Reviewer's comments:
*1) LFTs for **subject 101021** normalized despite continuation of silodosin therapy. Therefore, silodosin was unlikely to have caused laboratory abnormality in this patient.*

*2) **Subject 122046** was discontinued from the trial due to abnormal liver function tests. Neither the investigator nor sponsor provided an assessment of causality for LFT abnormalities. His concomitant medications were glucosamine/chondroitin for osteoarthritis; Diovan and bisoprolol for hypertension; levothyroxine for hypothyroidism; Lipitor for hypercholesterolemia; and disopyramide for cardiac arrhythmia.*

*3) **Subject 268038** discontinued prematurely due to perceived lack of efficacy.*

*4) No additional information is available for **subjects 125001** or **268038**.*

With the exception of subject 101021, it is impossible to determine causality for LFT abnormalities in these subjects based on the limited information provided.

European and Japanese Studies:
The sponsor submitted preliminary laboratory data from a completed European Phase 3 study in which subjects were randomized to receive silodosin 8 mg (N=390), tamsulosin 0.4 mg (N=393) or placebo (N=194) once daily for 12 weeks. Liver function test data were reviewed.

Compared to placebo, there was no meaningful difference in mean change from baseline in serum ALT, AST or total bilirubin for silodosin (Table 7.16). A slightly greater percentage of silodosin subjects experienced a shift in serum AST and ALT than those on placebo (Table 7.17).

Table 7.16, Change from baseline in serum liver function tests, European Phase 3 trial

Analyte	Silodosin (N=390)	Placebo (N=194)
AST (U/L)	0.3	0.1
ALT (U/L)	-0.3	-0.6
Total Bilirubin (umol/L)	-0.20	+0.1

Table 7.17 Subjects experiencing laboratory parameter shift from normal at baseline to high post-baseline, European Phase 3 trial

Analyte	Silodosin (N=390) N (%)	Placebo (N=194) N (%)
AST	4 (1.0)	1 (0.5)
ALT	12 (3)	3 (1.5)
T. Bili	13 (3.3)	9 (4.6)

No subject on silodosin or placebo had post-treatment elevations in serum transaminase >3X ULN or total bilirubin >2X ULN in the European Phase 3 study.

The study reports from the Japanese Phase 2 and 3 trials used to support silodosin approval in Japan were also included in the NDA submission. In the Phase 2 study, subjects were assigned to silodosin 4 mg (N=89) or 8 mg (N=92), or placebo (N=89) once daily for 4 weeks. In the Phase 3 trial, subjects received silodosin 8 mg, tamsulosin 0.2 mg or placebo once daily for 12 weeks. In both trials, there was no statistically significant difference in mean change from baseline to endpoint in serum bilirubin, AST or ALT between placebo and silodosin groups.

Two subjects in the Phase 2 trial, both assigned to silodosin 8 mg daily, developed an increase in serum AST or ALT >3X ULN at week 4. Only abnormal laboratory values were provided – as total bilirubin was not listed, it was presumably normal for both patients. Time course of abnormal liver function tests in each subject is shown in Tables 7.18 and 7.19 respectively.

Table 7.18 Liver Function Tests, Subject 39-3

#39-3, 70 y.o. M, no PMHx			
Analyte	**Baseline**	**Week 4**	**Follow-up #1**
AST(nl 10-40 U/L	37	**126**	32
ALT(nl 5 – 45 U/L)	22	**79**	18

Table 7.19 Liver Function Tests, Subject 59-4

#59-4, 65 y.o. M with h/o HTN				
Analyte	**Baseline**	**Week 4 (6/16/00)**	**Follow-up #1 (6/26/00)**	**f/u #2 (7/3/00)**
AST	40	**122**	46	43
ALT	45	**212**	96	56
ALP (nl 74-223 IU/L)	336	**433**	395	328
GGT (nl 0-60 IU/L)	19	**69**	78	63

Reviewer's comments:

1) *The minimal transaminase elevation seen in subject 39-3 without an accompanying increase in total bilirubin is not considered clinically significant.*

2) *No other information is provided on these subjects, including concomitant medications.*

3) *Causality for transaminase elevation in these subjects can not be determined, but a contributory role of silodosin can not be excluded.*

No silodosin subjects in the Japanese Phase 3 study developed transaminase elevation >3X ULN.

Post-marketing:

The sponsor has been submitting serious, unexpected adverse event reports to the IND. As of July 30, 2008, there have been seven such reports involving hepatic function disorder, all occurring outside the U.S. Narratives follow:

2006-05221 (10/12/06)

This case was a report of a 74-year-old male patient who experienced ***hepatic function disorder*** and ***jaundice*** while using silodosin for bladder outlet obstruction (BOO) associated with BPH. Silodosin 4 mg bid was prescribed in August, 2006. Concomitant medications listed were several herbal preparations (taurocholate, equistem avense, triticum aestivum, pulsatilla pratensis and populus tremuloides), but no prescription products.

On [redacted], the patient underwent colonoscopy for evaluation of hemoccult-positive stool, and was subsequently diagnosed with large intestine carcinoma. Surgery for the carcinoma was performed on [redacted] b(6)
Silodosin was held during the peri-operative period, but was resumed on September 5, 2006.

On September 19, 2006, the patient was found to have abnormal liver function tests , and two days later, the patient developed jaundice and diffuse abdominal pain. Silodosin was discontinued. A drug-induced lymphocyte stimulation test of silodosin was negative. Jaundice and liver function test abnormalities resolved. Time course of liver function tests in this patient is found in Table 7.20.

Reviewer's comment: A drug-induced lymphocyte stimulation test (DLST) is widely used for the diagnosis of drug-induced pneumonia and liver injury in Japan. A DLST is considered positive if the stimulation index (SI) is 180% or greater. In Western countries, DLST for diagnosing specific drug hypersensitivity is considered to be unreliable.[6]

The treating physician considered the event "probably related" to silodosin since it developed after restarting silodosin.

Table 7.20 Liver Function Tests, Subject 2006-05221

Date	AST	ALT	GGT	ALP	Tbili
9/5/06	Silodosin re-started				
9/5/06	30	28	45	184	1.3
9/19/06	29	88			
9/21/06	**341**	**303**	**603**	**706**	**1.8**
9/21/06	Silodosin discontinued				
9/25/06	30	106	284	405	0.5
9/28/06	25	66	194	322	0.6

Reviewer's comment: This case is confounded by concomitant use of an herbal medication and recent surgery for colon cancer.

The positive de-challenge suggests that silodosin could be responsible for liver function test abnormalities in this subject.

[6] Matsuno, O., et. al. *Drug-Induced Lymphocyte Stimulation Test is not Useful for the Diagnosis of Drug-Induced Pneumonia.* **Tohoku J. Exp. Med.**, 2007, 212, 49-53.

2006-04503 (2/1/07)

This report involved a 68-year-old male patient who developed ***pyonephrosis (bilateral), hepatic function abnormal*** and ***jaundice*** while on silodosin. The patient was prescribed silodosin 8 mg daily on July 14, 2006, for BPH-related bladder outlet obstruction. On [redacted] the patient developed diarrhea, vomiting and fever. The following day, he became jaundiced. Liver function tests were abnormal, and the patient was hospitalized for suspected acute cholangitis. Silodosin was discontinued. b(6)

The patient was treated with intravenous cefazolin. Abdominal CT scan revealed fatty liver and no biliary obstruction. Tests for hepatitis A, B and C were negative. Cefazoline was replaced with panipenam on August 1, 2006. The patient was subsequently diagnosed with bilateral renal abscesses and pyogenic spondylitis. His clinical condition improved.

The reporting physician believed that the relationship of hepatic function disorder and jaundice to silodosin was not assessable.

Time course for serum liver function tests are shown in Table 7.21. Baseline values were not provided for this patient.

Table 7.21 Liver Function Tests, Subject 2006-04503

Analyte	[redacted]	8/8/06	9/4/06
AST	**79**	31	14
ALT	**158**	49	26
ALP	**239**	**575**	**523**
GGT	**278**	**89**	---
TBili	**2.97**	0.70	0.5

b(6)

Reviewer's comment: This patient's diffuse liver function test abnormalities are likely due to sepsis.

2007-02194 (7/11/07)

This was a report of an 84-year-old male patient who developed ***subacute fulminant hepatitis*** while on silodosin. Silodosin 8 mg daily was prescribed for bladder outlet obstruction associated with BPH in June, 2006. On October 24, 2006, silodosin was discontinued. On [redacted] the patient underwent a total gastrectomy for gastric cancer. Silodosin was resumed on November 22, 2006. b(6)

In addition to silodosin, the patient was taking domoperidone (started 11/7/06) and levercol (started 11/22/06). He also "sometimes drinks [alcohol]."

Reviewer's comment: Levercol is an herbal preparation containing fish liver extract that is available only in Japan. Information from a website that exports Levercol describes it as an "oral liquid for nutriment." [7]

[7] *http://www.airgreen.co.jp/company/products_e.html*

Domperidone is an anti-dopaminergic drug used for the treatment of nausea and vomiting. It is available over-the-counter in Japan. It can cause elevations in serum AST and ALT. Extrapyramidal phenomenon is listed as a rare side effect in the product monograph.[8]

A blood test performed on December 8, 2006, showed abnormal liver function tests which persisted on a subsequent test on January 12, 2007. On ——— the patient was admitted to a hospital for further evaluation. Silodosin was discontinued. b(6)

The patient's clinical status and hepatic function deteriorated, and on ——— he was transferred to another hospital. Laboratory tests for this patient are displayed in Table 7.22. b(6)

Liver failure was treated with steroid therapy and plasma exchange. Tests for viral hepatitis (hepatitis B, C, CMV, EBV) and autoimmune disease (ANA, AMA) were negative. The patient recovered from the event and he was discharged from the hospital on ——— b(6)

The result of DLST for silodosin was 126% and for another medicine (not specified) was 138%.

Table 7.22 Laboratory Test Results, Patient 2007-02194

	Date						
Analyte (nl range)	**9/29/06**	**1/12/07**	**1/15/07**	**2/15/07**	**3/13/07**	**4/15/07**	**5/15/07**
AST (IU/L)	27	**1400**	**1880**	26	49	32	26
ALT (IU/L)	27	**1100**	**1640**	50	80	66	59
INR (0.9-1.2)	1.08	1.2	**2.07** (on 1/31/07)	1.48	1.20	1.11	1.03
GGT (IU/L)	13	**217**	**257**	**92**	81	160	124
T-Bili (0.2-1.3mg/dL)	1.0	1.0	1.3	**1.7**	0.9	0.6	0.3
Albumin (3.2-5 g/dL)	4.2			2.8			**2.5**
LDH (110-210 U/L)	148	**850**	**897**	**427**	**356**	**205**	158
CK (38-174 IU/L)	126	**1297**	**1110**	**623** (on 2/19)	32	31	21
Serum glucose (70-110 mg/dL)	90	**48**		92	88	255	89

The patient was subsequently diagnosed with hepatic cirrhosis (Child Pugh Grade A) as a consequence of this event.

The company (Kissei) considered the relationship between the event and silodosin to be possible.

[8] From Domperidone Product Monograph by Pharmascience, Inc., dated October 10, 1997.

Reviewer's comments:

1) *It is not stated whether Levercol and domperidone were also discontinued at the time of presentation.*
2) *Concomitant elevation of LDH and CPK suggests myositis, either alone or in addition to hepatitis. Myositis can cause elevation of AST and ALT.*
3) *Given the temporal relationship between initiation of Levacol and domperidone and laboratory abnormalities, these drugs are also suspect agents. His history of alcohol use and gastric cancer are additional confounding factors.*

2007-05415 (12/7/07)

This report involved an 89-year-old male patient who experienced ***jaundice*** and ***hepatic function disorder*** while on silodosin for bladder outlet obstruction associated with BPH. Silodosin 4 mg daily was initiated on 11/25/06. On June 7, 2007, silodosin dosage was reduced to 4 mg once every two days for an unspecified reason.

On November 13, 2007, the patient developed bilirubinuria and jaundice. Laboratory tests revealed elevated values of serum transaminases and total bilirubin, as shown in Table 7.23. Silodosin was discontinued.

Evaluation of jaundice included "CT, echography, MRI and gastrocamera." CT scan revealed a "shadow" in the liver. Ursodesoxycholic acid 300 mg tid was initiated for treatment of jaundice. On [redacted], a tumor of the right lobe of the liver and obstructed bile duct were confirmed. Urso was discontinued. b(6)

The patient underwent excision of the right lobe of the liver and bile duct. A hepatocholangiojejunostomy and jejunostomy were performed. Pathologic examination revealed a grade 3 hepatocellular carcinoma with metastases to the "lymph node and cholecyst." Following surgery, jaundice and bilirubinuria improved, and the patient was discharged from the hospital.

The sponsor stated that given the size of the hepatocellular carcinoma, it was unlikely to have developed during the course of treatment with silodosin.

Table 7.23, Liver Function Tests, Patient 2007-05415

Analyte	6/5/07 (baseline)	11/13/07
AST	21	**86**
ALT	24	**110**
Total bilirubin	---	**3.4**

Reviewer's comment: This patient's liver function abnormalities are a result of biliary obstruction secondary to hepatocellular carcinoma, and are not related to silodosin therapy.

2008-00648 (2/14/08)

This report was solicited during a postmarketing study in Japan and involved a 77-year-old male patient who developed ***liver disorder*** and ***jaundice*** while receiving silodosin 8 mg daily for BPH-related bladder outlet obstruction. Silodosin had been initiated in December, 2007. The patient had a history of chronic hepatitis C, hypertension, insomnia, spinal column stenosis and arrhythmia. Concomitant

medications were proheparum (since 11/22/00), amlodipine (since 12/28/04), senna (since 10/1/01), triazolam (since 8/5/02) and mexilitine (since 4/23/04).

A routine medical examination on [redacted], revealed abnormal liver function tests, and the patient was hospitalized for further evaluation. Silodosin was discontinued. Neo-minophagen C was initiated for treatment of liver disorder. Biliary obstruction was excluded by ultrasound. Liver function tests gradually improved without additional therapy (Table 7.24). b(6)

Table 7.24 Liver Function Tests, Patient 2008-00648

Date	AST	ALT	ALP	GGT	T. BILI	D. BILI
8/28/07	33	22	208	17	1.03	0.1
10/23/07	38	20	263	19	0.68	0.05
[redacted]	**662**	**635**	**346**	**361**	**4.45**	**2.74**
[redacted]	Silodosin discontinued					
12/25/07	**99**	**156**	**283**	**276**	**3.33**	2.10
1/4/08	**64**	**156**	**262**	**233**	**2.58**	1.12
1/22/08	**79**	**73**	**329**	**170**	**1.63**	0.47

The physician considered the adverse events as probably related to silodosin.

Reviewer's comment: The temporal relationship of hepatic decompensation to initiation of silodosin therapy suggests that silodosin may be contributory. However, the patient's prior history of hepatitis C complicates the clinical picture. In addition, results of diagnostic testing for other possible causes of hepatic disorder are not provided.

2008-03848 A 65 year-old male patient experienced **liver disorder** while on silodosin for BOO associated with BPH. In mid-May, 2008, silodosin 8 mg daily and a Chinese medicine (Hachimi-jio-gan) were prescribed for BOO. On [redacted], laboratory data showed AST and ALT values of approximately 3000, respectively. Silodosin was discontinued and the patient was hospitalized. The patient had a history of alcohol abuse. At the time of this report the patient had not recovered from acute liver disorder. The sponsor considered the event to be possibly related to silodosin. b(6)

Reviewer's comments:

1. *Hachimi-jio-gan is a Chinese herbal formulation that contains Rehmannia root, Poria whole plant, Chinese yam root, Asiatic dogwood aerial part, Barrenwort aerial part, Water plantain aerial part, Astragalus root and Cassia bark. This preparation was initiated simultaneously with silodosin. Therefore, it too is considered suspect.*

2. *The patient's history of alcohol abuse is a confounding factor.*

2008-04048 A male patient of uncertain age who had been treated with silodosin for BOO associated with BPH, developed liver disorder. The details, including the outcome of the event, are unknown at this time. The event was serious because of involved or prolonged inpatient hospitalization.

Reviewer's comment: There is insufficient information to make a meaningful assessment of causality in this case.

Reviewer's comment: The Division of Pharmacovigilance II (DPV II) was consulted to review the post-marketing hepatic adverse event reports involving silodosin. Six cases were forwarded to DPV II. The seventh, patient ID 2008-04048, was received later and was not reviewed by DPV II. The DPV II consultant's conclusions follow:

Two cases of jaundice (cases #2006-05221, #2006-04503) were possibly due to gallstones. Both reported a rapid improvement of liver function tests (less than 2 weeks) after silodosin discontinuation, a timeline not usually associated with DILI.

Case #2007-05415 (jaundice) appeared to be related to the patient's diagnosis of hepatic cancer. The events improved after the patients hepatic cancer was resected.

Case #2008-03848 (ALT, AST around "3000") in a "hard drinker" reported too little information to make any causality assessment.

The two remaining cases (cases #2007-02194, #2008-00648) were possibly related to the use of silodosin. Case #2007-02194 reported fulminant hepatitis with hepatic encephalopathy and coagulopathy in an 84-year-old male with gastric cancer. The hepatic events occurred 16 days after restarting silodosin postgastric resection surgery. Silodosin was discontinued and the transaminases and bilirubin improved. Case #2008-00648 reported jaundice in a 78-year-old male with chronic hepatitis C 2.5 months after beginning silodosin therapy. Silodosin was discontinued and transaminases and bilirubin improved. Although both cases are confounded by underlying medical conditions (gastric surgery and chronic hepatitis, respectively) both cases reported the events began within 90 days of initiating therapy and gradually improved after dechallenge. Based on the reported timelines a contributory effect from silodosin to the events could not be ruled out.

Therefore, DPV II suggests the following be specified in the product Approval Letter:

1. The adverse event terms *jaundice* and [redacted] should be included in the postmarketing adverse events section of the silodosin label.
2. To ensure timely evaluation of serious [redacted] epatic events (e.g. jaundice, hepatitis) the sponsor should submit all serious [redacted] epatic events as expedited 15-day Alert Reports. b(4)
3. The sponsor should obtain comprehensive follow-up of all expedited reports of serious hepatic adverse events.

Summary of silodosin effect on liver function tests

1) Controlled Trials:
   a. In U.S. Controlled Phase 3 clinical trials (N=457 on silodosin), a single silodosin subject experienced AST elevation >5X ULN during treatment which normalized despite continuation of silodosin. No subject experienced concomitant elevation of serum transaminase and total bilirubin.
   b. In the European Phase 3 study (N=390 on silodosin), no subjects on silodosin experienced transaminase elevation >3X ULN or total bilirubin >2X ULN.
   c. In the controlled Japanese database, two silodosin treated subjects in the Phase 2 study (N=182 on silodosin) experienced transaminase elevation

>3X ULN without concomitant bilirubin increase during treatment. No silodosin subjects in the Japanese Phase 3 study developed transaminase or bilirubin elevation.

Data from controlled clinical trials do not suggest that silodosin has a clinically meaningful adverse effect on hepatic function.

2) In U.S. open-label extension study, SI04011 (N=661), three silodosin subjects experienced an elevation in AST or ALT >3-5X ULN and a single silodosin subject had an ALT >5X ULN during treatment. In one case, liver function tests returned to normal despite continuation of silodosin. In the three remaining cases, insufficient information was provided to determine causality.

3) To date, there have been seven post-marketing reports of hepatic dysfunction in the setting of silodosin use.
   a. In two of these cases (2006-04503 and 2007-05415), silodosin was clearly not related to liver dysfunction.
   b. In one case (2008-04048), an assessment of causality is impossible based on the scant information provided.
   c. In the remaining four cases (2006-05221, 2008-00648, 2008-03848, 2008-04048), a relationship to silodosin can not be excluded. One of these cases (2008-00648) satisfies Hy's law criteria. Two of these patients recovered fully and a third had not. In the fourth (2007-02194), the patient had residual hepatic dysfunction, classified as Child-Pugh Class A hepatic cirrhosis.
   d. Thus far, there have been no deaths from liver failure or patients requiring a liver transplant.

