than that of placebo are shown in Table 3.5.2.

Table 3.5.2 Treatment-emergency adverse events in all U.S. Controlled Phase 3 trials

Adverse Event	Silodosin N (%)	Placebo N (%)
Retrograde ejaculation	131 (28.1)	4 (0.9)
Dizziness	15 (3.2)	5 (1.1)
Diarrhea	12 (2.6)	6 (1.3)
Orthostatic hypotension	12 (2.6)	7 (1.5)
Headache	11 (2.4)	4 (0.9)
Nasopharyngitis	11 (2.4)	10 (2.2)
Nasal congestion	10 (2.1)	1 (0.2)

Reviewer's comment: Common treatment-emergent adverse events with silodosin are consistent with those reported for other alpha-adrenergic receptor antagonists.

3.5.2 Deaths and Other Serious Adverse Events
In all controlled and uncontrolled U.S. studies, there were three deaths – two in patients receiving silodosin (acute MI; pulmonary embolism) and one in placebo (cerebral hemorrhage) – none were believed related to investigational treatment. The two deaths in the silodosin group occurred in the open-label extension study SI04011.

In Phase 3 study SI04009, six patients (3 on placebo, 3 on silodosin) experienced serious adverse events during the trial. SAE's in the silodosin group were acute MI in two patients and cervical radiculopathy in the third.

In Phase 3 study SI04010, there were 8 SAEs – five in the placebo group, three in the silodosin group. SAEs in the silodosin group were aggravated carotid artery stenosis, syncope and complete heart block. Syncope was believed to be treatment-related.

3.5.3 Discontinuations due to Adverse Events
The most common drug-related adverse event causing discontinuation in U.S. Phase 2/3 controlled and uncontrolled studies was retrograde ejaculation, occurring in 5.5% of silodosin patients.

3.5.4 Laboratory Parameters (U.S. Phase 3 controlled studies)
For US Phase 3 controlled studies, no significant difference was seen in change from baseline in any hematology parameter between drug and placebo groups.

For chemistry analytes, more silodosin patients in the US Phase 3 controlled studies experienced an increase from "normal" to "high" in serum AST, creatinine and GGT than those on placebo.

Table 3.5.4.1 Summary of Patients experiencing increase in laboratory analytes from "normal" to "high" during treatment – US Phase 3 Controlled Studies (Safety Population)

Analyte	Study Visit	placebo	silodosin
AST	>0-6 weeks	8/435 (1.8%)	12/432 (2.8%)
	>6 weeks	5/417 (1.2%)	12/414 (2.9%)
	Last observation	5/442 (1.1%)	13/452 (2.9%)
Creatinine	>0-6 weeks	5/435 (1.1)	3/423 (0.7%)
	>6 weeks	4/417 (1.0)	8/416 (1.9%)
	Last observation	4/442 (0.9%)	8/454 (1.8%)
GGT	>0-6 weeks	11/435 (2.5%)	12/432 (2.8%)
	>6 weeks	11/417 (2.6%)	17/416 (4.1%)
	Last observation	12/442 (2.7%)	18/454 (4.0%)

Reviewer's comment: The clinical significance of these laboratory changes is not clear and will be a review issue.

No significant difference in mean thyroid parameters of prolactin levels were observed between the two treatment groups in US Phase 3 controlled studies.

In both Phase 3 studies, more patients on silodosin developed a shift from "normal" at baseline to "high" at end of treatment in HgbA1C (4.3% vs. 1.4% in study SI04009; 5.4% vs. 2.4% in study SI040010).

3.5.5 Vital Signs (U.S. Phase 3 controlled studies)
No clinically significant difference in change from baseline in systolic or diastolic blood pressure was observed between the silodosin and placebo groups.

Silodosin subjects experienced an increase in heart rate compared to placebo patients (Table 3.5.5.1).

Table 3.5.5.1 Summary of Change from baseline in heart rate – US Phase 3 Controlled Studies (Safety Population)

Visit/Duration of Treatment	Statistic	Placebo (N=457)	Silodosin (N=466)
>0 to 6 weeks	Mean (SD)	0.9 (8.90)	1.3 (8.82)
	Median	0.0	0.0
>6 weeks	Mean (SD)	0.5 (9/42)	1.5 (9.86)
	Median	0.0	2.0
Last observation	Mean	0.7 (9.32)	1.4 (9.91)
	Median	0.0	1.0

Reviewer's comment: The small difference in change from heart rate between the two populations is most likely not clinically significant.