4) Considering data from clinical trials and post-marketing, the evidence is not convincing that silodosin adversely effects hepatic function. However, this reviewer believes that the following terms should be added to the *post-marketing adverse events* section of the label: jaundice and [redacted] should not be included because [redacted] b(4)

7.1.7 Vital Signs

Vital signs were measured at all clinic visits during Phase 2/3 trials. In controlled Phase 3 trials, silodosin treatment was associated with a slight reduction in mean systolic and diastolic blood pressure and a slight increase in pulse compared to placebo (Table 7.25).

Table 7.25 Summary of Change from Baseline to Week 12/ET in vital sign parameters, U.S. controlled Phase 3 trials (safety population)

Parameter	Statistic	Placebo N=457	Silodosin N=466
SBP	Mean (SD)	-0.2 (14.52)	-1.3 (13.22)
	Median	0	0
DBP	Mean (SD)	-0.2 (9.01)	-0.7 (8.40)
	Median	0	0
Pulse	Mean (SD)	0.7 (9.32)	1.4 (9.91)
	Median	0	1.0

Source NDA 22-206 ser 000, ISS, Table 2.8.1-4

In US controlled and uncontrolled studies, subjects receiving silodosin treatment for >12 weeks and up to 40 weeks experienced mean decreases in SBP and DBP and a slight increase in pulse (Table 7.26).

Table 7.26 Summary of Change from baseline in vital sign parameters, all US Controlled and Uncontrolled Studies (Safety Population)

Duration of Treatment	Parameter	Statistic	Silodosin (N=897)
>12 to 40 weeks	SBP	Mean	-3.3 (14.16)
		Median	-2.0
	DBP	Mean	-2.6 (8.57)
		Median	-2.0
	pulse	Mean	2.3 (10.23)
		Median	3.0

Source: NDA 22-206 ser 000, ISS, Table 2.8.1-6

7.1.8 Orthostatic Vital Signs

A test for postural hypotension was conducted 2-6 hours following the first dose of study drug in the two Phase 3 controlled trials. Blood pressure and pulse were measured after the patient had been supine for 5 minutes and again at 1 and 3 minutes after standing. The sponsor defined a positive result as follows:

- ≥30 mmHg decrease in SBP
- ≥20 mmHg decrease in DBP or
- ≥20 bpm increase in heart rate.

Study sites were instructed to record an adverse event of "significant change in blood pressure POSTURAL" when these measurement changes occurred in the absence of symptoms. When patients had symptoms during orthostatic tests, the specific symptoms were recorded as an adverse event.

The sponsor provided the number and percentage of patients who had a positive test result without symptoms (data shown in Table 7.27).

Table 7.27 Summary of Positive Orthostatic Results (Sponsor's Criteria) – US Phase 3 Controlled Studies (Safety Population)

Visit 3	Position	Silodosin N=466	Placebo N=457
Post-Dose	1 minute after standing	6 (1.3%)	2 (0.4%)
	3 minutes after standing	9 (1.9%)	2 (0.4%)

Source: NDA 22-206, ser 000, ISS, Table 2.9.1-3

Reviewer's comment: Patients who had positive symptoms during routine orthostatic testing were not included in this summation but were recorded as adverse events.

Orthostatic tests were searched using more stringent criteria (ΔSBP≥ -20 mmHg, ΔDBP≥ -20 mmHg or Δ pulse ≥20 bpm heart rate), consistent with those used in clinical practice. Results are shown in Table 7.28.

Table 7.28 Summary of Positive Orthostatic Results (Strict Criteria) – US Phase 3 Controlled Studies (Safety Population)

Visit	Position	Silodosin N=466	Placebo N=457
Post-Dose	1 minute after standing	7 (1.5%)	4 (0.8%)
	3 minutes after standing	14 (3.0%)	2 (0.4%)

No subject had a systolic blood pressure <90 mmHg during orthostatic testing.

Reviewer's comment: Orthostatic hypotension is an expected side effect of α-antagonist drugs. The incidence of a positive orthostatic test among silodosin patients was not exceedingly high and was comparable to that observed in clinical trials of currently marketed alpha-antagonists (e.g. 6.6% of UROXATRAL patients).[9]

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

In the two controlled Phase 3 trials, ECGs were obtained at baseline, week 4 (visit 7) and week 12 (visit 8/ET). ECGs were evaluated by a centralized group of readers.

In addition to ECG monitoring during the Phase 3 trials, a formal thorough QT study was performed (Study SI05014).

[9] Uroxatral® approved label, dated 2/07

7.1.9.2 Standard analyses and explorations of ECG data

In Phase 3 controlled trials, a greater number of silodosin subjects than placebo subjects had a clinically significant, abnormal ECG at study endpoint than those on placebo – 2.8% versus 1.3%. However, a review of ECG abnormalities identifies no commonality among silodosin patients. There was no difference between silodosin and placebo groups in the incidence of the following ECG abnormalities -- prolonged QT interval, LBBB, second or third degree AV block, T wave inversion, or ST segment elevation.

7.1.9.3 Additional Exploration – effect of silodosin on the QT interval

This study was a double-blind, randomized, placebo- and moxifloxacin-controlled, 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. The supra-therapeutic silodosin dose (24 mg) was selected to approximate the "worst-case" scenario exposure (i.e in the setting of concomitant renal disease or use of potent CYP3A4 inhibitors).

The primary endpoint was change from baseline in the time-matched, placebo-corrected QTcI interval for each treatment group. Placebo-corrected, time-matched change from baseline for QTcF was a secondary endpoint.

At all time points measured, the upper bound of the two-sided 90% CI for the baseline- and placebo-corrected QTcI at Day 5 for silodosin 8mg and 24 mg was less than 10 msec. The upper bound of the 99% CI for moxifloxacin was greater than 10 msec at all time points, which confirmed the study's assay sensitivity.

The largest, time-matched, placebo-corrected change from baseline in the upper bound of the 90% CI for QTcF was slightly greater than 10 msec for both the 8 and 24 mg silodosin doses and occurred at hour 6.

Results are shown in Table 7.29.

Table 7.29 Point Estimates and 90% CIs corresponding to the Largest Upper Bounds for Silodosin (8 mg and 24 mg) and moxifloxacin (sponsor's analyses)

Treatment	Time (hour)	QTcI (ms)	QTcF (ms)
Silodosin 8 mg	6	3.42 (-2.94, 9.78)	4.49(-1.03, 10.01)
Silodosin 24 mg	6	1.39 (-5.03, 7.82)	4.63(-0.95, 10.21)
Moxifloxacin	6	9.59 (-0.36, 19.55)	---

Source: NDA 22-206 ser 000, SI05014 study report, Tables 14.2.1-1, 14.2.1-2, and 11.3.2-1

The IRTQT statistical reviewer performed an independent analysis of 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 a fixed effect and baseline QTc as covariates. By this analysis, the largest upper bounds of the 2-sided 90%

CIs for the mean differences between silodosin and placebo in the time-matched QTcF change from baseline are below 10 ms for both the 8 mg and 24 mg treatment groups (Table 7.30).

Table 7.30 Point Estimates and 90% CIs corresponding to the Largest Upper Bounds for Silodosin (8 mg and 24 mg)

Treatment	Time (hour)	ΔΔQTcF and 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)

Source: IRTQT Consultant Review, dated April 16, 2008

The QTIRT consultant concluded the following:

"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 24mg) and placebo were both below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline....Given the lack of dose-response in the primary statistical endpoint and the lack of exposure-response relationship for silodosin, the increase in silodosin exposures due to metabolic inhibition is not expected to prolong the QT interval. "

There have been no reports during clinical trials or in post-marketing experience to date of adverse events that may be related to QT prolongation (e.g. seizure, TdP, ventricular tachycardia or sudden death).

Reviewer's comment: The preponderance of evidence suggests that silodosin has no meaningful effect on the QT interval.

7.1.10 Human Carcinogenicity

Two carcinogenic findings occurred during the nonclinical development of silodosin and are described below.

1) In a 2-year oral carcinogenicity study in male rats administered doses up to 150 mg/kg/day, and in female rats at doses up to 250 mg/kg/day, an increase in thyroid follicular cell tumor incidence was seen in male rats receiving doses of 150 mg/kg ($p < 0.05$). These findings were believed to be test species specific. Silodosin induced stimulation of TSH secretion in the male rat as a result of increased metabolism and decreased circulating levels of T4.

   In clinical trials, no increased incidence of thyroid function test abnormalities were observed among silodosin treated patients compared to those receiving placebo.

2) In a 2 year oral carcinogenicity study in mice administered doses up to 200 mg/kg/day in males and 400 mg/kg/day in females, there were no significant tumor findings in male mice. Female mice treated for 2 years with doses of 150 mg/kg/day or greater had statistically significant increases in the incidence of mammary gland adenoacanthoma and adenocarcinomas ($p < 0.001$). The increased incidence of mammary gland neoplasms in female mice was considered secondary to silodosin-induced hyperprolactinemia measured in the treated mice.

   Elevated prolactin levels were not observed in clinical trials in silodosin treated patients.

There has been no signal of carcinogenicity during clinical development or in post-marketing.

7.1.11 Withdrawal Phenomena and/or Abuse Potential

No clinical investigations have been performed examining silodosin's potential to cause withdrawal symptoms. According to the sponsor, "based on the known pharmacology and pharmacokinetics of silodosin, and experience with other agents from this pharmacologic class, the likelihood of this occurring is considered low."

Reviewer's comment: This reviewer agrees with the sponsor's assessment.

7.1.13 Human Reproduction and Pregnancy Data

Silodosin has been studied in males only and is not indicated for use in women. Therefore, no human pregnancy data are available.

In preclinical studies conducted with male rats, sperm count, viability and fertility and implantation indices were decreased at doses 85 to 850 times the human male dose. These effects were reversible. Silodosin was not teratogenic when administered to pregnant rats during organogenesis at oral doses up to 1000 mg/kg/day (1,400 times the clinical dose of 8 mg/day).

7.1.14 Assessment of Effect on Growth

Silodosin has not been studied in pediatric subjects and is not indicated for use in pediatric patients.

7.1.15 Overdose Experience

Silodosin has been evaluated at doses up to 48 mg/day in healthy male subjects (study SI05008). The dose-limiting adverse event was postural hypotension, the incidence of which was dose proportional. The reader is referred to Appendix G for a review of study SI05008.

As of August 13, 2008, no adverse event reports of overdose with silodosin have been reported.

7.1.16 Postmarketing Experience

Silodosin was approved in Japan on January 23, 2006, and is marketed under the tradename Urief® by Kissei Pharmaceutical Company. Watson has included the most recent Periodic Safety Update Reports (PSUR) from Kissei that cover the time period from January 23, 2006, through July 30, 2007. In addition, Watson has been submitting reports of serious, unexpected adverse events to the IND. All of these events occurred outside the U.S., primarily in Japan.

During the first 18 months of marketing in Japan, approximately ——— patients received silodosin. As of July 30, 2007, a total of 2,559 adverse events for silodosin were reported to Kissei, as displayed in Table 7.31. Serious unlisted adverse events that were reported in more than one patient are displayed in Table 7.32. An unlisted case was one where at least one diagnosis or event was not covered by the current Core Safety Information (CSI) at the time of case entry. b(4)

Table 7.31 Japanese post-marketing adverse event reports for silodosin, 01/23/06 – 07/30/07

Reports	Number of cases
Serious unlisted	62
Serious listed	36
Non-serious, unlisted	417
Other (uncertain seriousness)	5
Non-serious, listed	2,039
Total (serious + non-serious cases)	2,559

Source: NDA 22-206, ser 000, PSUR 1/23/06 – 7/30/07, section 6, page 7.

Table 7.32 Serious unlisted adverse event reports (January 23, 2006 to July 30, 2007)

Adverse Event, Preferred Term	N
Loss of consciousness	10
Syncope	7
Dizziness	5
Hepatic function abnormal	4
Jaundice	4
Urinary retention	4
Diarrhea	4
Platelet count decreased	3
Cerebral infarction	3
Ileus	2
Road traffic accident	2
Toxic drug eruption	2
Hypotension	2
Death	2
Chest pain	2
Hyponatremia	2
Acute renal failure	2
Bradycardia	2
Angina	2

Source: NDA 22-206, ser 000, PSUR 1/23/06 Appendix 4A; PSUR 1/30/07 Appendix 3; PSUR 7/30/07 Appendix 3.

In addition, there was one report each of the following unlisted, serious adverse events: acute myocardial infarction, atrial fibrillation, pancytopenia, SIADH, tinnitus, fecal incontinence, cholangitis, fulminant hepatitis, liver disorder, skull fracture, convulsion, somnolence, dyspnea, drug eruption, hyperhidrosis, abdominal pain, musculoskeletal stiffness, constipation, frequent bowel movements, gastrointestinal motility disorder, malaise, contusion, white blood cell count decreased, cerebral ischemia, diplegia, headache, postural dizziness, syncope vasovagal, ejaculation disorder, eosinophilic pneumonia, epistaxis, erythema, purpura, rash, orthostatic hypotension.

Reviewer's comment: Line listings for the serious adverse events were submitted in the PSURs and included only patient's age, adverse event preferred term, duration of silodosin therapy, outcome and assessment of relatedness.

Based upon these postmarketing data, Kissei has recently updated the core safety information (CSI) for silodosin to include syncope and unconsciousness under "special precautions." In addition, a class statement on intraoperative floppy iris syndrome (IFIS) was added.

After the data lock of July 30, 2007, Kissei [redacted] The previous package insert version [redacted] Kissei is also considering [redacted]

b(4)

In the 120-day safety update, Watson has included a list of all 7-day and 15-day safety reports submitted to the IND through March 21, 2008. All of the events originated

outside the United States. New adverse events reported after July 30, 2007, and therefore,not included in Kissei's PSUR,are listed in Table 7.33.

Table 7.33 Silodosin Safety Reports Submitted to the IND since July 30, 2007 through March 21, 2008

Adverse Event, Preferred Term	N
Myocardial infarction	3
Loss of consciousness	3
acute renal failure	2
Death due to loss of consciousness	1
pneumonia	1
Bladder cancer	1
Suicide	1
Jaundice	1
Liver disorder	2
Erythroderma (dermatitis exfoliative)	1
sepsis	1
Blindness transient, abnormal sensation in eye	1
Internal hemorrhoids	1

Source: NDA 22-206 ser 0003, 120-day safety update, Table 2.

The safety reports coded as "loss of consciousness" were reviewed. In all instances, the subjects experienced syncope which was then coded as loss of consciousness.

Reviewer's comment: Syncope would not be unexpected in the setting of α-blocker therapy. A statement regarding the risk of syncope should be included under the "orthostatic effects" precaution of the silodosin label.

7.1.16.1 Notable Post-marketing Adverse Events

There have been three post-marketing, serious adverse event reports coded as "loss of consciousness resulting in death" which are described below.

2006-05972: A 74-ear-old male experienced loss of consciousness and died while taking silodosin for BOO associated with BPH.

b(6)

the patient was hospitalized for urinary retention. Urethral balloon catheter was placed, and was removed three days later. Silodosin 2 mg bid was started on . That evening the urethral balloon catheter was reinserted because urinary retention had not improved. Chlormadinone acetate (Gesin) was also initiated.

On , the patient suddenly lost consciousness in front of his wife during a meal. He was transported to a hospital where he died despite treatment. A CT scan of the chest performed at another hospital revealed aspiration pneumonia. The cause of patients' death was not known.

b(6)

Reviewer's comments:

- *Chlormadinone acetate is a synthetic derivative of 17-hydroxyprogesterone that, because of its antiandrogenic properties, has been used experimentally for the treatment of BPH.*

- *Timing of Chest CT scan relative to patient's death is not clear from the report.*

2006-06014: An 81-year-old male patient who had been treated with silodosin experienced loss of consciousness resulting in death. The patient had a history of diabetes mellitus, hypertension, cerebral aneurysm and cerebral infarction. Silodosin 4 mg bid was prescribed on ——— , for urinary retention. The following day the patient's urologist called to check on him and was informed that he had died in his bed that morning. The cause of death was not assessable. b(6)

2007-04894 A 79-year-old male patient treated with silodosin for BOO associated with BPH died. This case was collected in post-marketing surveillance. The patient had a history of angina pectoris, diabetes mellitus, and hyperlipidemia. On March 14, 2007, the patient was prescribed silodosin 4 mg bid. On an unspecified date, the patient was hospitalized (for unspecified reasons) and it was believed that silodosin was discontinued. The patient died on an unspecified date. The cause of death was not known.

Reviewer's comment: There is insufficient information for any of these three cases to determine causality or relationship to silodosin.

Other notable post-marketing serious adverse events are those related hepatic dysfunction (N=7), which are addressed in section 7.1.7.2.2.2, and cutaneous reactions (N=2), described below.

2006-06140 A 66-year-old male patient who had been treated with silodosin for BOO associated with BPH, developed "toxicoderma." Silodosin therapy was initiated on September 19, 2006, at a dose of 4 mg once daily, which was then increased to 4 mg bid on October 18, 2006. On October 26, 2006, the patient developed erythema and edema on his face and lower abdomen. Silodosin was discontinued the following day. He was diagnosed with toxicoderma and treated with a steroid. The event improved. The reporting physician considered the relationship to silodosin to be "highly probable."

2006-04959 A 91-year-old male developed "drug eruption" associated with subcutaneous hemorrhage 3 days after starting silodosin 8 mg daily for BOO associated with BPH. One week after the drug eruption began the patient discontinued silodosin.

Drug eruption continued to worsen and the patient was hospitalized. He had marked edema and erythema of the legs and erythema of the trunk and forearms. The patient was treated with ascorbic acid/calcium pantothenate, carbazochrome sodium sulfonate and tranexamic acid. He developed fever and an antibiotic was also started. Betamethasone injection was added for persistent fever. The patient improved and

by the eighth hospital day the skin eruption (classified as purpura) had mostly disappeared.

A patch test against silodosin was negative, as was a DLST test of silodosin. Results of a skin biopsy showed drug eruption, and given the temporal relationship, silodosin was considered to be the most likely causative agent.

Reviewer's comment: These adverse events may be related to silodosin, and should be added to the post-marketing adverse events section of the label.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

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 comments:

1) *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. In addition, data from patients receiving 4 mg of silodosin daily in Phase 2 study KMD3213 were not included in the ISS.*

2) *The quantity and duration of patient exposure are adequate.*

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Additional safety data for silodosin in BPH patients are available from foreign sources, as shown in Table 7.34.

Table 7.34 Phase 2/3 Foreign Studies – Patient Exposure

Study Site	Duration of exposure	Daily Dose Range (mg)	Total number of subjects on silodosin
Japan	4 weeks	0.2 - 4 mg	231
		8 mg	104
	13 weeks	8 mg	176
	52 weeks	8 mg	364
Europe	12 weeks	8 mg	390
			Total = 1265

Finally, at the time of NDA submission (December, 2007), an estimated — patients had received silodosin in Japan during the first eighteen months of post-marketing experience. b(4)

7.2.3 Adequacy of Overall Clinical Experience

The sponsor has met ICH guidelines for patient exposure for the BPH indication.

7.2.4 Adequacy of Routine Clinical Testing

Routine monitoring of laboratory values, ECGs, vital signs and adverse events was adequate in clinical trials.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The effect of both extrinsic (drug-drug interactions) and intrinsic factors (renal dysfunction, hepatic dysfunction) on metabolism of silodosin was adequate.

There are no data on the safety and efficacy of silodosin in patients with severe hepatic or severe renal insufficiency.

7.2.7 Adequacy of Evaluation for Potential Adverse Events; Recommendations for Further Study

The sponsor has adequately evaluated for potential adverse events.

7.2.9 Additional Submissions, Including Safety Update

Official submissions to NDA 22-206 since December 11, 2007:

2/7/2008:	Highlights of Clinical Pharmacology table
4/4/2008:	120-day Safety Update
5/2/2008:	Response to FDA Information Request Letter dated April 23, 2008
6/3/008:	Response to FDA Filing Communications Dated February 25, 2008, and May 12, 2008
7/10/2008:	Response to FDA Filing Communication Dated February 25, 2008, Response to FDA Information Request Letter Dated June 3, 2008 Response to FDA Information Request Email dated June 23, 2008.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The important safety findings are as follows:

- Retrograde ejaculation was the most frequently reported adverse event and occurred in over 30% of silodosin-treated subjects in U.S. Phase 2/3 clinical trials.

- Other common adverse events were diarrhea, dizziness, nasopharyngitis and orthostatic hypotension.
- All common adverse events observed in silodosin clinical trials are consistent with the side effect profile of α-antagonist drugs.
- Silodosin therapy is associated with a mean decrease in systolic and diastolic blood pressure of 1.1 and 0.5 mmHg, respectively, compared to placebo following up to 12 weeks of treatment. Pulse increased by 0.7 bpm over placebo. These changes in vital signs are not considered clinically significant.
- QT testing is adequate. There is no evidence to date to suggest that silodosin has a significant effect on the QT interval.
- Silodosin was not associated with any significant change in laboratory parameters.
- The majority of serious adverse events reported during post-marketing for silodosin were related to vasodilatory side effects (e.g. syncope, orthostatic hypotension) that are typical for members of the α-1-antagonist class of drugs.
- There have been seven post-marketing reports of significant liver dysfunction in patients treated with silodosin. None are clearly related to silodosin treatment. There was no signal in controlled clinical trials of silodosin causing an increase in hepatocellular enzymes or otherwise adversely affecting liver function.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Section 7.2 contains a description of the databases analyzed for this review.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The US Phase 2 study, in which silodosin doses of 4 mg and 8 mg daily were administered, provided information on dose response for adverse events. Only ejaculation disorders occurred at a greater frequency with the 8 mg silodosin dose (Table 7.35).

Table 7.35 Most Common Adverse Events, Phase 2 Study KMD-3213-US021-99

Adverse Event	8 mg silodosin (N=90) n (%)	4 mg silodosin (N=88) n (%)	Placebo (N=86) n (%)	p-value (across treatment groups)
Retrograde ejaculation	14 (15.6)	10 (11.4)	0 (0.0)	0.0001
Ejaculation failure	10 (11.1)	8 (9.1)	0 (0.0)	0.0021
Dizziness	5 (5.6)	9 (9.1)	6 (7.0)	0.6638
Positive orthostatic test	3 (3.3)	4 (4.5)	2 (2.3)	0.8419

Source: NDA 22-206 ser 000, KMD-3213-US021-99 study report, Table 6.2

In a trial to determine the maximum tolerated dose of silodosin (Study SI05008), healthy male subjects received silodosin 16, 24, 32, 40 or 48 mg once daily for three days (N=5 subjects per dose group). A general dose relationship was apparent for both symptomatic postural hypotension and maximum change from baseline in blood pressure (shown in Table 7.36 and Figure 7.3). The maximum tolerated dose was 48 mg as a result of these two effects.

Table 7.36 Number of episodes of symptomatic postural hypotension per dose group

Adverse Event	16 mg	24 mg	32 mg	40 mg	48 mg
Symptomatic postural hypotension	5	8	9	11	12
source: NDA 22-206 ser000, SI05008 study report, Table 14.3.1-2					

Figure 7.3 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 ser 000, SI05008 study report, Table 12.4-1

Reviewer's comment: Based on Phase 2 data, there is no significant difference in the tolerability of the 4 mg and 8 mg silodosin doses.

Postural hypotension is an expected dose-limiting effect for supra-therapeutic doses of alpha-antagonists.

7.4.2.2 Explorations for drug-demographic interactions

7.4.2.2.1 Race

No important differences were noted in the treatment exposure or disposition of patients by race (Figure 7.4).

Figure 7.4 Summary of Patient Disposition by Race – All U.S. Controlled and Uncontrolled Studies (Safety Population)

	Caucasian N=811	Non-Caucasian N=86
Number of Patients n(%)		
Completed	552 (68.1%)	58 (67.4%)
Discontinued	259 (31.9%)	28 (32.6%)
Treatment Exposure		
>0 to 6 Weeks	784 (96.7%)	82 (95.3%)
>6 to 12 Weeks	708 (87.3%)	72 (83.7%)
>12 to 40 Weeks	587 (72.4%)	60 (69.8%)
>40 Weeks	359 (44.3%)	36 (41.9%)
Discontinuation due to:		
Adverse Event	115 (14.2%)	12 (14.0%)
Protocol Violation	9 (1.1%)	0 (0.0%)
Voluntary Withdrawal	38 (4.7%)	4 (4.7%)
Lack of Efficacy	55 (6.8%)	5 (5.8%)
Lost to Follow-up	22 (2.7%)	6 (7.0%)
Other	20 (2.5%)	1 (1.2%)

Source: Table 1.2.2.3
Source: NDA 22-206 ser 000, ISS, Table 18

The incidence of treatment emergent adverse events, serious AEs and discontinuations due to an AE was similar between Caucasian and Non-Caucasian patients (Table 7.37).

Table 7.37 Incidence of adverse events by race, All US Controlled and Uncontrolled Studies (Safety Population)

	Caucasian		Non-Caucasian	
Assessment	Placebo (N=475)	Silodosin (N=501)	Placebo (N=68)	Silodosin (N=49)
Patients with at least 1 AE	196 (41.3%)	276 (55.1%)	27 (39.7%)	26 (53.1%)
Serious AE	6 (1.3%)	6 (1.2%)	1 (1.5%)	0 (0.0%)
Discontinuation due to an AE	7 (1.5%)	30 (6.0%)	3 (4.4%)	4 (8.2%)

Retrograde ejaculation was the most common treatment emergent adverse event in both Caucasians and non-Caucasians receiving silodosin (27.3% and 19.5%, respectively). There were no significant differences noted between race categories in other treatment emergent adverse events.

A review of data from US Phase 3 controlled trials for ECGs, clinical laboratory values, physical examination, vital signs and orthostatic tests does not suggest that silodosin has differential effects in patients due to race.

7.4.2.2.2 Age

Subjects ≥65 years of age made up 42.8% (N=384) of the US safety population. In addition, 10.7% (N=96) of subjects were ≥75 years of age.

No important differences were noted in the treatment exposure or disposition of patients by age group.

Common treatment emergent adverse events were similar in older and younger age groups. Among subjects ≥75 years of age, the incidence of orthostatic hypotension was slightly more frequent than in younger subjects (see Table 7.38).

Table 7.38 US Phase 2/3 Trials (Safety Population)

Adverse Event – Preferred Term	**Age <65 Years** N=513	**Age ≥65 Years** N=384	**Age ≥75 years** N=96
Retrograde ejaculation	195 (38.0%)	91 (23.7%)	13 (13.5%)
Diarrhea	21 (4.1%)	22 (5.7%)	7 (7.3%)
Dizziness	15 (2.9%)	19 (4.9%)	5 (5.2%)
Orthostatic hypotension	15 (2.9%)	14 (3.6%)	**5 (5.2%)**
Source: NDA 22-206 ser 000, ISS, Table 2.2.3-11			

On routine orthostatic testing performed after silodosin dosing, the incidence of a positive orthostatic test was not more frequent among elderly subjects (Table 7.39).

Table 7.39 Summary of Positive Orthostatic Test Results by Geriatric Status (Silodosin treated subjects only) – US Phase 3 Controlled Studies (Safety Population)

Time after Standing	<65 N=259	≥65 N=207	≥75 N=60
1 minute	4 (1.6%)	2 (1.0%)	1 (1.7%)
3 minutes	5 (1.9%)	4 (1.9%)	1 (1.7%)
Source: NDA 22-206 ser 000, ISS, Table 2.9.3-3			

There were no significant differences in laboratory data, physical examination, ECG or vital signs between subjects based on age.

b(4)

Reviewer's comment: Older patients (>75 years) may be slightly more sensitive to the orthostatic effects of silodosin. This information should be included in the ~~~ section of the label. Overall though it does not appear that geriatric status significantly impacts the safety of silodosin therapy.

7.4.2.3 Explorations for drug-disease interactions

7.4.2.3.1 Renal Insufficiency

In a Phase I clinical pharmacology study (study KMD-309), plasma concentrations of silodosin were approximately three times greater (3.11 for C_{max} and 3.22 for AUC) in subjects with moderate renal impairment (Ccr 27-49 mL/min) compared with subjects with normal renal function.

Because of the increased exposure to silodosin observed in subjects with renal impairment, the sponsor performed an analysis of treatment emergent adverse events in the four US Phase 2/3 trials according baseline renal function:

- Normal renal function – estimated creatinine clearance (CCr) >80 ml/min
- Mild renal impairment – CCr 50-80 ml/min
- Moderate renal impairment – CCr 30-50 ml/min.

An increased incidence of dizziness and orthostatic hypotension was observed in subjects with moderate impairment compared to those with only mild impairment or normal renal function (shown in Table 7.40).

Table 7.40Most Common Treatment Emergent Adverse Events by Baseline Renal Function, US Phase 2/3 Trials

Adverse Event – Preferred Term	Normal Renal Function N=620	Mild Renal Impairment N=245	Moderate Renal Impairment N=21
Retrograde ejaculation	213 (34.4%)	66 (26.9%)	5 (23.8%)
Dizziness	23 (3.7%)	8 (3.3%)	**3 (14.3%)**
Orthostatic hypotension	20 (3.2%)	6 (2.4%)	**2 (9.5%)**
Source: NDA 22-206 ser 000, ISS, Table 2.2.4-1, Parts 1.1, 2.2 and 3.1			

The safety of a single dose of silodosin in subjects with moderate renal impairment was assessed in a Phase 1 clinical pharmacology trial, KMD-309. Six subjects with impaired renal function (CCr 27-49 mL/min) and seven with normal renal function received a single dose of silodosin 4 mg. There was no difference in the incidence of treatment emergent adverse events between the two groups. Postural hypotension was reported by a single subject in each of the two treatment groups.

There are no data on the safety of silodosin in patients with severe renal insufficiency.

Reviewer's comment: The increased incidence of dizziness and orthostatic hypotension in patients with moderate renal impairment argues for a silodosin dose reduction in this population. Dosing recommendation will be addressed further in Section 8.3.1.

7.4.2.5 Explorations for drug-drug interactions

7.4.2.5.1 CYP3A4 inhibitors

As silodosin is a substrate of CYP3A4, the pharmacokinetics and safety of concomitant administration of silodosin with ketoconazole, a potent CYP3A4 inhibitor, were assessed in two Phase I trials (KMD-306 and SI06008). In both trials, concomitant administration of silodosin with ketoconazole led to a greater than three-fold increase in plasma silodosin concentration (both Cmax and AUC).

In study SI06008, an open-label, two-period crossover trial, 22 healthy adult male subjects, aged 18 to 45 years, received ketoconazole 400 mg daily for four days (Days -1 to 3) alone, and in combination with silodosin 8 mg on Day 2. Vital signs were measured

once daily. Orthostatic testing and laboratory evaluation was performed at screening only.

There were more adverse event reports with the combination than with silodosin alone, as shown in Table 7.41. Notably, orthostatic hypotension was more common in the setting of combination therapy.

Table 7.41 Summary of Treatment Emergent Adverse Events, Study SI06008

Assessment	Silodosin 8mg + Ketoconazole 400 mg N=22	Silodosin 8 mg Only N=22
At least 1 AE	11 (50%)	4 (18.2%)
Serious AE	0	0
AE Preferred Term		
Headache	7 (31.8%)	0
Nausea	3 (13.6%0	0
Pharyngolaryngeal pain	0	3 (13.6%)
Musculoskeletal chest pain	0	2 (9.1%)
Orthostatic hypotension	2 (9.1%)	0
Source: NDA 22-206 ser 000, SI06008 study report, Table 14.3.1-2		

Reviewer's comment: Vital signs were measured once daily. At no point during the study was a subject found to have an SBP< 90 mmHg or pulse >100 bpm.

Orthostatic vital signs would have been informative but were not performed.

In study KMD-306-UK, a two-period crossover trial, 16 healthy, adult male subjects, aged 18 to 45 years, received ketoconazole 200 mg daily for four days (Day -1 to Day 3), alone, and in combination with silodosin 4 mg on Day 2. Vital signs were measured pre-dose and at 2, 4, 8, 24, 48 and 72 hours post-dosing. Orthostatic testing was performed pre-dose and at 2, 4, and 8 hours following concomitant administration of silodosin and ketoconazole.

As in study SI06008, adverse events were more commonly reported following combination therapy than after silodosin alone (31.3% vs. 18.8% respectively). "Vasovagal attack," which occurred in 2 subjects during combination therapy and in one subject during silodosin monotherapy, was the most common treatment emergent adverse event. Subject #5 experienced a decrease in SBP by 50 mmHg (from 106 to 56 mmHg) on standing two hours after administration of ketoconazole with silodosin.
Subject #16 developed symptoms consistent with orthostatic hypotension at 4 hours after combination dosing, but orthostatic vital signs were not performed at that time. This same patient also experienced a decrease in SBP by 43 mmHg on standing (from 122 to 79 mmHg) 8 hours after administration of silodosin alone.

Reviewer's comment:. Recommendations for [redacted] *is discussed in section 8.2.1.* b(4)

7.4.2.5.2 Anti-hypertensive Agents

During Phase 3 studies, the sponsor permitted use of concomitant anti-hypertensive agents. In these studies, one of the 11 silodosin patients in whom positive orthostatic tests were observed was receiving a concomitant anti-hypertensive agent.

A comparison of the adverse event data from patients in the four US Phase 2/3 studies who were receiving concomitant antihypertensive medication with the adverse event data for the overall safety population is shown in Table 7.42. The incidence of dizziness and orthostatic hypotension was only slightly greater among patients receiving antihypertensive drugs. Not surprisingly, the incidence of hypertension was also greater.

Table 7.42 Treatment Emergent Adverse Events by concomitant use of cardiovascular medication, all US Controlled and Uncontrolled Trials (Safety Population)

Adverse Event – Preferred Term	Silodosin +Cardiovascular Medication N=323	Silodosin (General Safety Population) N=897
Retrograde Ejaculation	90 (27.9%)	286 (31.9%)
Diarrhea	17 (5.3%)	43 (4.8%)
Hypertension	16 (5.0%)	18 (2.0%)
Dizziness	15 (4.6%)	34 (3.8%)
Nasopharyngitis	13 (4.0%)	34 (3.8%)
Nasal Congestion	11 (3.4%)	24 (2.7%)
Orthostatic Hypotension	11 (3.4%)	29 (3.2%)
Headache	10 (3.1%)	24 (2.7%)

Source: NDA 22-206 ser 000, ISS, Tables 2.2.5-1 and 2.2.1-11

Reviewer's comment: Based on these data, concomitant administration of silodosin with anti-hypertensive agents does not appear to present an unreasonable risk to patients.

7.4.2.5.3 Pharmacodynamic Drug-Drug Interactions – PDE-5 inhibitors

In the U.S. controlled Phase 3 trials, use of PDE-5 inhibitors was permitted. Of eleven patients with a positive orthostatic test, one was taking a concomitant PDE-5 inhibitor.

To investigate the effect on blood pressure of concomitant administration of silodosin with a PDE-5 inhibitor, the sponsor conducted a drug interaction study of silodosin with sildenafil, tadalafil, and placebo (SI06002). Twenty-four healthy male subjects aged >45 years, including seven subjects >65 years, were enrolled. Subjects received silodosin 8 mg once daily with breakfast for three consecutive 7-day periods (total of 21 days). At the conclusion of each 7-day period, subjects also received a PDE-5 inhibitor (100 mg sildenafil, 20 mg tadalafil, or placebo) and were monitored for 12 hours. Orthostatic blood pressure tests were performed at 0, 1, 2, 3, 4, 6, 8, and 12 hours after study drug administration.

The maximum mean change from baseline in orthostatic vital signs was similar among the three treatment groups, as shown in Table 7.43.

Table 7.43. Summary of Maximum Mean Change From Baseline in Orthostatic Vital Signs by treatment group (All Subjects)

Vital sign parameter (upright – supine)	Silodosin + tadalafil (N=22)	Silodosin + sildenafil (N=22)	Silodosin + placebo (N=22)
SBP	-10.2	-5.0	-10.7
DBP	-5.2	-1.6	-2.6
Heart Rate	+14.2	+15.6	+13.9

Source: NDA 22-206 ser 000, SI06002 study report, Table 12.4-1

The greatest number of positive orthostatic tests at any time point were observed in the sildenafil+silodosin group, followed by sildenafil+tadalafil and then silodosin+placebo. (see shaded cells in Table 7.44).

Table 7.44. Number 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%)
	Total	59	67	58

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

There was no significant difference in the incidence of adverse events among the three treatment groups.

Reviewer's comments:

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, pre-existing cardiovascular disease). Any synergistic effect of silodosin and a PDE-5 inhibitor on blood pressure may be enhanced in patients with co-morbidities on multiple medications.*

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).*

4) *At the pre-NDA meeting held on April 10, 2007, DRUP advised the sponsor that "PDE5 inhibitor class labeling currently exists for concomitant use with all alpha blockers based on a large body of evidence from controlled clinical trials.* b(4)

5) *This small study does not support* b(4)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

The sponsor proposes a therapeutic dose of 8 mg once daily for the following reasons:

- 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.
- In the US Phase 2 study (KMD-3213-US021-99), there was no significant difference in the safety and tolerability of the 4 mg and 8 mg doses.
- In the US Phase 2 trial, the 4 mg dose did not perform as robustly as the 8 mg dose as measured by the primary efficacy instrument, the AUA-SI (-5.7 points for the 4 mg dose vs. -6.8 for the 8 mg dose). The 8 mg dose also resulted in greater improvement in Q_{max} (+3.4 ml/sec for 8 mg compared to +2.9 mL/sec for the 4 mg dose).

The sponsor recommends that silodosin be administered with food. A reduction in Cmax (~30%) and a minimal effect on AUC is observed when silodosin is taken with meals which the sponsor believes will minimize the possibility for adverse events associated with C_{max}.

Reviewer's comment: The 8 mg therapeutic dose taken once daily with food is acceptable.

8.2 Drug-Drug Interactions

b(4)

8.2.1 CYP3A4 inhibitors

In two phase I drug-drug interaction studies, co-administration of silodosin with ketoconazole, a potent CYP3A4 inhibitor that also inhibits P-gp, increased silodosin AUC and Cmax by 3.2 and 3.8-fold, respectively. The sponsor proposes f

b(4)

Reviwer's comment: This reviewer believes that CYP3A4 inhibitors should be contraindicated in patients taking silodosin.

b(4)

The effect of moderate CYP3A4 inhibitors on silodosin metabolism was not evaluated. The clinical pharmacology reviewer advises, and this reviewer agrees, that "caution should be exercised" when co-administering silodosin with moderate CYP3A4 inhibitors.

8.2.2 Digoxin

The interaction between silodosin and digoxin was investigated in a Phase 1, double-blind, placebo-controlled study (study KMD-307-UK), summarized in section 5.3.1.3 of this review.

More subjects experienced an adverse event while receiving the combination than when treated with digoxin alone (Table 8.1). The most common adverse events reported in the digoxin+silodosin group and that occurred more frequently than in the digoxin+placebo group are shown in Table 8.2. No serious adverse events were reported.