More silodosin subjects experienced a positive orthostatic test post-dose than placebo subjects at one minute after standing and at 3 minutes after standing (Table 3.5.5.2)

Table 3.5.5.2 Summary of Post-Dose Orthostatic Response – US Phase 3 Controlled Studies (Safety Population)

Visit	Position	Result	Placebo N=457	Silodosin N=466
Post-Dose	1 minute after standing	Negative	454 (99.6%)	459 (98.7%)
		Positive	2 (0.4%)	6 (1.3%)
	3 minutes after standing	Negative	454 (99/6%)	456 (98.1%)
		Positive	2 (0.4%)	9 (1.9%)

Reviewer's comment: Orthostatic testing was performed pre-dose and compared to a repeat test 2-6 hours after the first dose of double-blind therapy in both Phase 3 studies. A positive test was defined as any of the following:

- *Decrease in systolic blood pressure >30 mmHg*
- *Decrease in diastolic blood pressure >20 mmHg*
- *Increase in heart rate >20 bpm.*

ECGs:

In Phase 3 study SI04009, more silodosin patients had an abnormal ECG (clinically significant) at study endpoint than those on placebo – 5.6% versus 0.9%.

Reviewer's comment: A preliminary review of ECG abnormalities identifies no commonality among silodosin patients. Similar numbers of placebo and silodosin patients developed an ECG reading with "prolonged QT interval" during therapy – 24 on silodosin and 22 on placebo.

In Phase 3 study SI04010, 6 patients' ECGs in the silodosin group and 5 patients' ECGs in the placebo group were reported clinically significant by investigators after baseline.

Reviewer's comment: A preliminary review of ECG abnormalities identifies no commonality among silodosin patients.

Conclusion: From a clinical perspective, the NDA may be filed.

Clinical Review Comments:

1. Preliminary review of the safety data from the pivotal phase 3 studies reveals common treatment-emergent adverse events consistent with those reported for other alpha-adrenergic receptor antagonists.
2. Preliminary review of data from the thorough QT study does not appear to suggest that silodosin is associated with QT prolongation.
3. There are no clearly apparent deficiencies in the label based upon the initial filing review.
4. The effects of race, age and renal insufficiency on safety and tolerability of silodosin will be a review issue.
5. The acceptability of the 4 mg dose of silodosin in patients [redacted] will be a review issue.

b(4)

6. A preliminary review of study SI06002 suggests that this trial will support the [redacted] b(4)

7. The change from baseline in IPSS Irritative and Obstructive Subscales and the quality-of-life question are considered exploratory endpoints. The Division does [redacted] b(4)

8. In the US controlled Phase 3 trials, more silodosin patients experienced a shift from "normal" to "high" in serum AST, creatinine, HgbA1C, and GGT during treatment than those on placebo. The clinical significance of these changes is not clear but will be a review issue.

Recommended Regulatory Action: Comments #4-8 should be sent to the sponsor in the 74-Day letter.

APPEARS THIS WAY
ON ORIGINAL

Appendix 1
Phase 2: Study KMD3213-US021-99
This trial was a multi-center, randomized, double-blind, parallel group, placebo-controlled, dose-finding study designed to evaluate the efficacy, safety, and effective dosage of silodosin in male patients with BPH. Two-hundred and sixty-four eligible patients (age 45-75 years, maximum urine flow rate (Q_{max}) 4 – 15 ml/sec with MVV>125 mL, and American Urological Association symptom score (AUA-SS) ≥13) were randomized to receive 8 mg silodosin (n=90), 4 mg silodosin (n=88), or placebo (n=86) once daily.

Reviewer's comment: The AUA-SS is identical to the IPSS.

The study was comprised of a 4-week placebo run-in period; a 2-week dose adjustment period (patients assigned to the 8 mg dose group received 4 mg for one week before increasing to 8 mg); and a 6-week stable dosing period.