Table 8.1 Summary of Adverse Events, Silodosin-Digoxin DDI study (KMD-307-UK)

Treatment	Subjects (%) with adverse events	Severity of AE	Number of AEs
Digoxin + silodosin (N=16)	14 (87.5%)	Mild	31
		moderate	14
		Severe	0
		Total	45
Digoxin + placebo (N=10)	8 (80.0%)	Mild	21
		Moderate	5
		Severe	0
		NA	2
		Total	28

Source: NDA 22-206, ser 000, KMD-307-UK study report, Table 12.2-1.

Table 8.2 Frequency of Treatment-emergent Adverse Events – Number of adverse events (number of subjects with adverse event)

Adverse Event – Preferred Term	Digoxin + silodosin	Digoxin + placebo
Ejaculation disorder, NOS	4 (4)	0
Dizziness	4 (4)	1 (1)
Dizziness postural	3 (1)	3 (2)
Nausea	4 (4)	1 (1)
Vomiting NOS	4 (3)	2 (1)

Source: NDA 22-206, ser 000, KMD-307-UK study report, Table 14.3.1-4

Reviewer's comment: Although there were a greater number of adverse events reported during co-administration of digoxin and silodosin, there were no significant safety concerns identified that would preclude co-administration of the two drugs.

8.3 Special Populations

8.3.1 Renal Impairment

A clinical pharmacology study (study KMD-309) compared the pharmacokinetics of a single oral dose of 4 mg silodosin in Japanese subjects with moderate renal dysfunction (Ccr 27-49 mL/min) to Japanese subjects with normal renal function. In subjects with renal dysfunction, plasma concentration of silodosin increased approximately three-fold (3.11 for C_{max} and 3.22 for AUC). Based on these data the sponsor recommends

b(4)

*Reviewer's comments: This reviewer recommends that the dose of silodosin be reduced to 4 mg daily in patients with **moderate** renal impairment. In U.S. Phase 2/3 trials of silodosin 8 mg, there was a higher incidence of dizziness and orthostatic hypotension in patients with moderate renal impairment (Table 8.3).*

Table 8.3 Most Common Treatment Emergent Adverse Events by Baseline Renal Function, US Phase 2/3 Trials

Adverse Event – Preferred Term	Normal Renal Function N=620	Mild Renal Impairment N=245	Moderate Renal Impairment N=21
Retrograde ejaculation	213 (34.4%)	66 (26.9%)	5 (23.8%)
Dizziness	23 (3.7%)	8 (3.3%)	**3 (14.3%)**
Orthostatic hypotension	20 (3.2%)	6 (2.4%)	**2 (9.5%)**
Source: NDA 22-206 ser 000, ISS, Table 2.2.4-1, Parts 1.1, 2.2 and 3.1			

One of the 21 subjects with moderate renal impairment experienced the serious adverse event of syncope two days after starting silodosin 8 mg during study SI04010 (see section 7.1).

This reviewer believes that 4 mg would be acceptable in subjects with moderate renal impairment for the following reasons:

1) *A 4 mg dose would approximate a 12 mg dose in subjects with normal renal function. In study KMD3213-UK01-97 in which healthy adult male volunteers received single doses of 4 mg, 12 mg or 16 mg of silodosin, no syncope or postural hypotension was observed in the 12 subjects who received 12 mg silodosin.*
2) *In study KMD-309, a single dose of 4 mg silodosin was well-tolerated in subjects (N=6) with moderate renal impairment. There was no difference in the incidence of treatment emergent adverse events in these subjects compared to subjects (N=7) with normal renal function.*

As there are no data on the safety of silodosin in patients with severe renal insufficiency, use of silodosin in this population is not recommended.

8.3.2 Hepatic Impairment

In a Phase I study of the effects of hepatic dysfunction on silodosin metabolism, silodosin exposure was slightly lower in subjects with moderate liver dysfunction (Child-Pugh score 7-9) compared to age and weight-matched controls (total silodosin Cmax and AUC decreased by 0.8). The sponsor does not recommend a dose adjustment for subjects with moderate hepatic dysfunction.

Reviewer's comment: This reviewer and the DRUP clinical pharmacology reviewer agree that 8 mg silodosin once daily is an acceptable dose for patients with mild-moderate hepatic impairment.

The sponsor recommends [redacted] b(4)

Reviewer's comment: There are no data on the safety or pharmacokinetics of silodosin in subjects with severe hepatic impairment. Therefore, silodosin should not be used in this population. The DRUP clinical pharmacology reviewer has the same opinion.

8.4 Literature Review

The sponsor submitted 98 literature references to the NDA. In addition, twelve clinical references were submitted to the 120-day safety update. No additional literature review is planned.

8.5 Post-marketing Risk Management Plan

A post-marketing risk management plan has not been submitted.

Reviewer's comment: This reviewer believes that current safety issues associated with silodosin can be adequately managed with labeling and routine surveillance.

9 Overall Assessment

9.1 Conclusions

The evidence is adequate to support the efficacy of silodosin in the treatment of the signs and symptoms of BPH in men. From an efficacy standpoint, both pivotal Phase 3 trials showed statistically significant changes in the primary endpoint (IPSS) and the main secondary endpoint (Q_{max}) over baseline when compared to placebo at week 12/LOCF. Additional supportive efficacy data come from the U.S. controlled Phase 2 trial.

From a safety standpoint, no significant safety concerns were identified in a review of the 897 patients who received silodosin 8 mg once daily during the four US Phase 2/3 trials, nor with the 437 patients who received up to 52 weeks of silodosin.

9.2 Recommendation of Regulatory Action

In the opinion of this reviewer, silodosin 8 mg should be approved for the indication "treatment of the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)."

9.3 Recommendation of Post-Marketing Actions

Based on the post-marketing serious adverse event reports of hepatic dysfunction (see section 7.), the approval letter should include a request that the sponsor continue to submit reports of hepatotoxicity with serious outcomes as expedited (15-day) alerts and to provide follow-up on these reports.

9.4 Labeling Review

The following major labeling changes are recommended and have been made to the proposed label:

1) Contraindication of silodosin in patients taking potent CYP3A4 inhibitors.U
2) Moderate CYP3A4 inhibitors should be used with caution.
3) Reduction of dose to 4 mg daily in patients with moderate renal impairment (CCr 30-50 ml/min).
4) Addition of the following adverse events to the post-marketing experience section of the label: [redacted] *, jaundice,* [redacted] b(4)
5) Removal of [redacted] b(4)
6) Removal of [redacted] Presentation of results from the PDE-5 drug-interaction study (SI04009) is acceptable. b(4)

Addendum, dated October 7, 2008:
At the time this review was written, the Establishment Evaluation was pending. On October 7, 2008, the Office of Compliance gave an overall acceptable recommendation for the manufacturing facilities. Thus, this application is recommended for **approval** from a Clinical Perspective.

Appendix A – U.S. Controlled Phase 2 Trial

"A pilot Phase II, placebo-controlled, double-blind study of KMD-3213 (silodosin) in patients with the signs and symptoms of BPH" (Study KMD 3213-US021-99)

Trial start date: April 13, 2000 **Trial end date:** June 8, 2001

A.1 Objectives:

The objectives of the trial were to determine the safety, efficacy, effective dosage and tolerability of KMD-3213 in male patients with BPH.

A.2 Design and Conduct of the Study:

The trial was a multi-center (30 U.S. sites), double-blind, placebo-controlled, parallel group, 8-week treatment study in 264 men (45 - 75 years of age) with signs and symptoms of BPH. BPH was defined by the following:

- Presence of bladder outlet obstruction [peak urine flow (Q_{max}) between 4 and 15 mL/sec, with a minimum voided volume >125 mL];
- AUA-SS $\geq$13.

Following a placebo run-in period, eligible patients were randomized in equal numbers to receive 4 mg of silodosin (n=88), 8 mg of silodosin (n=90), or placebo (n=86), administered once daily within 1 hour after the morning meal. During the dose-adjustment period, patients randomized to active treatment initiated therapy with 4 mg qd of silodosin. Patients randomized to the 8 mg group had their dose increased from 4 mg to 8 mg after 1 week. At the end of the dose adjustment period, patients entered the 6-week stable dosing period and remained on the dose level to which they were randomized.

Efficacy was assessed by the change in total AUA-SS and Qmax from baseline to LOCF.

A.2.1 Schedule of Study Assessments

The study consisted of a pre-treatment phase (Screening and Visits 1 and 2), an eight-week double-blind treatment phase (Visits 3-7) which included two weeks of dose titration for subjects assigned to silodosin 8 mg, and a one-week post-treatment phase. At Visit 3, qualified subjects were randomized to receive silodosin 4 mg, silodosin 8 mg or placebo once daily within one hour after the morning meal for eight weeks. The first dose of study medication was administered at the clinic. The treatment phase concluded with Visit 7 in which subjects underwent end-of-study evaluations.

Subjects returned 24-27 hours after Visit 7 for a final evaluation and were then discharged from the study. Subjects with abnormal lab values or unresolved AEs were scheduled for a return visit 7 days after discharge.

Clinical laboratory evaluation was performed clinic visit and included a complete blood count (CBC); liver function tests; chemistry panel, PSA and urinalysis.

Vital signs were measured after the first dose (Visit 3) every 30 minutes through 4 hours post-dose and every 60 minutes through 8 hours post-dose. At subsequent visits, vital signs were measured once following dosing, prior to orthostatic testing.

Orthostatic testing was conducted at each follow-up clinic visit and was performed within 30 minutes to 1 hour post-dose. Blood pressures and heart rate were measured in the supine position and at 1 and 3 minutes after standing. A positive orthostatic test was defined as any of the following at 1 or 3 minutes:

- systolic blood pressure >30 mmHg
- diastolic blood pressure >20 mmHg
- heart rate >20 BPM
- Symptoms upon change of position such as lightheadedness, fainting, blurring or temporary loss of vision, profound weakness, or syncope

A.3 Entry Criteria:

Inclusion criteria

1) Male between 45 and 75 years of age, inclusive
2) Provided written informed consent before any screening procedures were performed
3) Had infravesical obstruction resulting from BPH
4) Had bladder outlet obstruction, as defined by a Q_{max} between 4 and 15 mL/sec with a minimum voided volume of >125 mL
5) If not on antihypertensive medications, had a sitting diastolic blood pressure (DBP) ≥50 mmHg and <95 mmHg. If receiving any allowed antihypertensive medications, had a sitting DBP of ≥75 mmHg and <95 mmHg
6) Had a body weight within 25% of their ideal body weight
7) Were able to comply with protocol procedures
8) No clinical evidence of prostate cancer
9) Were receiving no more than one antihypertensive agent
10) Chest X-ray with no clinically significant findings within the past 12 months
11) If patient had a previous history of cancer, he must have been cancer free and have completed treatment at least 5 years prior to study entry. Certain malignancies such as basal cell carcinoma were considered on a case-by-case basis.
12) AUA Symptom score ≥13.

Exclusion Criteria

1) A history of allergy to alpha blockers or alpha/beta-blockers, and/or patients who had experienced a hypotensive episode upon starting therapy with an alpha blocker.
2) Infravesical obstruction in the past 6 months resulting from:
   - Inflammatory or infectious conditions; or a history of vesicle neck contracture; prostate carcinoma; Mullerian duct cysts; Urethral obstruction due to stricture/valves/sclerosis or other urethral tumor; bladder calculi; or Detrusor-sphincter dyssynergia.
3) Ambulation requiring assistance (i.e., canes, walkers, etc.)
4) History of a pathological fall or, syncope during the last year
5) Positive orthostatic test
6) History of postural symptoms
7) History of angina pectoris
8) History of documented myocardial infarction within 1 year of study entry
9) History of congestive heart failure
10) Prosthetic heart valves, cardiac devices, or prior endocarditis
11) Documented cardiac arrhythmia at screening or a known history of a cardiac arrhythmia that required medication
12) History of peripheral or central neurological disease
13) Prior transurethral resection of the prostate (TURP), open prostatectomy, or any other surgical procedure related to the prostate; or any procedure to reduce size or volume of the prostate gland (e.g., TUNA)
14) Prior pelvic surgery for malignancy or bowel resection
15) Urinary tract infection (UTI) as defined by a single positive urine culture.
16) History of urinary retention within 3 months prior to the screening visit
17) History of genitourinary malignancy
18) Use of any of the following medications for cardiovascular reasons 30 days prior to screening and for the duration of the study. Patients may have changed to an acceptable alternate medication. These patients must have demonstrated stability on the new medication by Visit 3
    a. alpha adrenergic blocking agents
    b. alpha adrenergic agonists
    c. diuretics
    d. beta blockers
19) Use of any of the following medications 14 days prior to screening and for the duration of the study: any drugs with anticholinergic activity, antispasmodics, parasympathomimetics and cholinomimetics; systemic ketoconazole; diuretics; beta blockers (for non-cardiovascular indications).
20) Use of Proscar®/Propecia® (finasteride) for BPH or alopecia within 6 months prior to screening
21) Use of natural products or herbal preparations for the treatment of BPH within 3 months prior to screening
22) If treated with alpha adrenergic blockers for BPH previously, no symptomatic response after 1 month of treatment
23) Renal dysfunction (creatinine >2.5 mg/dL, blood urea nitrogen (BUN) >40 mg/dL, or creatinine clearance <70 mL/min/1.73 m2)

24) A diagnosis of bladder, ureter, or kidney stones within the last 3 years and no prior instrumentation at any time to treat stones
25) Clinical laboratory test results outside the limits specified below for the following parameters: Hemoglobin: <12.0 g/dL; Leukocytes: <2,500/mm3; Creatinine: >2.5 mg/dL; BUN: >40 mg/dL
26) Liver function tests >2 times the established upper limit of normal
27) Poorly controlled diabetes mellitus (HgbA1C >10%) or hypertension (SBP ≥160 mmHg and DBP ≥95 mmHg)
28) Clinically significant abnormal chest X-ray
29) Body weight outside of ±25% of the patient's ideal body weight
30) Participation in an investigational study within 60 days prior to the screening visit
31) Patient history suggestive of a positive HIV status
32) A positive blood hepatitis test (Hepatitis B and C) within 5 years prior to screening.

A.4 Study Population Demographics and Baseline Disease Characteristics:

A total of 264 patients were randomized to study treatment. Demographic and baseline disease characteristics of placebo and silodosin groups were similar and are shown in Table A.1.

Table A.1 Demographic and Disease Characteristics, study US021-99

	8 mg silodosin (N=90)	4 mg silodosin (N=88)	Placebo (N=86)	p-value
Age (mean)	58.7	60.4	59.2	0.2758
Race, n(%)				0.7246
Caucasian	82 (91.1)	80 (90.9)	76 (88.4)	
Black	1 (1.1)	3 (3.4)	2 (1.2)	
Asian	0	1 (1.1)	2 (2.3)	
Hispanic	6 (6.7)	3 (3.4)	6 (7.0)	
Other	1 (1.1)	1 (1.1)	0	
AUA-SS (mean) (SD)	20.8 (5.3)	19.7 (5.1)	19.7 (5.2)	0.2895
Qmax (cc/sec) (mean) (SD)	9.6 (2.7)	9.7 (3.0)	10.1 (2.7)	0.5813
Source: NDA 22-206 ser 000, US021-99 study report, Tables 4.4, 9.49 and 9.53				

A.5 Primary and secondary endpoints:

Co-primary efficacy endpoints were change from baseline in AUA-SS and Q_{max} at LOCF.

Secondary efficacy endpoints were:

- Change from baseline in the overall AUA-SS and Qmax at each visit during the double-blind treatment period up to and including Visit 7 (Day 84), and

- Proportion of responders at each visit during the double-blind treatment period up to and including Visits 7 (Day 84). Responders were defined as patients who had a ≥30% improvement in Qmax and a ≥25% improvement in overall AUA-SS.

A.6 Withdrawals, Protocol Violations, and Compliance:

Of the 264 patients randomized, 29 discontinued the study prematurely. The most common reasons for discontinuation were adverse events in the 8 mg and 4 mg groups and withdrawal of consent in the placebo group. Causes of premature discontinuation are shown in Table A.2.

Table A.2. Patient Disposition (Randomized Population), study US021-99

	Treatment Group			
	Silodosin 8 mg N=90	Silodosin 4 mg N=88	Placebo N=86	Total
Number of Patients n (%)				
Completed	77 (85.6)	81 (92.0)	77 (89.5)	235
Discontinued	13 (14.4)	7 (8.0)	9 (10.5)	29
Discontinuation due to:				
Adverse Event	10 (11.1)	5 (5.7)	0	15
Lost to follow-up	1 (1.1)	0	1 (1.2)	2
Withdrew consent	2 (2.2)	1 (1.1)	3 (3.5)	6
Lack of efficacy	0	1 (1.1)	0	1
Protocol violation	0	0	2 (2.3)	2

From NDA 22-206, study report US021-99, Table 4.1

A.6.1 Protocol Deviations

Protocol deviations were classified as major (non-compliance with study medication, use of prohibited concomitant medications and/or missing baseline AUA symptom score or Qmax values) or minor. Major protocol violations occurred in 11/90 (12.2%), 7/88 (8.0%), and 7/86 (8.1%) patients in the 8 mg, 4 mg, and placebo groups, respectively. The most common protocol violation among silodosin patients was non-compliance with study medication (>120% compliant).

A.6.2 Compliance

Patient compliance was assessed by return of unused medication to the investigator. Subjects with marked non-compliance missing 4 consecutive doses or a total of ≥5 doses) during the run-in phase were discontinued before randomization.

Treatment compliance (80 – 120% compliance) was 84/90 (93.3%), 87/88 (98.9%), and 81/86 (94.2%) patients in the 8 mg, 4 mg, and placebo groups, respectively (p=0.2404).

A.7 Efficacy analysis:

A.7.1 Primary efficacy

The primary efficacy analysis was performed on the modified intent-to-treat (mITT) population using last observation carried forward (LOCF). The mITT population was defined as patients with a baseline evaluation and at least one post-baseline AUA symptom score or Q_{max} measurement.

Statistically significant changes in total AUA-SS and Q_{max} were observed for both silodosin 4 mg and 8 mg compared to placebo (Tables A.3 and A.4).

Table A.3 Mean Change from Baseline in AUA-SS, US021-99

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value (vs. placebo)
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)	

Source: NDA 22-206 ser 000, US021-99 study report, Table 5.1

Table A.4 Mean Change from Baseline in Qmax

Treatment Group	N	Mean Change from Baseline at end-of-study (SD)	p-value (vs. placebo)
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)	

Source: NDA 22-206 ser 000, US021-99 study report, Table 5.2

A.8 Safety analysis

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

A.8.1 Extent of Exposure

Mean duration of exposure was not statistically significantly different among the three treatment groups – 49.8, 53.5 and 52.5 days for the 8 mg, 4 mg and placebo groups, respectively (p=0.1785).

A.8.2 Serious Adverse Events:

There were no deaths or serious adverse events during the study.

A.8.3 Premature discontinuation due to adverse events:

A total of 10 patients in the 8 mg group (including 7 patients who discontinued prior to the 8 mg dose increase) and 5 patients in the 4 mg group discontinued the study due to one or more adverse events. No placebo patients discontinued due to an adverse event (AE). The most common AE leading to discontinuation was retrograde ejaculation (N=4 total; 2 per dose group).

A.8.4 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 occurring more often in the silodosin groups than in placebo are shown in Table A.5.

Table A.5. Most Frequently (>2%) Reported AEs, Study US021-99

Adverse Event	8 mg n (%)	4 mg n (%)	Placebo n (%)	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
Dizziness	5 (5.6%)	8 (9.1%)	6 (7.0%)	0.6638
Diarrhea NOS	5 (5.6)	0	4 (4.7)	0.0692
Bacteriuria	4 (4.4)	6 (6.8)	3 (3.5)	0.6010
Fatigue	4 (4.4)	2 (2.3)	1 (1.2)	0.5114
Headache NOS	3 (3.3)	7 (8.0)	6 (7.0)	0.4044
Nasal congestion	3 (3.3)	4 (4.5)	1 (1.2)	0.4966
Erectile disturbance	3 (3.3)	2 (2.3)	0	0.3764
Sinusitis NOS	3 (3.3)	2 (2.30	2 (2.3)	1.0000
Urinary tract infection NOS	3 (3.3)	0	0	0.1087
Abdominal pain NOS	2 (2.2)	2 (2.3)	0	0.5507
Heart rate increased	2 (2.2)	1 (1.1)	0	0.7753
Somnolence	2 (2.2)	1 (1.1)	0	0.7753

Source: NDA 22-206 ser 000, US021-99 study report, Table 6.2

A.8.5 Laboratory evaluation

A.8.5.1 Hematology (CBC and PT/PTT)
No clinically meaningful difference in mean change from baseline in any hematology parameter was observed between the placebo and silodosin treatment groups.

No statistically significant differences were observed in categorical changes (decrease, increase, or no change) from baseline to visit 7.

A.8.5.2 Chemistry
No clinically meaningful difference in mean change from baseline in any chemistry parameter was observed between the placebo and silodosin treatment groups.

Compared to placebo, significantly more patients in the silodosin groups experienced a decrease in serum glucose– 47/90 (52.2%), 55/88 (62.5%) and 32/86 (37.2%) in the 8 mg, 4 mg and placebo groups, respectively (p=0.0373). Line listings were reviewed and the changes observed are not considered clinically meaningful.

A.8.6 Vital Signs
A statistically significant difference in mean change from baseline in systolic blood pressure, but not in diastolic pressure, was observed among treatment groups (Table A.6)

Table A.6, Mean (SD) Change from Baseline to Endpoint in Blood Pressure, US021-99

	8 mg	4 mg	Placebo	Overall p-value
SBP	1.2 (16.5)	-5.4 (13.5)	-3.0 (12.2)	0.0285
DBP	0.7 (9.0)	-1.3 (10.4)	-2.2 (8.6)	0.5288
Heart rate	-0.8 (10.0)	0.3 (10.6)	1.5 (8.2)	0.9952

Source: NDA 22-206 ser 000, US021-99 study report, Tables 9.71, 9.72

Reviewer's comment: Because the effect of the 4 mg and 8 mg doses on BP and heart rate was discordant, no clinically meaningful conclusion can be drawn from these data.

Orthostatic testing was conducted 30 minutes to 1 hour post-dose at all treatment visits. More silodosin patients than placebo patients had a positive orthostatic test result, though the difference among groups was not statistically significant. (Table A.7).

Table A.7 Summary of Patients with a Positive Orthostatic Test Result at any timepoint (Safety Population), US021-99

Treatment Group	Number of Patients with a Positive Orthostatic Test Result n (%)
8 mg	3 (3.3)
4 mg	4 (4.5)
Placebo	2 (2.3)
p-value	0.8419

Among patients with a positive orthostatic test, there were no SBP values <90 mmHg.

A.8.7 Physical Examination

No increased incidence of physical examination abnormalities.

A.8.8 ECGs

The proportion of patients with an abnormal ECG while on treatment was similar among the three treatment groups. According to the sponsor there was no clear pattern of abnormality noted among silodosin patients.

A.9 Conclusion

Results of this Phase 2 study support the efficacy of silodosin in the treatment of BPH and the selection of 8 mg as the therapeutic dose. No significant safety concerns were identified in this trial.

Appendix B – US Controlled Phase 3 Trial SI04009

"A multicenter, randomized, double-blind, placebo controlled, parallel evaluation of the efficacy and safety of silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia."

Trial start date: May 4, 2005 **Trial end date:** August 16, 2006

B.1 Objectives

Primary:
To test the hypothesis that the effectiveness of silodosin 8 mg given once daily for 12 weeks is superior to placebo for the relief of symptoms of benign prostatic hyperplasia as measured by a baseline to endpoint change in the total score of the International Prostate Symptom Score (IPSS).

Secondary:

- To test the hypothesis that the effectiveness of silodosin is superior to placebo based on a baseline to endpoint change in the maximum urine flow rate (Q_{max}).
- To compare the safety of silodosin to placebo using an evaluation of adverse events, vital signs, ECGs, clinical laboratory tests, and physical exams.

B.2 Design and Conduct of the Study

The trial was a multi-center (49 U.S. sites), double-blind, placebo-controlled, parallel group, 12-week treatment study in 461 men (≥50 years of age) with signs and symptoms of BPH. BPH was defined by the following:

- Presence of bladder outlet obstruction [peak urine flow (Q_{max}) between 4 and 15 mL/sec, with a minimum voided volume ≥125 mL];
- International Prostate Symptom Score (IPSS) ≥13.

Following a 4-week, single-blind placebo run-in period, eligible subjects were randomized in a 1:1 ratio to receive 12 weeks of therapy with silodosin 8mg, or placebo, taken once daily with food at breakfast time. Efficacy was assessed primarily by the change in total IPSS score from baseline to endpoint [week 12 or last observation carried forward (LOCF)].

B.2.1 Schedule of Study Assessments

The study consisted of a screening visit, a 4-week single-blind placebo run-in phase (Visits 1 and 2), and a 12-week double-blind treatment period (Visits 3-8). At Visit 3, qualifying patients were randomized to receive silodosin 8 mg or placebo once daily. The first does of study medication was administered at the clinic.

The schedule of procedures in study SI04009 is shown in Figure 1.

Figure 1. Schedule of Events Flowchart, Study SI04009

Procedure	Scr W-8 to -4	V1 W-4	V2 W-2	V3* W0	V4 W0.5	V5 W1	V6 W2	V7 W4	V8/ET W12
Informed Consent	X								
Demographics	X								
Medical History	X								
Medication History	X								
Physical Exam with DRE		X							X[1]
ECG		X						X	X
Clinical Labs	X	X[2]						X[2]	X
Vital Signs		X[3]		X[3]				X	X
IPSS		X	X	X	X[4]	X	X	X	X
Q_{max}		X	X	X[5]		X	X	X	X
Post Void Residual Volume		X							
PK Plasma sample				X				X	
Adverse Events			X	X		X	X	X	X
Concomitant Medication		X	X	X		X	X	X	X
Documentation of Inc/Exc Criteria		X		X					
Dispense Investigational product		X	X	X			X	X	
Drug Accountability			X	X		X	X	X	X

*Randomization occurred at Visit 3.
[1]Excluding the digital rectal exam, complete urological history, and body weight and height.
[2]Excluding PSA, HbA_{1c}, and thyroid tests.
[3]Including an orthostatic test. For Visit 3, orthostatic test was conducted pre- and 2-6 hours post-dose.
[4]Performed through telephone contact.
[5]Pre-dose, and 2-6 hours post-dose.

Clinical laboratory evaluation included a complete blood count (CBC) liver function tests, chemistry panel, and urinalysis, collected at screening and visits 1, 7 and 8/end-of-treatment. Prolactin, PSA, HgbA1C and thyroid panel [thyroid-stimulating hormone (TSH); triiodothyronine (T_3); thyroxine, free and total (T_4)] were obtained only at baseline and visit 8/end-of-treatment.

Orthostatic testing was performed at Visit 1 and 3 (pre-dose and 2-6 hours post-dose). Blood pressures and heart rate were collected in the supine position and 1 and 3 minutes after standing. A positive orthostatic test was defined as any of the following at 1 or 3 minutes:

- systolic blood pressure >30 mmHg
- diastolic blood pressure >20 mmHg
- heart rate >20 BPM

Sites were instructed to record an adverse event of "significant change in blood pressure

POSTURAL" when these measurement changes occurred in the absence of symptoms When patients had symptoms during orthostatic tests, the specific symptoms were recorded as the adverse event. Therefore, the summation of these two types of adverse events (nonsymptomatic and symptomatic) comprises all positive orthostatic test results for the study. Finally, the number and percentage of patients who had a positive test result without symptoms were planned to be provided by treatment group, visit, and time point.

B.3 Entry Criteria:

Inclusion criteria:

1) Males 50 years of age or older on day of consent and who, in the opinion of the Investigator, were in good general health on the basis of medical history, physical examination, and laboratory results;
2) At Visits 1 and 3, had bladder outlet obstruction, as defined by a Q_{max} (peak urine flow rate) between 4 and 15 mL/sec, with a minimum voided volume of $\geq$125 mL;
3) At Visits 1 and 3, had an IPSS of $\geq$13;
4) Were able to comply with protocol procedures;
5) Provided written informed consent before beginning any investigational procedures.

Exclusion Criteria:

Patients were excluded if they met any of the following criteria at Visits 1 and 3 (except as noted):

1) Participation in a study involving the administration of an investigational compound within the past 30 days, or within 5 times the half-life of the prior investigational drug, whichever was longer (not evaluated at Visit 3);
2) Post-void bladder residual volume >250cc determined by ultrasound (not evaluated at Visit 3);
3) Intravesical obstruction from any cause other than BPH including vesicle neck contracture, Mullerian duct cysts, urethral stricture, valves, sclerosis, or other urethral tumor;
4) Bladder calculi;
5) History of, or current, neurogenic bladder and other conditions that might affect bladder function including detrusor-sphincter dyssynergia, prior CVA, spinal cord injury, brain or spinal cord tumors, multiple sclerosis, diabetic neuropathies, prior transient ischemic attacks, or dementia;
6) History of any type of procedure in the past that was considered intervention for BPH or bladder neck obstruction including prior TURP, bladder neck resection, thermotherapy, laser therapy, TUNA therapy, or any other minimally invasive surgical therapies specifically designed for relief of BPH;
7) An active urinary tract infection, or a history of recurrent urinary tract infections defined as greater than 3 per year in the past two years;
8) Current prostatitis or a diagnosis of chronic prostatitis, or at Visit 1, a history of prostatitis within the past 3 months or recurrent prostatitis more than 3 times in the last year;

9) History of urinary retention from a cause other than BPH, within the past 3 months;
10) History of prior prostate cancer, OR prostate cancer as suspected by TRUS, DRE or clinical acumen. Patients with a PSA greater than 10.0 ng/mL were excluded. Patients with a PSA between 4.0 and 10.0 had prostate cancer ruled out to the satisfaction of the Clinical Investigator with appropriate documentation of the physician's assessment (not evaluated at Visit 3);
11) History of prior invasive bladder cancer. Patients with superficial bladder cancers that had not recurred in 5 years were eligible for protocol inclusion;
12) Prior radiation to the pelvis regardless of the reason or dosage of radiation;
13) Bladder catheterization or bladder or prostate instrumentation within the past 30 days;

- History of, or current significant postural hypotension, and/or had experienced significant postural hypotension upon initiating therapy with an □-blocker. Significant postural hypotension was defined as any one of the following observations: systolic blood pressure (SBP) >30 mmHg; diastolic blood pressure (DBP) >20 mmHg, heart rate (HR) >20 BPM; or orthostatic symptoms (e.g. lightheadeness, fainting).

14) Any other current medical condition which precluded safe participation in the study, in the opinion of the investigator, including, but not limited to:
    - □angina pectoris
    - □severe CHF
    - □prosthetic heart valves
    - □cardiac devices
    - □poorly controlled hypertension (sustained SBP>160, DBP>95 mmHg)
    - □poorly controlled diabetes (HbA_{1c}>10% ULN)
    - □renal insufficiency (serum creatinine >2.0 mg/dL)
    - □liver insufficiency (any LFT>2xULN)
    - □abnormal chest x-ray within the last year
    - □endocarditis
    - □cardiac arrhythmias
    - □recurrent episodes of dizziness, vertigo, or loss of consciousness
    - □pelvic surgery for malignancy or bowel resection
    - □hematuria which had not been appropriately evaluated to determine safe patient participation;
15) After Visit 1 (except where noted), were currently receiving medications which precluded safe participation in the study or that may have produced a confounding effect on the variables under study, including, but not limited to:
    - β-blockers (washed out by 10 days before Visit 1)
    - α-agonists (unless if, in the opinion of the investigator, the dose was stable and was not at a level that would have a significant impact on the IPSS and Qmax)
    - diuretics (unless if, in the opinion of the investigator, the dose was stable and was not at a level that would have a significant impact on the IPSS and Qmax)

- antispasmodics (unless if, in the opinion of the investigator, the dose was stable and was not at a level that would have a significant impact on the IPSS and Qmax)
- cholinomimetics (unless if, in the opinion of the investigator, the dose was stable and was not at a level that would have a significant impact on the IPSS and Qmax)
- anticholinergics (unless if, in the opinion of the investigator, the dose was stable and was not at a level that would have a significant impact on the IPSS and Qmax)
- tricyclic antidepressants or other psychiatric drugs with anticholinergic side effects that might have affected bladder function (may have been allowed if, in the opinion of the investigator, the dose was low and stable)
- ketoconazole, or other known potent inhibitors of CYP P450 3A4 (washed out by 10 days before Visit 1)
- natural/herbal products for the treatment of prostate conditions
- androgens or anti-androgens (washed out by 21 days before Visit 1

16) History of inadequate clinical response to the use of alpha blockers specifically for the relief of BPH symptoms;
17) History or current evidence of drug or alcohol abuse within the last 12 months;
18) History of allergy to α-blockers, or to any of the inactive agents used in this formulation.
19) Marked non-compliance (<80% or >120% compliant at Visits 2 or 3) during the 4-week, single-blind, placebo run-in;
20) Marked placebo response (greater than 30% decrease on the IPSS, or 3 mL/sec increase in Qmax at Visit 2 or pre-dose Visit 3) during the 4-week, single-blind, placebo run-in.
21) Uncontrolled hypo- or hyperthyroidism.

B.4 Study Population Demographics and Baseline Disease Characteristics:
Four-hundred and sixty-one male patients with BPH were randomized at 49 U.S. centers. Demographic and baseline disease characteristics of placebo and silodosin groups were similar and are shown in Table B.1.

Table B.1. Demographic and Disease Characteristics, Study SI04009

	Treatment Group		Overall N=461
	Placebo N=228 n (%)	Silodosin N=233 n (%)	
Race			
African American	12 (5.3)	5 (2.1)	17 (3.7)
Asian	4 (1.8%)	4 (1.7%)	8 (1.7%)
Caucasian	197 (86.4%)	207 (88.8)	404 (87.6)
Geriatric Status			
<65 years	130 (57.0)	136 (58.4%)	266 (57.7)
≥65 years	98 (43)	97 (41.6)	195 (42.3)
<75 years	203 (89.0)	206 (88.4)	409 (88.7)
≥75 years	25 (11.0)	27 (11.6)	52 (11.3)
IPSS (mean) (SD)	21.4 (4.91)	21.5 (5.38)	
Qmax (cc/sec) (mean) (SD)	9.0 (2.85)	9.0 (2.60)	

Source: NDA 22-206 ser 000, study report SI04009, Tables 11.2-1, 11.4.1-1 and 11.4.1-6

B.5 Withdrawals, Protocol Violations, and Compliance:

B.5.1 Withdrawals:

Of the 461 patients randomized, 416 completed the trial and 45 discontinued prematurely. Causes of premature discontinuation are shown in Table B.2. Discontinuation due to adverse events was more common among silodosin patients.

Table B.2. SI04009 Patient Disposition (Safety Population)

	Treatment Group		Overall N=461
	Placebo N=228	Silodosin N=233	
Number of Patients n (%)			
Completed	214 (93.9)	202 (86.7)	416 (90.2)
Discontinued	14 (6.1)	31 (13.3)	45 (9.8)
Discontinuation due to:			
Adverse Event	6 (2.6)	20 (8.6)	26 (5.6)
Protocol Violation	3 (1.3)	2 (0.9)	5 (1.1)
Voluntary Withdrawal	4 (1.8)	1 (0.4)	5 (1.1)
Lack of efficacy	0	2 (0.9)	2 (0.4)
Lost to follow-up	0	4 (1.7)	4 (0.9)
Investigator recommendation	0 (0)	1 (0.4)	1 (0.2)
Other	1 (0.4)	1 (0.4)	2 (0.4)

Source: NDA 22-206, study report SI04009, table 14.1.2

B.5.2 Protocol Violations

Protocol deviations were classified as major or minor. Major deviations were those that could potentially bias either the efficacy or safety conclusions of the study. Protocol deviations were more common among silodosin patients and were primarily due to lack of compliance with study medication (Table B.3).

Patients with major protocol deviations were included in the modified intent-to-treat (mITT) and safety populations, but not in the evaluable population.

Table B.3. Summary of Major Protocol Deviations (Safety Population), study SI04009

	Treatment Group		Overall N=461
	Placebo N=228	Silodosin N=233	
Number of Patients n (%)			
Patients without a Major Protocol Deviation	200 (87.7%)	184 (79.0%)	384 (83.3%)
Patients with a Major Protocol Deviation	28 (12.3)	49 (21.0%)	77 (16.7%)
Type of Major Protocol Deviation			
Lack of Compliance with Study Medication	12 (5.3%)	29 (12.4%)	41 (8.9%)
Inclusion/Exclusion Criteria Deviation	15 (6.6%)	21 (9.0%)	36 (7.8%)
Received Excluded Medication	0	5 (2.1%)	5 (1.1%)
Lack of Compliance to Protocol	2 (0.9%)	0 (0.0%)	2 (0.4%)

B.5.3 Compliance

Patient compliance was assessed by pill counts at each visit. Overall compliance was calculated at the conclusion of the single-blind placebo run-in period and the 12-week treatment phase. Subjects with marked non-compliance (<80% or >120% compliant at Visits 2 or 3) during the run-in phase were discontinued prior to randomization.

Mean compliance during the treatment phase was 95.4% for the silodosin group and 99.3% for placebo patients.

B.6 Efficacy analysis:

Primary and secondary endpoints:

The primary efficacy variable was the change from baseline to week 12/LOCF in the total score of the IPSS. Change from baseline to week 12/LOCF in Qmax was a secondary endpoint. Changes in the irritative and obstructive subscales of the IPSS and in the quality of life question from baseline to week 12/LOCF were also described, but were not pre-specified secondary endpoints.

Reviewer's comments:

The irritative subscale of the IPSS consists of Questions 2, 4, and 7:

- *How often have you had to urinate again less than 2 hours after you finished urinating? (Question 2)*
- *How often have you found it difficult to postpone urination? (Question 4)*
- *How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning? (Question 7)*

The obstructive symptoms subscale of the IPSS consists of Questions 1, 3, 5 and 6:

- *How often have you had a sensation of not emptying your bladder completely after you finished urinating?*
- *How often have you found you stopped and started again several times when you urinated?*
- *How often have you had a weak urinary stream?*
- *How often have you had to push or strain to begin urination?*

The quality of life question of the IPSS states, "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" Possible responses range from 0 (delighted) to 6 (terrible).

In a May 2, 2005, letter regarding the two protocols for studies SI04009 and SI04010, DRUP advised the sponsor that, "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 secondary efficacy variable was the change from baseline to week 12/LOCF in Qmax.

The primary population used for the efficacy analyses was the modified intent-to-treat (mITT) population [all randomized patients who provided data for the IPSS at Visit 3 (baseline); if a patient was incorrectly randomized, actual treatment given was planned to be used in all summary statistics and analyses]. As no patients were incorrectly randomized, the ITT population [all randomized patients who provided data for the IPSS at Visit 3 (baseline)] was equivalent to the mITT population for this study.

Efficacy data were also analyzed for the evaluable population -- (all patients in the mITT who completed the study and provided data for the primary efficacy variable at Visit 8 with no major protocol deviations). The safety population was defined as all randomized patients who received at least one dose of study drug. Study populations are summarized in Table B.4.

Table B.4. Study populations, SI04009

	Placebo	Silodosin	Total
Randomized	228	233	461
Safety	228	233	461
mITT	228	233	461
ITT	228	233	461
Evaluable	193	169	462

Primary analysis—Change in total IPSS from baseline to endpoint (week 12/LOCF)
For the primary endpoint, change in total IPSS from baseline to week 12/LOCF, silodosin was more effective than placebo ($p<0.0001$). Silodosin's statistical superiority over

placebo in total IPSS was achieved by the first post-baseline visit (week 1) and was maintained throughout the study.