The co-primary efficacy endpoints were change from baseline in AUA-SS total score and Q_{max} at last observation carried forward (LOCF).

Results:
Efficacy
Statistically significant changes in the AUA-SS total score and Q_{max} were observed for both silodosin 4 mg and 8 mg compared to placebo (Table 1 and Table 2).

Table 1. Mean Change from Baseline to LOCF in AUA-SS

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value
8 mg silodosin	90	-6.8 (5.8)	0.0018
4 mg silodosin	88	-5.6 (5.5)	0.0355
Placebo	83	-4.0 (5.5)	

Table 2. Mean Change from Baseline to LOCF in Qmax

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value
8 mg silodosin	90	+3.4 (5.7)	0.0174
4 mg silodosin	88	+2.9 (4.0)	0.0966
Placebo	83	+1.5 (4.4)	

Reviewer's comment: At the EOP-2 meeting on February 10, 2005, the sponsor presented data to show that results for the 4 mg dose were not significant when allowing for multiple comparisons. The results for the 8 mg dose were corrected for multiple comparisons using the Bonferroni method and were statistically significant.

Safety
Safety analyses were performed on the safety population (all randomized patients who received at least one dose of study medication).

Deaths, Serious Adverse Events
There were no deaths or serious adverse events during the study.

Most Common Treatment-Emergent Adverse Events
During the double-blind treatment period, the incidence of adverse events (AEs) was not significantly different among the three treatment groups. The most frequently (≥2%) reported adverse events observed during the double-blind treatment period and significantly more often in the silodosin group than in placebo are shown in Table 3.

Table 3. Frequently (>2%) Reported AEs, Study KMD3213-US021-99

Adverse Event	8 mg	4 mg	Placebo	p-value
Overall	64 (71.1)	59 (67.0)	55 (64.0)	0.6092
Retrograde ejaculation	14 (15.6)	10 (11.4)	0	0.0001
Ejaculation failure	10 (11.1)	8 (9.1)	0	0.0021

AEs leading to discontinuation:
A total of 10 patients in the 8 mg group and 5 patients in the 4 mg group discontinued the study due to one or more adverse events. Four of these patients discontinued due to reproductive AEs– ejaculation failure (n=2) and retrograde ejaculation (n=2).

Vital Sign Measurements:
Pulse
No significant difference in the mean change in heart rate from baseline to endpoint was observed among the three treatment groups.

Blood Pressure
At end of treatment, a mean increase from baseline in systolic blood pressure was observed in the 8 mg group (1.2±16.5 mmHg) and a mean decrease was observed in the 4 mg (-5.4±13.5 mmHg) and placebo (-3.0±12.2 mmHg) groups. This difference was statistically significant across treatment group (p=0.0285).

Reviewer's comment: The changes in systolic blood pressure observed in the three treatment groups are not considered clinically significant.

No statistically significant differences were observed across treatment groups in diastolic blood pressure.

Orthostatic Changes
Overall, 3/90 (3.3%), 4/88 (4.5%), and 2/86 (2.3%) patients in the 8 mg, 4 mg, and placebo groups, respectively, had a positive orthostatic test result. The difference across groups was not statistically significant.

Reviewer's comment: An orthostatic test was considered positive if any of the following occurred:

- *A decrease in diastolic blood pressure of >20 mmHg (or >10mm Hg if baseline DBP was <60 mm Hg);*
- *An increase in pulse rate of >20 bpm;*
- *The onset of symptoms associated with hypotension (e.g., dizziness, loss of consciousness, lightheadedness, fainting) occurred.*

Laboratory Parameters, ECG, Physical Exam

No clinically significant differences in laboratory parameters or ECG readings were observed among the three treatment groups.

APPEARS THIS WAY
ON ORIGINAL

Appendix 2

Phase 3 Study SI04009

This study was a multi-center, randomized, double-blind, placebo-controlled, parallel group safety and efficacy trial of silodosin 8 mg compared to placebo once daily in the treatment of the signs and symptoms of BPH. Four-hundred and sixty-one eligible patients (males at least 50 years of age with IPSS ≥13; Qmax between 4 and 15 mL/sec, with minimum voided volume ≥125 mL) were randomized to either silodosin 8 mg (N=233) or placebo (N=228) administered once daily. The study was comprised of two periods -- a 4-week single-blind placebo run-in period and a 12-week dosing period.