Table B.5. Change from baseline in IPSS total score (mITT), SI04009

Visit	Statistic	Placebo N=228	Silodosin (N=233)
Week 0 (baseline)	Mean (SD)	21.4 (4.91)	21.5 (5.39)
Week 1	Mean (SD)	19.4 (5.77)	17.6 (5.94)
Change	Mean (SD)	**-2.1 (4.65)**	**-4.5 (5.68)**
p-value		<0.001	
Week 12 (LOCF)	Mean (SD)	17.7 (6.55)	15.0 (6.96)
Change	Mean (SD)	**-3.6 (5.85)**	**-6.5 (6.73)**
p-value		<0.001	

Source: NDA 22-206 ser 000, SI04009 study report, Table 14.2.1-1

Secondary Analysis – Change in Qmax from baseline to endpoint

Silodosin had a statistically significant effect on the change from baseline in Q_{max} at all timepoints after the first dose (Table B.6).

Table B.6. Mean (SD) Change from baseline in Qmax (mL/sec (mITT), SI04009

Visit	Placebo N=228	Silodosin N=233	p-value
Week 0 (post-dose)	0.8 (3.05)	2.7 (3.48)	<0.0001
Week 1	1.1 (3.27)	2.2 (3.49)	0.0005
Week 2	1.4 (3.52)	2.6 (3.89)	0.0009
Week 4	1.4 (3.66)	2.4 (4.22)	0.0075
Week 12 (LOCF)	1.2 (3.81)	2.2 (4.31)	0.0060

Source: NDA 22-206 ser 000, SI04009 study report, Table 11.4.1-7

Additional Analyses:

Change from baseline to endpoint in IPSS irritative and obstructive subscales

Compared to placebo, silodosin also resulted in a statistically significantly greater decrease in IPSS irritative and obstructive from baseline to endpoint (Table B.7).

Table B.7 Summary of Change from baseline to endpoint in IPSS Irritative Symptoms Subscale and Obstructive Symptoms Subscale (mITT), SI04009

Visit	Statistic	Placebo N=228	Silodosin (N=233)
Irritative Subscale			
Week 12 (LOCF)	Mean (SD)	-1.4 (2.70)	-2.3 (2.97)
	p-value	0.0004	
Obstructive Subscale			
Week 12 (LOCF)	Mean (SD)	-2.2 (3.75)	-4.2 (4.32)
	p-value	<0.0001	

Source: : NDA 22-206 ser 000, SI04009 study report, Tables 11.4.1-3 and 11.4.1-4

Change from baseline to endpoint in QOL question

A higher percentage of silodosin subjects than placebo subjects fell into the more positive categories ("delighted", "pleased", "mostly satisfied") at Week 12/LOCF – 1.7%, 6.4%

and 25.3%, respectively, for silodosin vs. 1.3%, 5.7% and 16.2%, respectively, for placebo. No test for statistical significance was performed prospectively.

B.7 Safety analysis

Reviewer's comment: The original description of an adverse event (verbatim term) was recoded to a "preferred term" and "system, organ, class" using the standard MedDRA dictionary.

An audit of the SAS datasets and case report forms confirms that verbatim terms were correctly coded and categorized.

B.7.1 Extent of Exposure
Mean duration of exposure was slightly greater for placebo subjects -- 83 days -- versus 77.5 days for the silodosin group.

B.7.2 Serious Adverse Events:

Deaths: One death from hypertensive cerebral hemorrhage occurred after randomization in a 61 year-old patient receiving placebo.

Serious Adverse Events (Other): Eleven serious adverse events (SAEs) occurred in 6 patients (3 on placebo, 3 on silodosin) after randomization.

SAE's reported in the placebo group during the randomization phase were small bowel obstruction, myocardial infarction, and worsening diverticulitis.

SAE's in the silodosin group are summarized below (each SAE is underlined). No SAEs were considered by the investigators to be related to silodosin.

> *Patient 136019* was a 65-year-old Caucasian male who was randomized to silodosin on 31 October 2005. The patient had a past medical history of calcified aorta and coronary artery disease since 2003, exertional chest pain since September, 2005, and chronic obstructive lung disease and benign prostatic hyperplasia, both since 2003. Concomitant medications at the time of randomization were multivitamin, calcium, naproxen 500 mg daily, grape seed extract, flaxseed oil and glucosamine chondroitin.
>
> On 28 November 2005, the patient's wife called the clinic to report that he had been hospitalized since [redacted]. She reported that on [redacted] the patient came to an emergency room complaining of multiple episodes of heavy coughing at home. He was admitted to an intensive care unit with the diagnosis of acute myocardial infarction. The patient underwent a cardiac catheterization which showed critical multiple-vessel coronary artery stenosis and an urgent need for coronary bypass surgery. The patient developed congestive heart failure on the same day which was treated with IV Lasix. Levaquin and Vancomycin IV antibiotic therapies were also initiated on [redacted] for 4 days.

b(6)

On [redacted], the patient developed fever causing a delay in his cardiac surgery. An intra-aortic balloon pump (IABP) was inserted for cardiac support during the waiting period. On 25 November 2005, the patient developed respiratory failure with pneumonia.

On [redacted] the patient underwent quadruple coronary artery bypass graft surgery. His postoperative course was prolonged and complicated by congestive heart failure, pneumonia and respiratory failure requiring extended intubation and ventilatory support. The patient's condition improved slowly but he continued to have generalized fatigue secondary to reduced left ventricular function. He required long-term treatment with IV Lasix and oral Coreg. b(6)

The patient's hospital course was further complicated by group D Enterococcus bactermia on 20 December 2005. The bacteremia was treated with IV Zyvox. Respiratory failure resolved on 24 December 2005, and bacteremia resolved or [redacted] The patient was later transferred to another hospital for inpatient rehabilitation. b(6)

[redacted], the patient was discharged home. Pneumonia was reported as resolved at the time of discharge. The study drug was discontinued and the patient was terminated from the study on 07 January 2006. b(6)

The study blind was not broken and the investigator assessed acute myocardial infarction,respiratory failure, pneumonia, congestive heart failure and group D Enterococcus bacteremia events as not related to the study drug. The patient had pre-existing coronary artery disease since 2003 and chest pain on exertion since September 2005, prior to the administration of silodosin. The patient's hospital course was considered consistent with acute myocardial infarction in a patient with concomitant chronic obstructive lung disease.

Reviewer's comment: This reviewer agrees with the investigator's assessment that the adverse events in this subject were not related to study drug. This opinion is based on the review of the following documentation:

- *Narrative summary, SI04009 study report, page 61*
- *Case report form.*

Patient 101027 was a 68-year-old Caucasian male randomized to silodosin on 21 October 2005. The patient's past medical history was notable for hypertension since 2003, hypercholesterolemia since 2000, restless leg syndrome since 1995, bilateral hip arthritis since 2004, and benign prostatic hyperplasia since 1998. Information received on 25 November 2005, indicated that the patient tripped and fell on [redacted]. On [redacted], he came to an emergency room with the complaint of severe neck pain and numbness in the right arm. He was treated with Vicodin as needed for pain, Skelaxin 800mg BID, and oral methylprednisolone. b(6)

On [redacted] an MRI of the patient's spine revealed multi-level degenerative disk disease with spinal stenosis and severe radiculopathy. Surgery for herniated C4, C5 and C7 discs was recommended. On [redacted], the patient underwent a spinal surgery for decompression of C4-C5, C5-C6 anterior cervical spine with fusion and platting. Strength in his right arm improved postoperatively. b(6)

b(6)

On [redacted] the patient was discharged home in stable condition. The study drug was temporarily interrupted from 1 December 2005 through 4 December 2005. The study blind was not broken and the investigator assessed the event as not related to the study drug. Although this event occurred after a trip and fall, the pathology of the multi-level degenerative disk disease likely precedes the patient's entry in the study. The patient completed the study and entered into the open-label extension

Reviewer's comment: This reviewer agrees that radiculopathy is not related to study drug. However, it is possible that silodosin contributed to the patient's fall if he experienced pre-syncope before the event, but this is not clear from the narrative summary (SI04009 study report, page 62) or case report form.

Patient 112028 was a 70-year-old Caucasian male who was randomized to silodosin on 17 August 2005. His past medical history was notable for hypothyroidism since 1990, arthritis, and benign prostatic hyperplasia since January, 2005. Past medical history of coronary artery disease was not reported. Medications at time of randomization were levothyroxine 125 mcg daily, aspirin 325 mg daily and Aleve® 200 mg as needed.

On [redacted] the patient was admitted to an emergency room with a complaint of chest pain which occurred while playing softball. A cardiac catheterization was performed and revealed left main coronary artery thrombosis, proximal high-grade lesions in the left anterior descending artery (LAD), 80% occluded lesion of the circumflex artery and multiple high grade lesions in the right coronary artery. Cardiac ejection fraction was approximately 25%. The patient was diagnosed with an acute myocardial infarction. b(6)

On the same day the patient underwent an emergency three-vessel, off-pump coronary artery bypass graft surgery. He had a normal post-operative recovery and was discharged home on the fifth postoperative day [redacted] The study drug was stopped and the patient was discontinued from the study on 21 November 2005. The study blind was not broken and the investigator assessed the event as not related to the study drug. Although the patient did not report a history of coronary artery disease, "the genesis of a thrombotic occlusion of a coronary artery for elderly males is typically in an atherosclerotic narrowing. This patient seems to have had silent coronary artery disease in multiple vessels likely preceding the patient's entry in the study." b(6)

Reviewer's comment: Based on review of the narrative summary and the case report form, this reviewer agrees that the patient's coronary artery disease likely preceded initiation of silodosin therapy and that the adverse event of acute MI is not likely related to study drug.

B.7.3 Premature discontinuation due to adverse events:
More patients on silodosin discontinued therapy prematurely due to an AE than those on placebo – 20 (8.6%) versus 6 (2.6%), respectively. The most common AE in silodosin subjects leading to discontinuation was retrograde ejaculation (N=9, 3.9%). The

remaining AEs associated with premature discontinuation among silodosin patients were myocardial infarction (N=2), asthenia (N=2), dizziness (N=1), increased appetite (N=1), diarrhea (N=1), hypothyroidism (N=1), sexual dysfunction (decreased sexual gratification) (N=1), urinary retention (N=1) and dry eye (N=1).

All events of retrograde ejaculation and asthenia and the single event of diarrhea were considered related to study drug by the investigator.

B..4 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 B.8.

Table B.8 Most Common (>2%)
Silodosin Treatment Emergent Adverse Events (Safety Population), SI04009

Adverse Event – MedDRA preferred term	Silodosin n (%)	Placebo n (%)
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)

Source: NDA 22-206 ser 000, SI04009 study report, Table 12.2.2-1

Reviewer's comment: The common treatment-emergent adverse events observed with silodosin are consistent with those reported for other α-1--adrenergic antagonists.

Verbatim terms linked to the preferred term "retrograde ejaculation" included "orgasm, no semen," "orgasm, semen force reduced," "orgasm semen quantity reduced," and "retrograde ejaculation."

B.7.5 Laboratory evaluation

Assessment of laboratory evaluation was based on the integrated database which combined results from both U.S. controlled Phase 3 trials, and is discussed in the body of the NDA review (Section 7.1.5).

Extreme individual outlier data from this study are addressed, however, in section B.7.5.1.

B.7.5.1 Extreme Individual Outliers

Patient 140020, TSH change of 23.5 mIu/mL from baseline.
This patient had a history of asthma, gastroesophageal reflux disease, degenerative joint disease, seasonal allergies, erectile dysfunction, and BPH. His Visit 1 TSH value (21 September 2005) was <0.004 µIu/mL (normal range 0.4 to 4.0 µIu/mL). The investigator marked this value as clinically significant and referred the patient back to his primary care physician for follow-up.

The patient remained in the study and his TSH value at Visit 8 (1 February 2006) was 23.5 Iu/mL. The Investigator did not mark this value as clinically significant, and provided no comment on this finding, yet an adverse event of hyperthyroidism with an onset date of 6 December was recorded (no resolution date was provided). There is no indication in the CRF that the patient was seen by his primary care physician. The patient completed the study and entered into the open-label extension.

Reviewer's comment: Given the patient's baseline TSH abnormality, it appears that he had a history of thyroid dysfunction that pre-dated silodosin therapy. Therefore, the post-treatment elevation in TSH is unlikely to be related to study drug.

Patient 114070, GGT change of 684 U/L from baseline.
This patient had a history of type II diabetes mellitus, arthritis and BPH. Concomitant medications were subcutaneous insulin 70/30 and diclofenac 75 mg daily.

His Visit 1 GGT value (15 February 2006) was 101 U/L (normal range 0-51 U/L). The Investigator flagged this value as not clinically significant; however, since other liver function tests were elevated, a repeat lab evaluation was ordered and the result (performed 6 March 2006) was 70 U/L. The Visit 7 value (12 April) was 151 U/L, a value the Investigator flagged as not clinically significant. The Visit 8 value (12 June) was 754 U/L, which the Investigator suggested was clinically significant. However, the Investigator provided no comment about this finding. No adverse events were recorded that would have suggested a cause for the laboratory abnormality.

Liver Function Tests, Pt 114070

Analyte (nl range)	Baseline (2/15/06)	Visit 7 (4/12/06)	Visit 8/ET (6/12/06)
AST (0-37 U/L)	42	90	48
ALT (0-47 U/L)	34	58	46
GGT (0-51 U/L)	101	**151**	**754**
T Bili (0-1.1 mg/dL)	0.4	0.8	0.5

The sponsor's assessment for patient 114070 follows: "The elevation in AST and GGT began before the initiation of silodosin therapy, suggesting an alternative

cause for liver dysfunction. GGT is a very sensitive enzyme for detecting the onset of biliary obstruction, cholangitis, or cholecycstitis. Additionally, the AST/ALT ratio is usually greater than 1 in patients with more chronic liver diseases, and the last three ratios noted were indeed 1.3, 1.6, 1.0. This patient appears to have presented with a chronic biliary disease which had an onset before the start of the study.

Reviewer's comment: The cause of this patient's GGT elevation is unclear based on the limited data provided. However, an isolated GGT elevation does not necessarily indicate significant hepatic disease.

Patient 114034, AST change of 195 from baseline. This patient had a history of arthritis, hyperlipidemia, hypertension, cardiomyopathy, inguinal hernia, cholecystectomy, colon polyps, a cardiac stent, and BPH. Concomitant medications included lisinopril 40 mg qd, lipitor 20 mg qd, aspirin 325 mg qd, thiamine 100 mg qd, folic acid 400 mcg qd, niacin 25 mg qd, omega 3 and fish oil.

His Visit 1 AST value (17 October 2005) was 22 U/L (normal range 0-37 U/L). The sample from Visit 7 was hemolyzed and no results were available. A Visit 8 value (13 February) was 34 U/L. The subject returned to the study clinic on 15 March for a follow-up and the patient's AST value was 218 U/L, a value the Investigator flagged as clinically significant (ALT and GGT were also elevated). However, the Investigator provided no explanation or comment about this finding. No adverse events were recorded that would have suggested a cause for this finding.

Liver Function Tests, Pt. 114034

Analyte (nl range)	Baseline (9/29/05)	2/13/06	3/15/06	4/7/06
AST (0-37 U/L)	16	34	**218**	24
ALT (0-47 U/L)	26	26	69	38
GGT (0-51 U/L)	48	48	120	60
T Bili (0-1.1	1.3	2.0	0.6	2.0

The sponsor's assessment of this patient's elevated AST follows: The 117-day delay in these LFT changes from the start of silodosin therapy, and the rapidity at which they returned to normal while the patient was still receiving silodosin, do not suggest that this event was related to silodosin use. The presentation of LDH and AST after silodosin therapy suggests a possible sub-acute myocardial infarction occurring during the second week of March 2006; the medical history of this patient makes the possibility of this event very likely. If accompanying values for troponin, creatine kinase, and LDH isoenzymes had been available, this hypothesis could have been further explored.

B.7.6 Vital Signs

Compared to placebo, silodosin treated subjects experienced a greater mean decrease in systolic and diastolic blood pressure at all post-treatment time points relative to baseline (Table B.9).

Table B.9. Change from Baseline for Systolic and Diastolic Blood Pressure (Study SI04009)

	Placebo N=228	Silodosin N=233
Systolic Blood Pressure		
Week 4	-1.2 (13.66)	-2.9 (12.73)
Week 12/ET	-0.7 (15.48)	-1.9 (12.93)
Diastolic Blood Pressure		
Week 4	-1.0 (8.85)	-1.2 (8.57)
Week 12/ET	-0.6 (9.32)	-1.3 (8.80)

Source: NDA 22-206 ser 000, SI04009 study report, Table 14.3.5-19

Orthostatic testing was performed at Visit 3 pre-dose and then 2-6 hours following the first dose of double-blind therapy. A higher percentage of silodosin patients had a positive orthostatic test at 1 and 3 minutes compared to placebo.

Table B.10 Positive Orthostatic Tests, SI04009

Timepoint	Placebo	Silodosin
1 minute after standing	1/227 (0.4%)	3/229 (1.3%)
3 minutes after standing	1/227 (0.4%)	3/229 (1.3%)

B.7.7 Physical Examination

No increased incidence of breast or thyroid exam abnormalities was observed in silodosin group.

B.7.8 ECGs

No clinically meaningful ECG changes were apparent in silodosin group compared to placebo.

B.8 Conclusion

Results of this study support the efficacy and safety of silodosin in the treatment of BPH.

Appendix C – US Controlled Phase 3 Trial SI04010

"A Multi-Center, Randomized, Double-Blind, Placebo Controlled, Parallel Evaluation of the Efficacy and Safety of Silodosin in the Treatment of the Signs and Symptoms of Benign Prostatic Hyperplasia."

The study design and endpoints for this trial were identical to those of Study SI04009 with the exception that pharmacokinetic sampling was not performed in SI04010.

C.1 Study Population Demographics and Baseline Disease Characteristics:

A total of 462 male patients with BPH were randomized at 42 U.S. centers. Demographic and baseline disease characteristics of the primary efficacy population (mITT) are shown in Table C.1. Silodosin and placebo treatment groups were similar.

Table C.1. SI04010 Demographic and Disease Characteristics

	Treatment Group		Overall N=462
	Placebo N=229 n (%)	**Silodosin** N=233 n (%)	
Race			
African American	10 (4.4)	9 (3.9)	19 (4.1)
Asian	2 (0.9)	1 (0.4)	3 (0.6)
Caucasian	202 (88.2)	218 (93.6)	420 (90.9)
Hispanic	11 (4.8)	5 (2.1)	16 (3.5)
Other	4 (1.7)	0	4 (0.9)
Geriatric Status			
<65 years	119 (52.0)	123 (52.8)	242 (52.4)
≥65 years	110 (48.0)	110 (47.2)	220 (47.6)
<75 years	199 (86.9)	200 (85.8)	399 (86.4)
≥75 years	30 (13.1)	33 (14.2)	63 (13.6)
IPSS (mean) (SD)	21.2 (4.92)	21.2 (4.88)	
Qmax (cc/sec) (mean) (SD)	8.7 (2.67)	8.4 (2.48)	

Source: NDA 22-206 ser 000, SI04010 study report, Tables 11.2-1, 14.2.1-2 and 14.2.2-1

C.2 Withdrawals, Protocol Violations, and Compliance:

C.2.1 Withdrawals:

Of 462 patient randomized, 416 completed the trial and 46 discontinued prematurely. Causes of premature discontinuation are shown in Table C.2.

C.2 SI04010 Patient Disposition (Safety Population)

	Treatment Group		Overall
	Placebo N=228 n (%)	Silodosin N=233 n (%)	N=461
Discontinuation due to:			
Adverse Event	4 (1.7)	10 (4.3)	14 (3.0)
Protocol Violation	0	1 (0.4)	1 (0.2)
Voluntary Withdrawal	10 (4.4)	5 (2.1)	15 (3.2)
Lack of efficacy	2 (0.9)	0	2 (0.4)
Lost to follow-up	3 (1.3)	2 (0.9)	5 (1.1)
Investigator recommendation	0	0	0
Other	5 (2.2)	4 (1.7)	9 (1.9)

From NDA 22-206, study report SI04009, table 14.1.2

C.2.2 Protocol Violations

Approximately 11% of all patients had a major protocol deviation. Types of violations were lack of compliance with study medication [11 (4.8%) placebo, 13 (5.5%) silodosin], inclusion/exclusion criteria errors [13 (5.7%) placebo, 11 (4.7%) silodosin] and receiving excluded medications [6 (2.6%) placebo, 2(0.8%) silodosin].

C.2.3 Compliance

Mean compliance was similar between the two groups -- 98.6% for silodosin and 99.9% for placebo.

C.3 Efficacy Analysis

The efficacy analyses were performed on the modified intent-to-treat (mITT population – all randomized patients who provided IPSS data at Visit 3 according to actual treatment received). No patients were incorrectly randomized in this study. Therefore, the ITT population (all randomized patients who provided data for the IPSS at Visit 3) is equivalent to the mITT population for this study.

Primary analysis—Change in total IPSS from baseline to endpoint (week 12/LOCF)

Silodosin resulted in a significantly greater change in IPSS total score than placebo at Week 12/LOCF, the primary endpoint (Table C.3). Statistical superiority over placebo was achieved by the first post-baseline visit (week 1) and was maintained throughout the study.

Table C.3. Summary of Change from Baseline in IPSS Total Score by Treatment Group and Visit (mITT)

Visit	Statistic	Placebo N=229	Silodosin N=233
Week 0 (baseline)	Mean (SD)	21.2 (4.92)	21.2 (4.88)
Week 1	Mean (SD)	18.5 (6.31)	16.2 (6.20)
Change	Mean (SD)	-2.7 (4.69)	-5.0 (5.38)
p-value		<0.001	
Week 12 (LOCF)	Mean (SD)	17.7 (6.95)	14.9 (6.82)
Change	Mean (SD)	-3.4 (5.83)	-6.3 (6.54)
p-value		<0.001	

Source: NDA 22-206 ser 000, SI04010 study report, Table 14.2.1-1

Secondary analysis—Change in Qmax from baseline to endpoint

Silodosin had a statistically significant effect on the change from baseline in Qmax immediately following the first dose and at week 12/LOCF, but not at intermediate time points (Table C.4).

Table C.4. Change from baseline in Qmax (mL/sec) (mITT)

Visit	Placebo N=228	Silodosin (N=233)	p-value
Week 0 (Post-Dose)	2.1 (4.26)	2.9 (3.41)	**0.0494**
Week 1	2.2 (3.76)	2.9 (3.69)	0.0583
Week 2	2.2 (4.56)	2.9 (4.14)	0.209
Week 4	2.0 (4.44)	2.7 (3.86)	0.189
Week 12 (LOCF)	1.9 (4.82)	2.9 (4.53)	**0.0431**

Source: NDA 22-206 ser 000, SI04010 study report, Table 14.2.2-1

Additional Analyses:

Change from baseline to endpoint in IPSS irritative and obstructive subscales

Compared to placebo, silodosin also resulted in a statistically significantly greater decrease in IPSS irritative and obstructive from baseline to endpoint (Table C.5).

Table C.5 Summary of Change from baseline to endpoint in IPSS Irritative Symptoms Subscale and Obstructive Symptoms Subscale (mITT)

Visit	Statistic	Placebo N=228	Silodosin N=233
Irritative Subscale			
Week 12 (LOCF)	Mean (SD)	-1.3	-2.4
	p-value	<0.001	
Obstructive Subscale			
Week 12 (LOCF)	Mean (SD)	-2.1	-3.9
	p-value	<0.0001	

Source: NDA 22-206 ser 000, SI04010 study report, Table 14.2.1-2

Change from baseline to endpoint in QOL question

For every visit after Visit 3, a higher percentage of silodosin patients than placebo patients fell into the more positive categories (i.e. mixed; mostly satisfied; pleased; or delighted) on the quality of life question. The positive effect of silodosin on the QoL question was statistically significant at all visits after Visit 3, according to a post-hoc analysis.

C.4 Safety analysis

C.4.1 Extent of Exposure

The extent of exposure to study drug is summarized in Table C.6.

Table C.6. Extent of Exposure (days) by Treatment Group (Safety Population)

	Placebo (N=229)	Silodosin (N=233)
Mean	80.0 (20.46)	83.2 (16.06)
Median	85.0	85.0

Source: NDA 22-206 ser 000, SI04010 study report, Table 12.1-1

C.4.2 Serious Adverse Events

Deaths: No deaths occurred after randomization in this study.

Serious adverse events (Other): Eight serious adverse events occurred in seven patients following randomization. Three of these SAEs were reported in three silodosin patients – complete heart block, syncope and carotid artery stenosis. Only syncope was considered by the investigator to be related to silodosin use. The narrative summary of the SAE of syncope is provided below.

> *Patient 272046* was an 85-year-old Caucasian, mildly obese male, who was randomized to silodosin. He entered the double-blind treatment phase on ——— The patient was a wheelchair user and had a past medical history of type II diabetes mellitus with retinopathy and nephropathy, hypercholesterolemia since 2000, peripheral vascular disease, hypothyroidism, hypertension since 1995, coronary artery disease, status post coronary artery bypass graft in 1992 and benign prostatic hyperplasia since 1970. The patient also had a past history of smoking 1 pack of cigarettes per day for 40 years. He had ceased smoking 20 years ago. His concomitant medications included Maxzide 75/50 1/2 tablet daily since 2000, and Cozaar 25mg daily since 2004, both for hypertension. He had also been on prazosin daily (unknown dosage) since 1993 for BPH. b(6)
>
> On ———, one day after the start of the study drug, the patient was admitted to the hospital for syncope, after reportedly being found "passed out" for about 10 minutes in his wheelchair at the airport by his wife. The patient, however, claimed he had merely fallen asleep while resting in his wheelchair. b(6)
>
> Upon initial physical examination, the patient was found to be alert and oriented with a blood pressure of 80/40 mmHg and heart rate of 70 beats per minutes. He denied chest pain, shortness of breath, lightheadedness or palpitations. There was no neurological deficit or evidence of seizure activity. His electrocardiogram showed normal sinus rhythm with an old left bundle branch block and ventricular

bigeminy and trigeminy. The patient was treated with oxygen and oral glucose 15gms empirically.

Laboratory findings were within normal limits for electrolytes, WBC, Hgb, CPK and Troponin. Myocardial infarction was excluded. His echocardiogram showed depressed left ventricular function with an ejection fraction of 35-40%, septal hypertrophy and impaired relaxation consistence with diastolic dysfunction, dilated left atrium, aortic stenosis, and mild tricuspid regurgitation. There was no evidence of any mural thrombosis. CT scan of the head showed faint bilateral basal ganglia calcification. The patient remained asymptomatic and he was discharged home on

b(6)

Follow-up by the clinic noted that the patient was still taking prazosin, a contraindicated medication, after the start of the study drug. The Investigator felt that the usage of prazosin, in addition to the study drug, may have led to a hypotension episode with resulting syncope. Both prazosin and the study drug were discontinued. Treatment assignment for this patient was unblinded at the Investigator's request and the Investigator assessed the event as possibly related to study drug.

Reviewer's comment: This reviewer agrees with the investigator's assessment.

C.4.3 Premature discontinuation due to adverse events:
A greater number of patients on silodosin discontinued therapy due to an adverse event than those of placebo – 10 (4.3%) versus 4 (1.7%), respectively. AEs leading to discontinuation in silodosin patients were retrograde ejaculation (N=4), orthostatic hypotension (N=2), and one event each for diarrhea, dizziness, syncope (patient 272046, discussed above), and priapism. Investigators judged the events of dizziness, syncope, priapism, one case of orthostatic hypotension, and all cases of retrograde ejaculation, to be related to silodosin use.

C.4.4 Common Treatment Emergent Adverse Events:
More patients receiving silodosin experienced an adverse event than those on placebo – 51.9% vs. 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 C.7.

Table C.7. Most Common (>2%)
Silodosin Treatment Emergent Adverse Events (Safety Population)

Adverse Event – MedDRA preferred term	Silodosin n (%)	Placebo n (%)
Retrograde Ejaculation	63 (2.7.0)	2 (0.9)
Dizziness	9 (3.9)	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)

NDA 22-206 ser 000, SI04010 study report, Table 12.2.2-1

C.4.5 Laboratory evaluation

Assessment of laboratory evaluation was based on the integrated database which combined results from both U.S. controlled Phase 3 trials, and is discussed in the body of the NDA review (Section 7.1.5).

Extreme individual outlier data from this study are addressed, however, in section C.4.5.1.

C.4.5.1 Extreme Individual Outliers

Patient 252002, TSH change.

This patient with a history of hypothyroidism had a baseline TSH value of 1.19μIU/mL. Concomitant medication was levothyroxine 0.15 mcg daily. After approximately four weeks of placebo lead-in, the patient started silodosin therapy. Following approximately 12 weeks of silodosin therapy, the patient's TSH value was 8.2 μIU/mL. No comment was provided by the Investigator and an adverse event was not noted. According to the sponsor, presumably because of the patient's history of hypothyroidism, the Investigator felt that this change was secondary to less-than-ideal medical management.

Reviewer's comment: This reviewer agrees with the investigator's assessment.

Patient 272046, PSA change

This patient had a baseline PSA value of 4.46 ng/mL. After approximately four weeks of placebo lead-in, the patient started silodosin therapy. Following one day of silodosin therapy, the patient experienced a serious adverse event of syncope, was hospitalized, and silodosin therapy was discontinued. After the resolution of the adverse event, the patient returned for an early termination visit (five days after silodosin initiation, four days since last dose) during which clinical labs were evaluated. At this visit, PSA was 77.8 ng/mL, a value be considered artifactual. The Investigator recorded this as an unrelated adverse event and referred the patient to his previous physician for follow-up on this matter.

Reviewer's comment: Given that the PSA elevation occurred after only a single dose of silodosin, this laboratory abnormality is unlikely to be related to study drug.

Patient 273020, platelet changes

This patient was a 77 years old and had a history of macular degeneration, irregular heart beat and arthritis. Baseline platelet value on 12/06/05 was 393 x 10^9cells/L. After approximately four weeks of placebo lead-in, the patient started silodosin therapy. Following approximately four weeks of silodosin therapy the platelet count was 409 x 10^9 cells/L After approximately eight more weeks of therapy (approximately 12 total weeks of silodosin dosing) the patient's laboratory values were checked during the termination visit. The platelet value at that time was 1,137 x 10^9 cells/L. A repeat platelet count was 1,108 x 10^9 cells/L. The Investigator

recorded thrombocytosis as an unrelated adverse event. The patient had no prior history of hematological conditions.

Patient 278013, hematocrit and serum creatinine changes
This patient had a baseline hematocrit of 40.6%. After approximately four weeks of placebo lead-in, the patient started silodosin therapy. Following approximately five weeks of silodosin therapy the hematocrit value was 33.3%. After approximately six more weeks of therapy (approximately 11 total weeks of silodosin dosing) the patient's laboratory values were checked during the termination visit. The hematocrit value was 29.4%. Over this same time course, the patient's serum creatinine rose 3.6 mg/dL. Approximately five weeks later, the patient was diagnosed with chronic renal failure secondary to multiple myeloma. The Investigator recorded multiple myeloma as an unrelated serious adverse event on the case report form with a start date approximately five weeks after the termination visit. The patient had no prior history of hematological or cancer conditions.

Patient 289019, prolactin change.
This patient had a baseline prolactin value of 9.3 ng/mL (nl<20 ng/mL). After approximately four weeks of placebo lead-in, the patient started silodosin therapy. Following approximately 12 weeks of silodosin therapy, the patient's prolactin value was 29.0 ng/mL. The Investigator provided no comment on this change, nor was an adverse event recorded. It should be noted that the patient's original screening prolactin was 17.3, and the patient had to be re-screened in order to qualify for the study (to obtain the 9.3 ng/mL value). Presumably the Investigator was not impressed by this change since the patient had a previously elevated value before therapy. The patient had no history of endocrine disorders.

Reviewer's comment: Among the extreme laboratory outliers, there is no commonality to suggest that silodosin was responsible for the abnormalities observed.

C.4.6 Vital Signs

Compared to placebo, silodosin treated subjects experienced a greater mean decrease in systolic and diastolic blood pressure at all post-treatment time points relative to baseline (Table C.8).

Table C.8. Mean (SD) Change from Baseline for Systolic and Diastolic Blood Pressure (Study SI04010)

	Placebo N=228	**Silodosin** N=233
Systolic Blood Pressure		
Week 4	-0.5 (13.79)	-1.8 (12.62)
Week 12/ET	0.4 (13.65)	-0.5 (13.78)
Diastolic Blood Pressure		
Week 4	-0.0 (8.27)	-0.9 (8.13)
Week 12/ET	0.3 (8.72)	-0.3 (8.09)

Source: NDA 22-206 ser 000, SI04010 study report, Table 14.3.5-19

Orthostatic testing was performed at Visit 3 pre-dose and then 2-6 hours following the first dose of double-blind therapy. A higher percentage of silodosin patients had a positive orthostatic test at 1 and 3 minutes compared to placebo.

Table C.9. Summary of Orthostatic Test Results By Treatment, SI04010

	Placebo	Silodosin
Timepoint (Pre-Dose)		
1 minute after standing	1/229 (0.4)	3/233 (1.3)
3 minutes after standing	0/229 (0)	3/233 (1.3)
Timepoint (Post-Dose)		
1 minute after standing	1/228 (0.4)	3/233 (1.3)
3 minutes after standing	1/228 (0.4)	6/233 (2.6)

C.4.7 Physical Examination

No increased incidence of breast, thyroid or other physical exam abnormalities was observed in the silodosin group.

C.4.8 ECGs

Compared to placebo, no clinically meaningful ECG changes over time were apparent in patients taking silodosin.

C.5 Conclusion

Results of this study support the efficacy and safety of silodosin in the treatment of BPH.

Appendix D – Thorough QT Study SI05014

Study SI05014, "A Double-Blind, Randomized, Parallel Group Trial to Define the Electrocardiographic Effects of Silodosin, Using a Therapeutic and a Supratherapeutic Dose, Compared with Placebo and Moxifloxacin (a Single Blinded Positive Control) in Healthy Male Subjects: A Thorough QT ECG Trial"

Trial start date: December 9, 2003. Trial end date: March 18, 2004.

D.1 Objectives:
Primary:

- to evaluate the effect of silodosin on the time-matched changes form baseline in the corrected QT interval (QTc) of the electrocardiogram (electrocardiogram) using an individual correction method (QTcI).

Secondary:

- to evaluate the effect of silodosin on change from baseline in ECG parameters (QTcF, QTcB, heart rate, PR interval, QRS interval, uncorrected QT interval, and morphological patterns);
- to determine the correlation between QTcI change from baseline and plasma concentration of silodosin and its primary metabolites;
- to assess the general safety and tolerability of treatments.

D.2 Design and conduct summary:
This trial was a double-blind and double-dummy (except for the use of moxifloxacin), randomized, placebo controlled, four-arm parallel group investigation in 188 healthy male subjects. The study consisted of an up to 28 day screening period followed by a 6-day treatment period in which subjects were confined to the study clinic.

Subjects were randomized to receive one of the following four treatment regimens (N=45 per group):

- 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.

Reviewer's comment: subjects assigned to moxifloxacin did not receive placebo on days 1-4 of dosing.

Moxifloxacin was used as a positive control for QT prolongation to assess assay sensitivity.

The supratherapeutic silodosin dose (24 mg) was selected to approximate the exposure that may occur in the target population under circumstances in which plasma silodosin concentrations may be significantly elevated (e.g. concomitant renal disease or use of potent CYP3A4 inhibitors). The silodosin 8 mg dose is the expected marketed dose.

The sponsor used a parallel trial design in light of the long half-life of silodosin and its primary metabolite, KMD-3213G. Five days of dosing with silodosin was required to achieve steady state.

Five 12-lead ECGs were obtained within a 1-3 minute window (providing five ECGs for each time point) at baseline (Day -1) and on Day 5 at the following time points: -0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, and 23.5 hours relative to dosing. These ECG data were used for the primary analysis of change from baseline in the time-matched, placebo-corrected QTcI interval. The five replicate QT/QTc measurements at each time point were average for each subject to determine the hourly mean QT/QTc values. Both time-matched and time-averaged analyses of change in QTcI were performed.

Plasma sampling occurred on Day 5 at -0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 23.5 hours relative to dosing for analysis of silodosin and its primary metabolites, KMD-3213G and KMD-3293.

The study schedule is shown in Figure D.1.

		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

From NDA 22-206, study SI05015 report, p. 17

Reviewer's comment: Orthostatic testing was performed at screening only.

All ECGs were read by a "limited number" of board-certified cardiologists. Readers were blinded to subject demographics, treatment study time, and study day. Inter- and intra-reader variability were assessed through re-read of a subset of ECGs and reported.

D.3 Study Population

A total of 188 subjects were randomized in approximately a 1:1:1:1 ratio in the study and 186 completed the trial. Two subjects (n=1 on silodosin 8 mg; n=1 on silodosin 24 mg) discontinued prior to completion. Subjects ranged in age from 18 to 45 years. The majority (67%) was white; 29% were black. Demographic characteristics were similar among the four treatment groups.

D.4 Eligibility Criteria

D.4.1 Inclusion Criteria

Healthy men aged 18 to 45 years with a BMI of 18-32 kg/m2 (inclusive).

D.4.2 Exclusion Criteria

1. Hypersensitivity or allergy to silodosin, moxifloxacin, or related compounds, or any of the inactive ingredients used in the study drug formulations.
2. Participation in any other investigational study within a period of 30 days prior to Day 1.
3. A first degree relative with Long QT Syndrome.
4. Abnormal 12-lead ECG, with clinically significant abnormalities of rate, rhythm, or conduction as follows:
    a. Heart rate <45 or >90 bpm, after a 5 minute supine rest;
    b. PR interval > 220 msec;
    c. QRS interval > 120 msec
    d. QTcF or QTcB (to be determined by Investigator) >430 msec
    e. QTcF < 300 msec;
    f. Any degree of fascicular block, bundle branch block, or intraventricular conduction delay;
    g. QRS and/or T wave that the Investigator judged to be unfavorable for consistently accurate QT measurements (e.g., indistinct QRS onset, low amplitude T wave, inverted or terminally inverted T wave, merged T/U waves, indistinct T wave offset, or prominent U wave that affects QT measurement);
    h. Neuromuscular artifact that could not be readily eliminated.
5. Were smokers, defined as having smoked in the past 3 months.
6. Had any disease or condition which, in the opinion of the investigator, might compromise the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, hepatic, or central nervous system; or other conditions that may interfere with the absorption, distribution, metabolism or excretion of study drug; or would place the subject at increased risk (e.g. pre-existing orthostasis).
7. Had the presence of an abnormal laboratory value which was considered clinically significant.
8. Had a positive screen for Hepatitis B, Hepatitis C, or HIV.
9. Had received any prescription or over-the-counter drug therapy (occasional use of

acetaminophen is permitted) within 15 days prior to Day 1, or 5 half-lives of the active substance, whichever was longer. Moderate and potent inhibitors of cytochrome P450 3A4 could not be taken within 30 days of Day 1. Herbal, nutritional, or dietary supplements were allowed according to investigator discretion.