The primary efficacy endpoint was change from baseline to endpoint [week 12/Visit 8 (LOCF)] in the total score of the International Prostate Symptom Score (IPSS). Change from baseline to endpoint in Q_{max} was the secondary efficacy endpoint.

The primary efficacy analysis was performed on the modified intent-to-treat (mITT) population [all randomized patients who at least provided data for the primary efficacy variable at Visit 3 (baseline); if patient was incorrectly randomized, actual treatment given was planned to be used in all summary stats and analyses].

Results

As no patients were incorrectly randomized, the ITT population is equivalent to the mITT population for this study.

Silodosin resulted in a significantly greater change in IPSS total score than placebo at endpoint (Table 1).

Table 1. Mean Change from Baseline in IPSS

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value
8 mg silodosin	233	-6.5 (6.73)	<0.0001
Placebo	228	-3.6 (5.85)	

Silodosin also had a statistically significant effect on the change from baseline in Qmax at endpoint.

Table 2. Mean Change from Baseline in Qmax (ml/sec)

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value
8 mg silodosin	233	2.2 (4.31)	0.0060
Placebo	228	1.2 (3.81)	

Safety

Common Treatment Emergent Adverse Events
More patients receiving silodosin experienced an adverse event than those on placebo -- 58.4% vs. 33.8%, respectively.

Treatment-emergent adverse events that occurred in >2% of patients receiving silodosin and at an incidence numerically higher than that of placebo are shown in Table 3.

Table 3. Most Common Silodosin Treatment Emergent Adverse Events

Adverse Event – MedDRA preferred term	Silodosin	Placebo
Retrograde Ejaculation	68 (29.2)	2 (0.9)
Headache	8 (3.4)	3 (1.3)
Diarrhea	7 (3.0)	1 (0.4)
Dizziness	6 (2.6)	4 (1.8)
Nasal congestion	6 (2.6)	0
Orthostatic hypotension	6 (2.6)	5 (2.2)
Insomnia	5 (2.1)	0
Sinusitis	5 (2.1)	2 (0.9)

Reviewer's comment: Adverse events observed with silodosin are consistent with those reported for other alpha blockers.

Serious Adverse Events
One death occurred in a patient receiving placebo.

Six patients (3 on placebo, 3 on silodosin) experienced serious adverse events during the trial. SAE's in the silodosin group were acute MI in two patients and cervical radiculopathy in the third.

AEs leading to discontinuation:
More patients on silodosin discontinued therapy due to an AE than those on placebo – 20 (8.6%) versus 6 (2.6%). The most common AE in silodosin subjects leading to discontinuation was retrograde ejaculation (9, 3.9%).

Vital Signs:
There was no significant difference in mean systolic or diastolic blood pressure or pulse at week 12 between the two treatment groups. There was also no significant difference in change from baseline to LOCF in SBP or DBP between the two groups.

Appendix 3

Phase 3 Study SI04010

The design of this study was identical to that of Phase 3 trial SI04009.
462 men with signs and symptoms of BPH were enrolled and randomized to either silodosin 8 mg (N=233) or placebo (N=229) once daily.

Results
Efficacy
Silodosin resulted in a significantly greater change in IPSS total score than placebo at Week 12 (Table 1).

Table 1. Mean Change from Baseline in IPSS at Week 12 (LOCF) (mITT)

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value
8 mg silodosin	233	-6.3 (6.54)	<0.0001
Placebo	228	-3.4 (5.83)	

Silodosin also improved Qmax significantly over placebo at Week 12 (Table 2).

Table 2. Mean Change from Baseline in Qmax at Week 12 (LOCF) (mITT)

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value
8 mg silodosin	233	1.9 (4.82)	<0.0431
Placebo	228	2.9 (4.53)	

Safety
Treatment Emergent Adverse Events
More patients receiving silodosin experienced an adverse event than those on placebo – 51.9% versus 39.7%, respectively.

Treatment emergent adverse events that occurred in >2% of patients receiving silodosin and at an incidence numerically higher than that of placebo are shown in Table 3.

Table 3. Most Common Silodosin Treatment Emergent Adverse Events

Adverse Event – MedDRA preferred term	Silodosin N=233 n (%)	Placebo N=229 n (%)
Retrograde Ejaculation	63 (27.0)	2 (0.9)
Dizziness	9 (3.9)	1 (0.4)
Diarrhea	7 (3.0)	1 (0.4)
Nasopharyngitis	6 (2.6)	3 (1.3)
Orthostatic hypotension	6 (2.6)	2 (0.9)
Abdominal pain	5 (2.1)	0
PSA increased	5 (2.1)	2 (0.9)

Deaths
No deaths occurred after randomization in the study.

Serious Adverse Events
There were 8 SAEs – five in the placebo group, three in the silodosin group. SAEs in the silodosin group were aggravated carotid artery stenosis, syncope and complete heart block. Syncope was believed to be treatment-related.

Discontinuations due to Adverse Events
Fourteen patients were discontinued due to adverse events (10 in silodosin group; 4 in placebo). Of these ten, four were discontinued secondary to retrograde ejaculation.

Laboratory Evaluation
More patients on silodosin had a positive orthostatic test post-dose than those on placebo, as shown in Table 7.

Visit	Position	Treatment Group	
		Placebo	Silodosin
Week 0 (Pre-Dose	1 minute after standing	2 (0.9%)	0 (0.0%)
	3 minutes after standing	0	0
Week 0 (2-6 hours post-dose)	1 minute after standing	1 (0.4%)	3 (1.3%)
	3 minutes after standing	1 (0.4%)	3 (1.3%)

Reviewer's comment: A positive orthostatic test was defined as
- *Δ systolic blood pressure >30 mmHg*
- *Δ diastolic blood pressure >20 mmHg*
- *Δ heart rate >20 BPM*
- *Symptoms upon change of position such as lightheadedness, fainting, blurring or*
- *temporary loss of vision, profound weakness, or syncope*

ECG
More silodosin patients had an abnormal ECG (clinically significant) at study endpoint than those on placebo – 5.6% versus 0.9%.

Reviewer's comment: A preliminary review of ECG abnormalities identifies no commonality among silodosin patients. Similar numbers of placebo and silodosin patients developed an ECG reading with "prolonged QT interval" during therapy – 24 on silodosin and 22 on placebo.

Laboratory
Preliminary review finds no difference in mean change from baseline to LOCF for any laboratory parameter between silodosin and placebo groups.

NDA Number: 22-206 **Applicant: Watson** **Stamp Date: 12/13/07**

Drug Name: Rapaflo™ (silodosin) NDA Type: standard, original application

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: KMD-3213-US021-99 Study Title: A Pilot, Phase II, Placebo-Controlled, Double-Blind Study of KMD-3213 in Patients with the Signs and Symptoms of Benign Prostatic Hyperplasia (BPH) Sample Size: 264 Arms: 3 Location in submission: Module 5 – 5.3.5.1	X			
EFFICACY					

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 SI04009 Indication: signs and symptoms of BPH Pivotal Study #2 SI040010 Indication: signs and symptoms of BPH	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Dose-finding Phase 2 and both Phase 3 trials were performed in the U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Thorough QT study is submitted
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				N/A
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Dose-finding Phase 2 and both Phase 3 trials were performed in the U.S.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. The effects of race, age and renal insufficiency on safety and tolerability of silodosin will be a review issue.
2. The acceptability of the 4 mg dose of silodosin in patients [redacted] will be a review issue. b(4)
3. A preliminary review of study SI06002 suggests that this trial will support the [redacted] b(4)
4. The change from baseline in IPSS Irritative and Obstructive Subscales and the quality-of-life question are considered exploratory endpoints. [redacted] b(4)
5. In the US controlled Phase 3 trials, more silodosin patients experienced a shift from "normal" to "high" in serum AST, creatinine, HgbA1C, and GGT during treatment than those on placebo. The clinical significance of these changes is not clear but will be a review issue.

Olivia Easley — 2/8/08
Reviewing Medical Officer — Date

Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Olivia Easley
2/8/2008 01:44:59 PM
MEDICAL OFFICER

George Benson
2/8/2008 02:23:48 PM
MEDICAL OFFICER