10. Had consumed alcohol, caffeine-, xanthine-, or grapefruit-containing foods or beverages within 48 hours prior to Day 1 or during the confinement period.
11. Had a positive urine drug screen for cocaine, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opioids, ethanol, or phencyclidine.
12. Had a history of alcohol or drug abuse, illicit drug use or physical dependence to any chemical substance within the last six months.
13. Had donated ≥ 500 mL blood or blood products within 45 days prior to first dosing day.

D.5 Endpoints

D.5.1 Pharmacodynamic Analysis

D5.1.1 Primary

The primary endpoint was change from baseline in the time-matched, placebo-corrected QTcI interval for each treatment group. A single QT value for each time point was calculated from the mean of five replicate QT values at that time point.

A 90% confidence interval (CI) for the mean difference in time-matched, baseline- and placebo-corrected QTcI at Day 5 was determined for each treatment group. If the upper limit of the 90% CI for QTcI for a silodosin dose was less than 10 msec, it would be concluded that that silodosin dose did not prolong the QTc interval to a clinically significant degree.

A mixed ANCOVA model, with treatment group and corresponding ECG interval baseline value as a covariate, was used to compare the change from baseline between the placebo and two silodosin dose groups. A sample size of 45 subjects per group was planned to provide at least 80% power to shown that the upper limit of each 90% confidence interval would fall below 10 msec.

D.5.1.2 Secondary

Placebo-corrected, time-matched change from baseline along with 90% CI for QTcF, QTcB and QT interval were also calculated for each treatment group.

Additional secondary endpoints were placebo-corrected change from baseline in time-averaged QT, QTcF QTcB, QTcI, HR, PR and QRS intervals for silodosin 8 mg and 24 mg.

D.5.2 Pharmacokinetic Analysis

D.5.2.1 Concentration Data and Pharmacokinetic Parameters

Blood for pharmacokinetic sampling was obtained for all subjects on Day 5 of the trial at the following time points: 0.25 hour pre-dose - (trough level), and 1, 1.5, 2, 3, 4, 6, 8, 10, and 23.5 hours post-dose. Plasma concentration data for silodosin and each metabolite was used to calculate the following pharmacokinetic parameters: C_{max}, T_{max}, $AUC_{(0\text{-}1qc)}$, $AUC_{[0\text{-}inf]}$, Kel, $T_{1/2}$, and T_{max}.

D.5.2.2 PK/PD Correlation

A PK/PD analysis was planned to explore the relationship between the placebo- and baseline-corrected QTcI at each plasma concentration. A linear mixed effects model was planned to estimate the slope (β) and slope standard error of the plasma concentration relative to QTcI (placebo- and baseline-adjusted QTcI) interval for each analyte and silodosin dose. The expected maximum QTcI effect for each dose was planned to be estimated as a function of the slope and average maximum plasma concentration (Cmax) for each analyte and silodosin dose with 90% confidence intervals.

A PK/PD correlation analysis for moxifloxacin was not planned unless the pharmacodynamic results indicated that moxifloxacin failed as a positive control.

D.5.3 Safety Endpoints

Safety was assessed by vital sign (BP and pulse) measurement, 12-lead ECGs, adverse event review, and laboratory evaluation (hematology, serum chemistry, urinalysis).

D.6 Withdrawals, Compliance, and Protocol Violations

Of 188 subjects enrolled in the trial, 186 completed all protocol requirements. Two subjects voluntarily withdrew prior to receiving treatment. No subject withdrew due to an adverse event.

There were no major protocol deviations identified during the study.

Study medication was dispensed by clinic personnel.

D.7 Pharmacokinetic and Pharmacodynamic Analysis

D.7.1 Pharmacokinetic Analysis
Steady state exposure of silodosin and its primary metabolites are shown in Table D.1.

Table D.1 Steady State Exposure of Silodosin and Primary Metabolites, SI05014

	Treatment Group					
	Silodosin 8 mg N=47			Silodosin 24 mg N=44		
	Silodosin	KMD-3213G	KMD-3293	Silodosin	KMD-213G	KMD-3293
$AUC_{(0\text{-}1qc)}$ ng*hr/mL	259.4	908.4	310.4	801.5	2883.1	993.9
$AUC_{(0\text{-}inf)}$ ng*hr/mL	299.3	1828.3	389.8	899.2	4935.9	1150.2
C_{max} (ng/mL)	42.5	56.2	28.9	143.9	195.3	104.1
T_{max} (hour)	2.3	4.9	3.7	2.4	5.2	3.8
$T_{1/2}$ (hour)	7.6	18.5	8.8	6.6	14.9	7.0

Source: NDA 22-206 ser 000, SI05014 study report, Table 11.2.1-1

Reviewer's comment: In SI06008, a drug-interaction study of silodosin with ketoconazole, co-administration with ketoconazole increased silodosin AUC and Cmax by 3.2 and 3.8-fold, respectively.

Moderate renal impairment increased the AUC of total (bound and unbound) silodosin and KMD 3213G by 3.13 and 3.77-fold, respectively. Cmax values for total silodosin and KMD 3213G were higher by 3.11- and 1.92 fold, respectively.

Therefore, the supratherapeutic dose of silodosin used in this study appears to have achieved serum drug levels close to what would be observed in a "worst-case" scenario (e.g. renal impairment or co-administration with a potent CYP3A4 inhibitor).

D.7.2 Pharmacodynamic Analyses

D.7.2.1 Primary Comparison of Silodosin and Placebo (Time-Matched Analysis of QTcI)
At all time points measured, the upper bound of the two-sided 90% CI for the baseline- and placebo-corrected QTcI at Day 5 for silodosin 8mg and 24 mg was less than 10 msec. The upper bound of the 99% CI for moxifloxacin was greater than 10 msec at all time points which confirmed the study's assay sensitivity. Results are shown in Table D.2.

Table D.2. QTcI Placebo- and Baseline-Adjusted Confidence Intervals by Treatment Group and Time Point (Evaluable Population)

Time Point Post-Dose (Hour)	Treatment Group	Least-Squares Mean Difference of Change from Placebo in QTcI Interval (two-sided 90% Confidence Interval)*
-0.25 hr	Silodosin 8 mg	1.53 (-4.83, 7.88)
	Silodosin 24 mg	1.36 (-5.07, 7.79)
	Moxifloxacin	0.26 (-9.68, 10.20)
1 hour	Silodosin 8 mg	-0.04 (-6.39, 6.32)
	Silodosin 24 mg	-0.53 (-6.95, 5.90)
	Moxifloxacin	0.90 (-9.04, 10.84)
1.5 hr	Silodosin 8 mg	2.20 (-4.17, 8.56)
	Silodosin 24 mg	1.60 (-4.83, 8.03)
	Moxifloxacin	4.50 (-5.46, 14.45)
2 hr	Silodosin 8 mg	2.03 (-4.34, 8.39)
	Silodosin 24 mg	-2.23 (-8.66, 4.20)
	Moxifloxacin	
3 hr	Silodosin 8 mg	-0.18 (-6.56, 6.19)
	Silodosin 24 mg	-.20 (-6.64, 6.23)
	Moxifloxacin	6.29 (-3.68, 16.25)
4 hr	Silodosin 8 mg	0.94 (-5.42, 7.31)
	Silodosin 24 mg	-0.37 (-6.79, 6.06)
	Moxifloxacin	8.09 (-1.87, 18.05)
6 hr	Silodosin 8 mg	3.42 (-2.94, 9.78)
	Silodosin 24 mg	1.39 (-5.03, 7.82)
	Moxifloxacin	9.59 (-0.36, 19.55)
8 hr	Silodosin 8 mg	0.27 (-6.10, 6.65)
	Silodosin 24 mg	-2.86 (-9.30, 3.58)
	Moxifloxacin	6.91 (-3.05, 16.87)
10 hr	Silodosin 8 mg	0.20 (-6.17, 6.58)
	Silodosin 24 mg	-0.27 (-6.71, 6.16)
	Moxifloxacin	5.82 (-4.15, 15.80)
23.5 hr	Silodosin 8 mg	1.28 (-5.09, 7.65)
	Silodosin 24 mg	-0.58 (-7.03, 5.87)
	Moxifloxacin	1.81 (-8.15, 11.78)

* for moxifloxacin, a 99% confidence interval is presented

Source: NDA 22-206 ser 000, SI05014 study report, Tables 11.3.2-1 and 11.3.2-2

D.7.2.2 Secondary Comparisons of Silodosin and Placebo

D.7.2.2.1 Time-Averaged Analysis of QTcI
The placebo-corrected mean change from baseline in QTcI at Day 5 for silodosin 8 mg and 24 mg were -1.7 and 1.4 msec, respectively. For moxifloxacin, the mean change from baseline was 4.0 msec (expected 5 - 10 msec).

D.7.2.2.2 Time-Matched Analysis of QTcF, QTcB
At a single time point (6 hours post-dose), the upper limit of the 90% CI for the baseline and placebo-corrected QTcF at Day 5 for silodosin 8 mg and 24 mg was greater than 10 msec.

For QTcB, the upper limit of the 90% CI crossed 10 msec at nearly all time points for the 24 mg dose group and at six time points for the 8 mg silodosin group. Least squares mean change for QTcB and QTcF for moxifloxacin were not provided.

Results of both analyses are shown in Table D.3.

Table D.3 Placebo-Subtracted Least-Squares Mean Change from baseline in QTcF and QTcB (90% Confidence Intervals), SI05014

Time Point	Treatment Group	QTcF (two-sided 90% CI)	QTcB (two-sided 90% CI)
-0.25 hr	Silodosin 8 mg	2.32 (-3.20, 7.83)	3.46 (-3.04, 9.96)
	Silodosin 24 mg	1.61 (-3.97, 7.19)	1.87 (-4.70, 8.44)
1 hr	Silodosin 8 mg	2.03 (-3.49, 7.55)	4.29 (-2.20, 10.79)
	Silodosin 24 mg	1.65 (-3.93, 7.23)	6.33 (-0.24, 12.90)
1.5 hr	Silodosin 8 mg	3.45 (-2.08, 8.97)	4.90 (-1.61, 11.41)
	Silodosin 24 mg	2.99 (-2.60, 8.57)	7.20 (0.61, 13.78)
2 hr	Silodosin 8 mg	2.73 (-2.79, 8.26)	3.39 (-3.12, 9.90)
	Silodosin 24 mg	-0.37 (-5.96, 5.21)	3.49 (-3.09, 10.08)
3 hr	Silodosin 8 mg	2.70 (-2.84, 8.24)	2.13 (-3.46, 7.71)
	Silodosin 24 mg	2.13 (-3.46, 7.71)	7.59 (1.01, 14.17)
4 hr	Silodosin 8 mg	3.66 (-1.87, 9/18)	7.08 (0.57, 13.59)
	Silodosin 24 mg	2.18 (-3.40, 7.76)	6.29 (-0.28, 12.86)
6 hr	Silodosin 8 mg	**4.49 (-1.03, 10.01)**	**6.53 (0.02, 13.03)**
	Silodosin 24 mg	**4.63 (-0.95, 10.21)**	**10.30 (3.73, 16.87)**
8 hr	Silodosin 8 mg	1.31 (-4.23, 6.85)	**4.08 (-2.45, 10.61)**
	Silodosin 24 mg	0.00 (-5.59, 5.60)	**5.46 (-1.14, 12.06)**
10 hr	Silodosin 8 mg	1.08 (-4.47, 6.62)	1.91 (-4.62, 8.44)
	Silodosin 24 mg	2.06 (-3.52, 7.65)	7.42 (-0.83, 14.00)
23.5 hr	Silodosin 8 mg	2.46 (-3.07, 7.99)	3.85 (-2.67, 10.37)
	Silodosin 24 mg	0.76 (-4.84, 6.37)	2.50 (-4.11, 9.10)

Reviewer's comment: The IRTQT statistical reviewer performed an independent analysis of the electronically submitted ECG data from this study using QTcF. The ANCOVA model was used to compare the change from baseline between placebo and treatment groups, with treatment as a fixed effect and baseline QTc as covariates. By this analysis, the largest upper bounds of the 2-sided 90% CIs for the mean differences between silodosin and placebo in the time-matched QTcF change from baseline are below 10 ms for both the 8 mg and 24 mg treatment groups (Table D.4).

Table D.4 Point Estimates and 90% CIs corresponding to the Largest Upper Bounds for Silodosin (8 mg and 24 mg)

Treatment	Time (hour)	ΔΔQTcF and 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)

Source: IRTQT Consultant Review, dated April 16, 2008

D.7.3 Pharmacokinetic-Pharmacodynamic Relationships

A statistical model was used to explore the PK/PD relationship. 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. Results demonstrate no statistically significant correlation between plasma concentration and QTcI change at Cmax (as shown in Table D.5).

Table D.5 Pk/PD Correlation Analysis for Silodosin, KMD-3213G, and KMD-3293 Concentration by Treatment Group

Analyte/ Treatment Group	Slope (SE) relative to plasma concentration and QTcI	90% CI for slope	Expected max QTcI Effect	90% CI for max QTcI effect	p-value
Silodosin					
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					
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					
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	-1.056, 2.767	0.777

Source: NDA 22-206 ser 000, SI05014 study report, Tables 11.3.3-1, 2 and 3

D.8 Outlier Analysis

QTcI >500 msec

There were no QTcI readings >500 msec at baseline or during treatment for any dose group.

QTcI increase > 30msec and >60 msec

A similar percentage of silodosin and placebo subjects had QTcI changes from baseline between 30 and 60 msec. While no subject had >60 msec change from baseline on placebo, 3 silodosin subjects (1 on 8 mg; 2 on 24 mg) had this finding (Table D.6).

Table D.6 Outlier Analysis by Treatment Group, SI05014

Maximum QTcI change from baseline, msec	Placebo	Silodosin 8 mg	Silodosin 24 mg	Moxifloxacin
30 – 60 msec	10 (21.7%)	9 (19.6%)	15 (23.1%)	17 (36.2%)
>60 msec	0	1 (2.2%)	2 (4.5%)	1 (2.1%)

Source: NDA 22-206 ser 000, Table 14.2.1-12

D.9 ECG Morphology Analysis

New negative T wave changes were noted in 12.2% of subjects on placebo and in 8.7% and 0% respectively in the silodosin 8 mg and 24 mg dose groups. No subjects in any dose group developed new abnormal U waves, new Q waves, new 2nd or 3rd degree heart block, or new LBBB.

D.10 Safety Analysis

D.10.1 Extent of Exposure

Ninety-three subjects were exposed to at least one dose of silodosin 8 or 24 mg daily for 5 days. Ninety-one of these subjects received the full five days of therapy.

D.10.2 Adverse Events

More silodosin patients reported an adverse event than patients assigned to placebo or moxifloxacin (Table D.7). The most common adverse events among silodosin patients are shown in Table D.8. A dose-response relationship was observed for the following AE's: headache, orthostatic hypotension, fatigue, and diarrhea.

Table D.7 Incidence of Adverse Events by Treatment Group, Study SI05014

	Placebo N=46	Silodosin 8 mg N=48	Silodosin 24 mg N=45	Moxifloxacin N=47
Subjects with AEs	19 (41.3%)	26 (54.2%)	22 (48.9%)	14 (29.8%)

Source:

	Placebo	Silodosin 8 mg	Silodosin 24 mg
Retrograde ejaculation	0	8 (16.7%)	5 (11.1%)
Headache	3 (6.5%)	5 (10.4%)	7 (15.6%)
Nasal congestion	0	6 (12.5%)	2 (4.4%)
Orthostatic Hypotension	2 (4.3%)	3 (6.3%)	4 (8.9%)
Fatigue	1 (2.2%)	3 (6.3%)	4 (8.9%)
Diarrhea	0	1 (2.1%)	3 (6.7%)
Dizziness	0	2 (4.2%)	1 (2.2%)
Pharyngitis	0	2 (4.2%)	1 (2.2%)

Source: NDA 22-206 ser 000, SI05014 study report, Table 14.3.1-3

Reviewer's comment: Orthostatic vital signs were measured only at screening. Presumably, subjects with the adverse event of orthostatic hypotension reported symptoms consistent with postural hypotension (e.g. dizziness), but this is not explicitly stated in the study report.

D.10.3 Deaths and Serious Adverse Events

No deaths or serious adverse events occurred during the study.

D. 10.4 Vital Signs

No clinically significant difference in mean change from baseline to Day 5 in SBP or pulse was observed between silodosin and placebo groups (Table D.8).

Mean Change from baseline to Day 5 in SBP and Pulse by Treatment Group

	Placebo	Silodosin 8 mg	Silodosin 24 mg
SBP			
2.5 hour post-dose	1.2 (12.0)	-0.7 (8.5)	-1.0 (8.0)
8 hr post-dose	2.2 (9.7)	1.5 (7.3)	-0.9 (11.1)
16 hr post-dose	1.6 (9.3)	1.2 (7.6)	0.0 (8.9)
Heart Rate			
2.5 hours post-dose	6.6 (6.9)	5.6 (8.9)	4.5 (11.1)
8 hours post-dose	7.2 (6.8)	8.2 (6.5)	7.2 (11.8)
16 hrs post-dose	1.6 (6.3)	1.2 (7.5)	-1.2 (10.9)

Source: NDA 22-206 ser 000, SI05014 study report, Table 14.3.5-12

D. 10.4.1 Vital Sign Outliers

Two silodosin 8 mg subjects had an SBP reading <90 mmHg during treatment compared to none on placebo or on silodosin 24 mg.

Sub

Subject	Dosing Day and Time	SBP	DBP	Heart Rate
611	Day 4; 8 hours post-dose	84	60	71
674	Day 5; pre-dose	89	52	57

D.10.5 Orthostatic Testing

Orthostatic testing was performed at screening only and not during active treatment, so the effect of supra-therapeutic doses of silodosin on postural vital signs was not assessed during the study.

D.10.6 Laboratory Evaluation

No clinically significant changes in any laboratory parameter were observed from baseline to endpoint.

D.10.7 Summary

Results of this thorough QT study suggest that silodosin has no meaningful effect on QT interval or other ECG parameter.

Appendix E: PDE-5 Inhibitor DDI Study SI06002

"An open-label evaluation of the pharmacodynamic interaction of silodosin with sildenafil, tadalafil, and placebo."

Trial start date: October 17, 2006
Trial end date: November 22, 2006

E.1 Objectives:
Study objectives were to evaluate the orthostatic effects and safety of co-administration of a single dose of 100 mg sildenafil, 20 mg tadalafil, and placebo, when taken after 7, 14, or 21 daily doses of 8 mg silodosin in healthy target-aged male subjects.

E.2 Design and Conduct of the Study:
This was an open-label, randomized sequence, placebo-controlled, crossover study in 24 healthy male subjects age ≥45 years, including seven subjects ≥65 years. Eligible subjects received silodosin 8 mg once daily with food at breakfast time for three consecutive 7-day periods (total of 21 days). At the conclusion of each 7-day period, subjects was confined to the study clinic for approximately 12 hours during which a PDE- 5 inhibitor (100 mg sildenafil, 20 mg tadalafil, or placebo) was administered in the morning on an empty stomach and orthostatic blood pressure tests were performed at 0, 1, 2, 3, 4, 6, 8, and 12 hours post-dose. Adverse events were collected throughout the study. Upon discharge from the third 7-day period, a physical exam and a blood draw for clinical labs were performed.

Reviewer's comment: On the days of concomitant dosing with the PDE-5 inhibitor/placebo, study drug was administered on an empty stomach in the morning to simulate a "worst-case" scenario.

The recommended starting dose of sildenafil is 50 mg, with an increase to a maximum of 100 mg if needed. The recommended starting dose of tadalafil is 10 mg (dose range 5-20 mg).

A positive orthostatic test was defined by one or more of the following observations:

- *Decrease in SBP>30 mmHg*
- *Decrease in DBP >20 mmHg*
- *Increase in heart rate >20 bpm*
- *Symptoms upon change of position such as lightheadedness, fainting, blurring or temporary loss of vision, profound weakness, or syncope.*

E.3 Entry Criteria:
Inclusion criteria: