

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 22-206

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-206	Submission Date(s): 12/12/2007, 2/5/2008, 4/4/2008, 5/2/2008, 7/10/2008
Brand Name	Rapaflo
Generic Name	Silodosin
Reviewer	Doanh Tran, Ph.D.
Team Leader (Acting)	Sandhya Apparaju, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Watson
Relevant IND(s)	56,605
Submission Type	Original
Formulation; Strength(s)	Immediate release capsule, 4 and 8 mg
Indication	Benign prostatic hyperplasia (BPH)

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1 Executive Summary

1.1 Recommendation

The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 22-206 for silodosin acceptable from a Clinical Pharmacology perspective, provided the labeling comments are adequately addressed.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Silodosin is a new molecular entity in the class of α -adrenergic receptor (AR) antagonist (also known as alpha blocker). Silodosin has selectivity for the α_{1a} receptor relative to the α_{1b} receptor. Silodosin is metabolized into 2 major metabolites, namely KMD-3213G and KMD-3293 of which KMD-3213G may partly contribute to silodosin's pharmacologic activity.

Silodosin is being developed for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The NDA includes 19 Phase 1 pharmacokinetic (PK) studies, 1 Phase 1 pharmacodynamic study, 1 QT study, and 10 Phase 2 and Phase 3 studies. The Clinical Pharmacology section is also supported by 14 in vitro studies focusing mainly on metabolism and protein binding.

The Clinical Pharmacology section of the NDA includes assessments of absorption, distribution, metabolism, and excretion (ADME) properties, single and multiple-dose pharmacokinetics (PK), effect of age, hepatic impairment, renal impairment, food, and CYP3A4 inhibition on the PK of silodosin. Effect of silodosin on the PK of other drugs was evaluated in an in vivo interaction study with digoxin and in vitro CYP enzyme inhibition and induction studies.

The proposed dose is 8 mg capsule once daily with food. It is supported by PK studies and safety and efficacy trials using the same dose and dosing schedule.

Pharmacokinetics: To mimic the proposed administration instruction, pharmacokinetic studies of silodosin were generally conducted under fed state. Following single oral dose of 8 mg silodosin, silodosin reached a T_{max} (mean \pm SD, same hereafter) at 2.4 ± 1.1 hour. The AUC and C_{max} values were 290.6 ± 105.4 ng*hr/mL and 54.5 ± 26.0 ng/mL, respectively. The PK of silodosin was dose proportional between 4 and 8 mg. Silodosin exhibited linear PK up to doses of 24 mg. Steady state was reached after 7 days. There was little accumulation (~10%) of silodosin after 7 daily doses. The following table presents steady state PK parameters for silodosin and its major metabolites KMD-3213G and KMD-3293 following 7 daily doses of 8 mg silodosin in the target age population (mean 57.2 years old, range 45.0 – 70.9 years old).

Moiety	AUC ₀₋₂₄ , ng*hr/mL	C _{max} , ng/mL	T _{max} , hr	T _{1/2} , hr
Silodosin	373.4 \pm 164.94	61.6 \pm 27.54	2.6 \pm 0.90	13.3 \pm 8.07
KMD-3213G	1660.5 \pm 647.23	102.4 \pm 36.51	5.5 \pm 2.29	24.1 \pm 16.62
KMD-3293	373.0 \pm 141.72	34.3 \pm 12.58	4.1 \pm 1.29	13.1 \pm 7.10

Exposure to KMD-3213G is about 4.5 times that of silodosin. Since its relative binding affinity to the α_1 -AR is 1/8 that of silodosin, it may partly contribute the overall pharmacologic activity of silodosin.

The oral bioavailability of silodosin based on plasma concentration of silodosin was 32%. The bioavailability based on plasma concentration of metabolite KMD-3213G was higher (47%), suggesting the presence of first pass metabolism.

Silodosin is highly bound (~97%) to plasma protein, mainly to α 1-acid glycoprotein. Silodosin has an apparent volume of distribution of 49.5 L.

Silodosin is metabolized to a glucuronide conjugate, KMD-3213G, via UGT2B7 (UDP-Glucuronosyltransferase-2B7). Its second major metabolite, KMD-3293, is formed via alcohol dehydrogenase and aldehyde dehydrogenase. A number of minor metabolites are formed via CYP3A4 pathway. In vitro studies indicated CYP3A4 is not involved in the formation of the two major metabolites. However, co-administration with the CYP3A4 inhibitor ketoconazole significantly increased the exposure of silodosin and its 2 major metabolites.

Following oral administration of 8 mg [14 C]-silodosin, 54.9% of radioactivity was excreted in feces and 33.5% was excreted in the urine. 2.9% of the administered dose was excreted in the urine as the unchanged drug. Following intravenous administration, the total body clearance was 10 L/hour.

Pharmacodynamics: The primary endpoint in both phase 3 studies (SI04009 and SI04010) was the change from baseline to last observation carried forward (LOCF) in the international prostate symptom score (IPSS). The results provided by the Clinical reviewer, Dr. Olivia Easley, indicated that statistically significant reduction in IPSS score in silodosin treated patients compared to placebo was demonstrated in both phase 3 studies.

Effect on QT: A “thorough QT” study was conducted. The study administered silodosin 8 and 24 mg per day for 5 days. The review by the interdisciplinary review team for QT (IRT-QT) indicated that “no significant effect of silodosin was detected.”

Effects of intrinsic and extrinsic factors on the PK of silodosin:

Age: A phase 1 study was conducted to evaluate the effect of age. The results indicated that elderly men (mean age 69 years old) had higher silodosin AUC (15.3% higher) and longer $t_{1/2}$ (21% longer) compared to young men (mean age 24 years old). There was no change in silodosin C_{max} . Exposure to KMD-3213G was about 44% higher in the elderly. Since Phase 2 and Phase 3 safety and efficacy studies for silodosin were well represented by patients that were ≥ 65 years of age (42.8% or 384 out of 897 that were dosed at 8 mg silodosin once daily), no dosage adjustment is recommended for age.

Hepatic impairment: Moderate hepatic impairment decreased the AUC and C_{max} of total (bound and unbound) silodosin by 26%. However, unbound silodosin AUC and C_{max} increased by about 20 and 10%, respectively. Exposure to total and unbound KMD-3213G was lower in subjects with moderate hepatic impairment. No dose adjustment is needed for mild and moderate hepatic impairment. The effect of severe hepatic impairment was not evaluated.

Renal impairment: Moderate renal impairment increased the AUC of total (bound and unbound) silodosin and KMD 3213G by 3.13- and 3.77-fold, respectively. C_{max} values for total silodosin and KMD 3213G were higher by 3.11- and 1.92-fold, respectively, in subjects with moderate renal impairment. Slightly lower magnitude of difference was observed for unbound concentrations; Unbound AUC values were higher by 2.01- and 2.67-fold while C_{max} values were higher by 1.49- and 1.31-fold for silodosin and KMD 3213G, respectively. Based on safety data from phase 3 trials and the observed PK changes, a dose of 4 mg once daily is recommended for patient with moderate renal impairment. A review of safety data

by the Medical Officer, Dr. Olivia Easley indicated patients with mild renal impairment enrolled Phase 3 trials did not show an increased rate of adverse events compared to those with normal renal function. This reviewer concurs with the review team that no dosage adjustment is needed in patient with mild renal impairment. Due to lack of safety and PK information and the potential for significant increase in exposure, silodosin is not recommended for patients with severe renal impairment.

Race: A study to evaluate the effect of race on the PK of silodosin was not conducted. Cross-study comparison indicated that Japanese subjects on average had lower silodosin AUC and C_{max} and shorter $t_{1/2}$ than Caucasians and Blacks. However, the ranges of PK values overlapped between Japanese and Caucasian/Black populations.

Food: The effect of a high fat high calorie meal on the PK of silodosin was not evaluated. There were available data on the effect of low to moderate fat ($\leq 30\%$) and moderate calorie (~500 – 600 kcal) meals. The effect of a moderate fat moderate calorie meal was variable and decreased silodosin C_{max} by 18 – 43% and decreased AUC by 4.3 - 49% (across 3 studies). Patients should be cautioned to take silodosin with food as instructed to reduce risk of adverse events such as orthostatic hypotension. Phase 3 clinical trials were conducted with food.

CYP3A4 inhibition and induction: Co-administration with ketoconazole increased silodosin AUC and C_{max} by 3.2- and 3.8-fold, respectively. Ketoconazole coadministration increased both the AUC and C_{max} of KMD-3213G by 3.3-fold. However, silodosin's elimination $t_{1/2}$ was not changed. Because ketoconazole may potentially inhibit the transporter P-glycoprotein (P-gp) and silodosin is a P-gp substrate, it is not clear if the observed effects are due to inhibition of CYP3A4 or P-gp or both. Until this issue is resolved, labeling should encompass both pathways.

Due to risk of syncope at exposure equivalent to about 16 mg oral silodosin that was identified by the Medical Officer and the lack of available dosage strength <4 mg, silodosin is not recommended in patients taking strong inhibitors of CYP3A4.

The effect of moderate CYP3A4 inhibitors was not evaluated. Caution should be exercised when co-administering silodosin with moderate CYP3A4 inhibitors.

The effect of CYP3A4 induction on the PK of silodosin has not been evaluated.

P-glycoprotein inhibition: In vitro studies indicated that silodosin is a P-gp substrate. A drug interaction study with a strong P-gp inhibitor such as cyclosporine or itraconazole has not been conducted. As indicated above, a drug interaction study with ketoconazole, a CYP3A4 inhibitor that may also inhibit P-gp, showed significant increase in exposure to silodosin. Silodosin is not recommended in patients taking strong P-gp inhibitors.

Effects of silodosin on the PK of other drugs:

Digoxin: Co-administration of silodosin did not significantly affect the PK of digoxin, a P-gp substrate with narrow therapeutic index.

General enzyme activity: Effects of silodosin and its major metabolites KMD-3213G and KMD-3293 on enzyme inhibition and induction was examined in vitro. The results indicated that silodosin administration is not likely to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (i.e., all tested isoforms) or induce the activity of CYP1A2 and CYP3A4. By inference, induction of CYP2C8, CYP2C9, CYP2C19, and P-gp is also not expected.

Biopharmaceutics:

Formulations: Phase 3 trials for silodosin used 2 x 4 mg capsules for a total dose of 8 mg instead of a single 8 mg commercial capsule. This difference was adequately bridged with in vitro dissolution studies in 0.1 N HCL, pH 4.5 buffer, and pH 6.8 buffer. Some phase 1 and phase 2 studies used formulations that were different than the to-be-marketed (TBM) formulation. These formulations were either linked to the TBM formulation with in vitro dissolution data or addressed on a case-by-case basis.

Bioanalysis: Silodosin and its metabolites were measured in urine and plasma using validated assay and the assays were acceptable. Analytical methods for silodosin met the FDA recommended acceptance criteria of $\leq 20\%$ CV for precision and within $\pm 20\%$ relative error for accuracy at the lower limit of quantitation (LLOQ) and $\leq 15\%$ or within $\pm 15\%$, respectively, at all other concentrations. The precision and accuracy acceptance criteria for KMD-3213G and KMD-3293 LC/MS/MS assay conducted by _____ for Watson were expanded to $\leq 20\%$ and $\pm 20\%$ at all concentrations instead of only at the LLOQ. This deviation was accepted since these metabolites are expected to have a minor contribution to the overall effect of silodosin administration and the additional errors that may be introduced by expanding the acceptance criteria from 15% to 20% should not significantly alter the clinical interpretation of the safety and efficacy of silodosin. b(4)

An Optional Inter-Division Clinical Pharmacology briefing was held on July 31, 2008 with the following in attendance: Doanh Tran, Sandhya Apparaju, Dennis Bashaw, Hae-Young Ahn, George Benson, Olivia Easley, Lei Zhang, Gene Williams, John Lazor, Ping Zhao, Jian Wang, Chongwoo Yu, LaiMing Lee, Hyunjin Kim, and Isabelle Ragueneau-Majlessi.

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2 Question Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for silodosin?

Silodosin (also known as KMD-3213) is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

2.1.2 What are BPH and its current pharmacologic treatments?

BPH is a benign enlargement of the prostate. Common signs and symptoms include weak urine stream, difficulty starting urination, stopping and starting again while urinating, dribbling at the end of urination, frequent need to urinate, increased frequency of urination at night (nocturia), urgent need to urinate, and not being able to completely empty the bladder.

The symptoms associated with BPH are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by sympathetic nervous stimulation of α_1a adrenoceptors, which are abundant in the bladder neck, prostatic capsule, and prostatic urethra. Blockage of these receptors can cause smooth muscle in these areas to relax, resulting in an improvement in urine flow rate and a reduction in the symptoms of BPH. On the other hand, α_1b receptors are largely located on vascular smooth muscle and antagonist activity at these receptors may cause a relaxation of vascular smooth muscle and a decrease in the cardiac compensation mechanisms involved in regulating blood pressure.

Pharmacologic treatment of sign and symptoms of BPH includes alpha blockers and 5- α reductase inhibitors. As indicated above, alpha blockers relax muscles around the bladder neck and make it easier to urinate. Four alpha blockers are approved for treatment of BPH, namely terazosin (Hytrin), doxazosin (Cardura), tamsulosin (Flomax), and alfuzosin (Urotraxal). 5- α reductase inhibitors inhibit the conversion of testosterone (T) to dihydrotestosterone (DHT) and help shrink the size of the prostate gland. Two 5- α reductase inhibitors are approved for treatment of BPH, namely finasteride (Proscar) and dutasteride (Avodart). Combination of alpha blocker and 5- α reductase inhibitor also can be used (finasteride and doxazosin or dutasteride and tamsulosin).

2.1.3 What is silodosin?

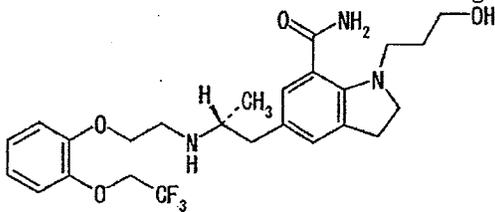
Silodosin's molecular structure is presented in figure 1. It includes 1 chiral center. The drug substance being reviewed in this NDA

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Silodosin is an α -adrenergic antagonist (also known as alpha blockers) that has selectivity for the α_1a receptor relative to α_1b receptors. As with other agents in the alpha blocker class, silodosin's mechanism of action is blockage of alpha receptors and cause relaxation of the smooth muscle in the prostate and bladder neck that results in improvement of urine flow and reductions in symptoms of BPH.

In vitro binding studies showed that silodosin's $\alpha_1a:\alpha_1b$ binding ratio is 162:1, indicating that silodosin has selectivity to the α_1a receptors. This selectivity suggests that silodosin has the potential to have positive effect on BPH symptom while minimizing the effect on blood pressure.

Figure 1: Structure of silodosin. Molecular weight 495.53.



2.1.4 What are the sponsor's proposed dosage and route of administration?

The proposed standard dose is 8 mg orally once daily with food. The sponsor proposed a lower dose of 4 mg once daily

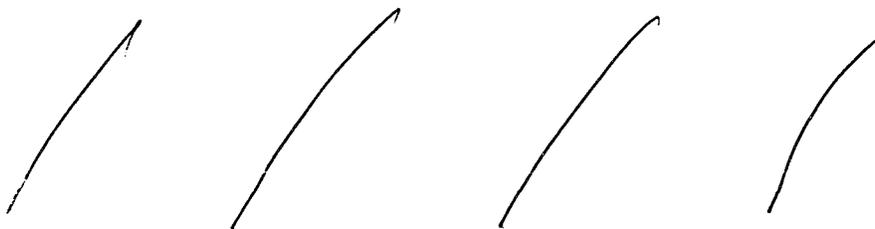
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2.2 General Clinical Pharmacology

2.2.1 What is the single dose PK of silodosin and its major metabolites KMD-3213G and KMD-3293? Single dose plasma PK for silodosin and its major metabolites following administration of the final 4 mg and 8 mg formulations manufactured by Watson was evaluated in study SI7004. The study enrolled 18 White and 4 Black young healthy males with mean (SD) age of 30 (8.2) years. To mimic the clinical use recommendation, silodosin was given with food (within 30 minutes after breakfast).

Table 1 shows a summary of silodosin PK parameters follow a single dose administration. There was high variability in AUC (36 – 45 %CV) and C_{max} (46 – 48 %CV). Doubling of the dose from 4 mg to 8mg approximately doubled the mean silodosin AUC and C_{max} . The mean silodosin Tmax were similar at approximately 2.3 and 2.4 hours for 4 mg and 8 mg doses, respectively. The mean $t_{1/2}$ values were 11.1 and 13.3 hours for 4 mg and 8 mg doses, respectively. There were insufficient data in some subjects that did not permit calculation of their $t_{1/2}$. There was high variability (121 %CV) in the silodosin $t_{1/2}$ values for the 8 mg dose. One subject (Subject ID SO7004-913) had a long calculated $t_{1/2}$ of 82.6 hours. This subject had a calculated $t_{1/2}$ of 23.5 hours on Day 7. If this subject was removed, the mean (SD) $t_{1/2}$ for the 8 mg dose would be 9.9 (2.75) hours.

Figure 2 shows the mean concentration time profile for silodosin. The mean concentrations rise to a single peak at 2 hours, then decline. Examination of individual concentration time profiles also :



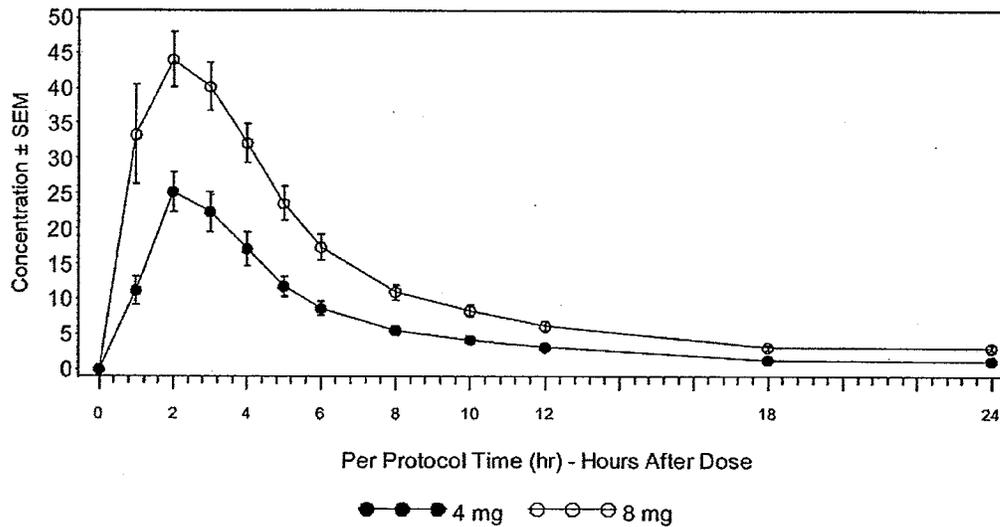
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Table 1: Summary of single-dose silodosin PK parameters (study SI7004). Data presented as mean (SD).

Parameter	4 mg (n=22)	8 mg (n=22)
AUC ₀₋₂₄ (ng*h/mL)	144.70 (65.73)	290.64 (105.43)
C_{max} (ng/mL)	28.72 (13.25)	54.50 (25.95)
Tmax (h)	2.3 (0.94)	2.4 (1.05)

$T_{1/2}$ (h)	11.1 (5.21)*	13.3 (16.09)**
* n=16, ** n=21		

Figure 2: Mean (SEM) silodosin plasma concentration (ng/mL) – single dose (study SI7004)



The PK parameters for major metabolites KMD-3213G and KMD-3293 following single-dose administration of 4 and 8 mg silodosin are presented in tables 2 and 3. After single-dose administration of silodosin, the AUC for metabolites KMD-3213G and KMD3293 were approximately 60 – 90% higher than AUC for silodosin parent compound. Their C_{max} values were lower than silodosin. Figures 3 and 4 show the mean concentration time profiles for these major metabolites.

Table 2: Summary KMD-3213G PK parameters following single-dose silodosin (study SI7004). Data presented as mean (SD).

Parameter	4 mg (n=22)	8 mg (n=22)
AUC ₀₋₂₄ (ng*h/mL)	233.73 (176.90)	513.63 (345.90)
C_{max} (ng/mL)	19.17 (8.49)	38.30 (16.01)
Tmax (h)	5.2 (3.35)	4.7 (1.29)
$T_{1/2}$ (h)	21.8 (24.91)*	13.0 (6.86)
*n=11		

Figure 3: Mean (SEM) KMD-3213G plasma concentration (ng/mL) following single dose silodosin – study SI7004

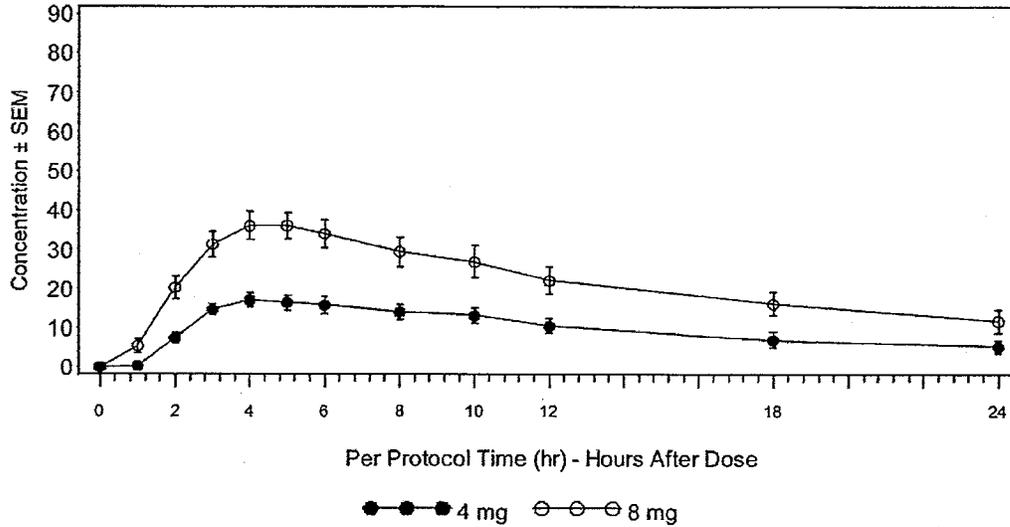
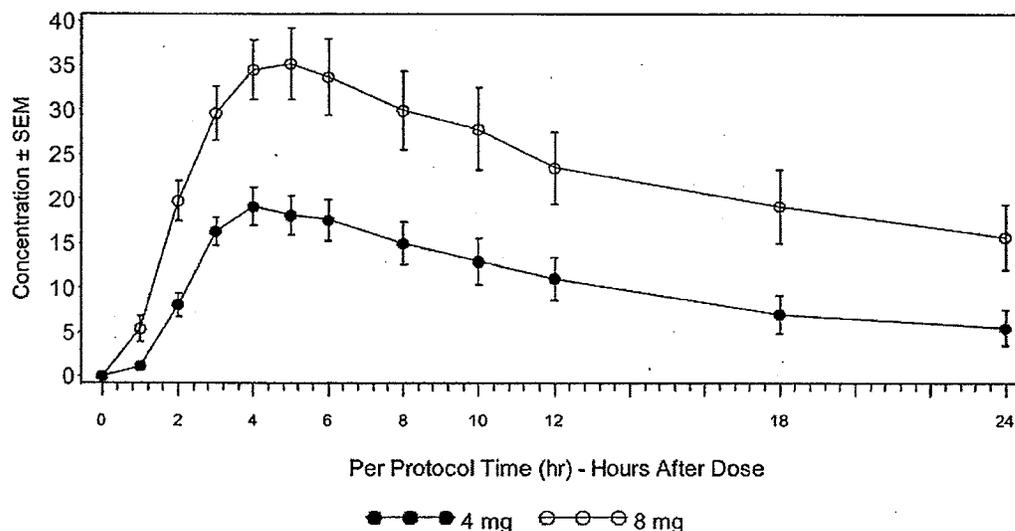


Table 3: Summary KMD-3293 PK parameters following single-dose silodosin (study SI7004). Data presented as mean (SD).

Parameter	4 mg (n=22)	8 mg (n=22)
AUC ₀₋₂₄ (ng*h/mL)	246.98 (215.55)	546.04 (393.69)
C _{max} (ng/mL)	20.75 (10.30)	39.78 (18.96)
T _{max} (h)	4.3 (1.67)	5.3 (4.30)
T _{1/2} (h)	19.1 (20.95)*	14.5 (8.61)**
*n=12, ** n=19		

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Figure 4: Mean (SEM) KMD-3293 plasma concentration (ng/mL) following single dose silodosin – study SI7004



2.2.2 What is the multiple dose PK of silodosin and its major metabolites KMD-3213G and KMD-3293?

SI06004 (multiple dose PK from the target age (≥ 45 years old) population):

Note: Study SI06004 is considered to be the primary PK study for silodosin because it was conducted in the target aged population. Study SI07004 provided single dose PK for Caucasian and Black populations as well as supporting multiple dose PK data.

Following oral administration of silodosin 8 mg once daily after breakfast for 7 days (study SI06004), the following mean (\pm SD) PK parameter values were obtained: $AUC_{0-24} = 373.4 \pm 164.9$ ng*hr/mL, $C_{max} = 61.6 \pm 27.5$ ng/mL, $T_{max} = 2.6 \pm 0.9$ hours, and $t_{1/2} = 13.3 \pm 8.1$ hours. Figure 5 shows the mean concentration time profile for silodosin and figure 6 shows a composite of the individual PK profiles. There was high inter-individual variability in the plasma silodosin concentrations. This study enrolled mostly White men of the target age range (mean age 57.2 years, age range 45.0 – 70.9 years).

Table 4 provides the calculated PK parameters for silodosin and major metabolites KMD-3213G and KMD-3293. Figures 7 and 8 show the mean PK profiles for the 2 major metabolites. Exposure (AUC) to KMD-3213G and KMD-3293 were approximately 450% and 100% of the parent silodosin. C_{max} for KMD-3213G and KMD-3293 were approximately 200% and 50% of the parent silodosin. The lower relative C_{max} values (compared to the relative AUC) for the metabolites is likely due to the time lag required for metabolism from silodosin, which is reflected in the delayed T_{max} of 5.5 and 4.1 hours for the metabolites compared to 2.6 hours for silodosin.

Table 4: Mean (SD) PK parameters following silodosin 8 mg once daily for 7 days in target age population (study SI6004), n=19 except * n=18

	AUC_{0-24} , ng*hr/mL	AUC ratio to silodosin	C_{max} , ng/mL	T_{max} , hr	$T_{1/2}$, hr

Silodosin	373.4 (164.94)	-	61.6 (27.54)	2.6 (0.90)	13.3 (8.07)
KMD-3213G	1660.5 (647.23)	4.45	102.4 (36.51)	5.5 (2.29)	24.1 (16.62)*
KMD-3293	373.0 (141.72)	1.00	34.3 (12.58)	4.1 (1.29)	13.1 (7.10)

*n=18 because t_{1/2} was not estimated in 1 subject

Figure 5: Mean (±SD) silodosin steady state plasma concentration time profile (SI6004)

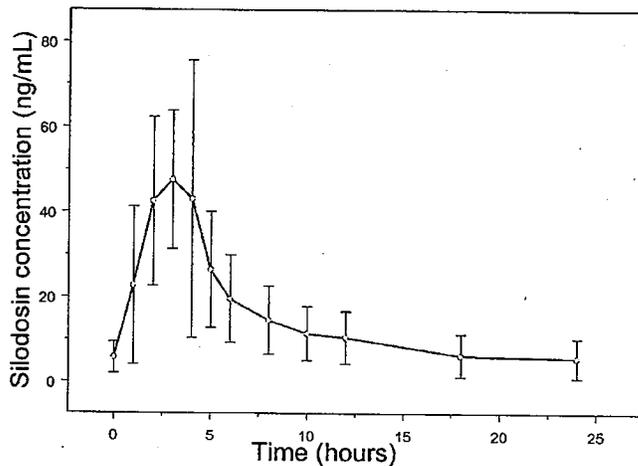
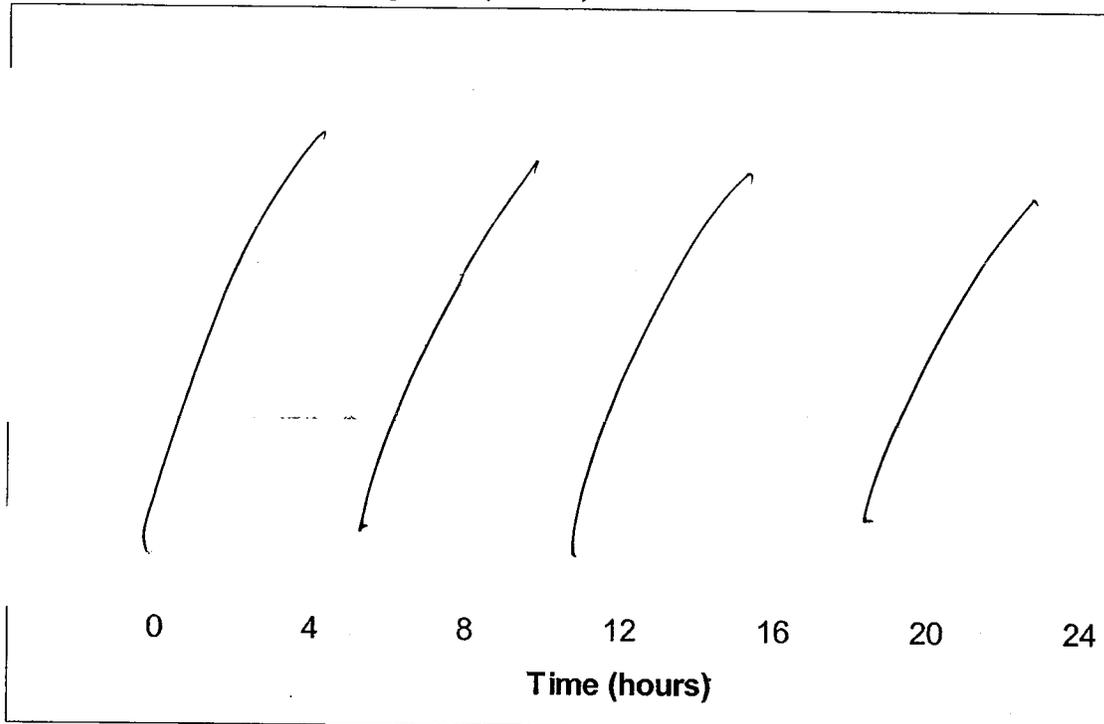


Figure 6: Silodosin individual PK profiles (SI06004)



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Figure 7: Mean (\pm SD) KMD-3213G steady state plasma concentration time profile (SI6004)

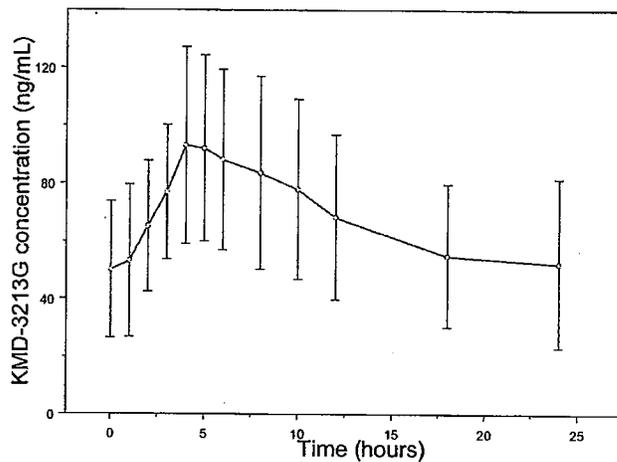
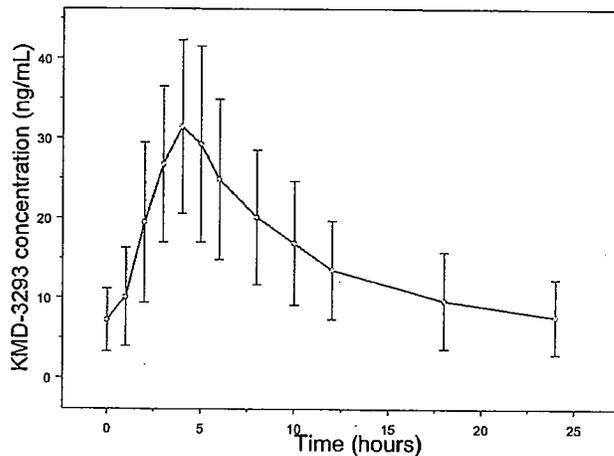


Figure 8: Mean (\pm SD) KMD-3293 steady state plasma concentration time profile (SI6004)



SI07004 (multiple dose PK from healthy young males (mean age 30 years):

Similar results were obtained in study SI07004 where 4 mg or 8 mg silodosin were administered once daily with food to young males (mean age 30 years, n=18 Whites and 4 Blacks). Table 5 provides the PK parameters. Compared to Day 1 data, there was little accumulation of silodosin by Day 7 (Table 5). KMD-3213G accumulated 2.6- to 2.8-fold. Interestingly, exposure to KMD-3293 was 30% - 40% lower on Day 7 compared to Day 1. It is not clear why exposure to KMD-3293 decreased with multiple dosing.

Table 5: Mean (SD) PK parameter following silodosin 4 mg or 8 mg once daily for 7 days in young males (study SI7004)

	AUC ₀₋₂₄ , ng*hr/mL	C _{max} , ng/mL	T _{max} , hr	T _{1/2} , hr	AUC ₀₋₂₄ ratio (Day 7/Day 1)
4 mg silodosin once a day for 7 days					
Silodosin	159.49 (69.96)	28.36 (12.40)	2.4 (0.73)	15.3 (7.46)	1.1

KMD-3213G	646.41 (464.40)	41.25 (19.95)	4.8 (1.94)	21.2 (12.47)	2.8
KMD-3293	173.64 (122.59)	17.07 (7.42)	3.8 (0.91)	12.0 (3.69)	0.7
8 mg silodosin once a day for 7 days					
Silodosin	297.34 (106.85)	51.14 (17.14)	2.5 (0.80)	14.4 (5.44)	1.0
KMD-3213G	1326.12 (801.11)	81.14 (37.00)	4.5 (1.44)	16.6 (7.32)	2.6
KMD-3293	321.22 (160.72)	32.32 (13.47)	3.7 (0.83)	10.8 (2.80)	0.6

Table 6 compares the AUC, C_{max} , and $t_{1/2}$ of silodosin across several studies conducted in the US and the UK. The results are generally consistent across studies. C_{max} was highest in study KMD3213-US012-99, which is expected since it was dosed under fasting conditions. Study SI05014 had low AUC and C_{max} values that may be partly due to its measurement on Day 5, which was not at steady state. $T_{1/2}$ varied across studies and the reason is not well understood.

Studies in Japanese generally showed lower $t_{1/2}$ values (see section 2.3.4). However, race may not be the cause of the lower $t_{1/2}$ in studies in Japanese, as $t_{1/2}$ also varies across these studies and overlapped with those observed in Caucasians and Blacks. A study in Caucasians (study KMD3213-UK01-97) showed mean $t_{1/2}$ of 3.7 – 5.5 hours in the dose range of 4 – 8 mg, with or without food.

Table 6: Silodosin PK parameters across several studies conducted in the US and the UK. Data presented as arithmetic mean (SD) unless indicated otherwise.

Study#	4 mg AUC	4 mg C_{max}	$T_{1/2}$	8 mg AUC	8 mg C_{max}	$T_{1/2}$
SI6004 – AUC 0-24 on day 7, with food				373.4 (164.94)	61.6 (27.54)	13.3 (8.07)
SI7004 – AUC ₀₋₂₄ on Day 7, with food	159.49 (69.96)	28.36 (12.40)	15.3 (7.46)	297.34 (106.85)	51.14 (17.14)	14.4 (5.44)
SI05010, AUC _{0-∞} , normal control, with food	194 (35.38)	35.0 (12.33)	9.3 (2.31)	327.8 (37.34)	46.8 (10.29)	9.0 (1.63)
306-UK, AUC _{0-∞} , with food	146 (48.6)	31.9 (8.83)	10.4 (3.67)			
SI6008, AUC _{0-∞} , with food				378.1 (168.5)	63.7 (22.8)	9.1 (5.5)
KMD3213-US012-99, solution of [¹⁴ C]KMD-3213, fasting,				325 (92)	77.3 (31.9)	12.1 (5.1)
SI05014 – AUC _{0-tqc} on Day 5, with food				259.4 (111.8)	42.5 (19.4)	7.6 (3.4)

2.2.3 What is the time to steady state for silodosin and its major metabolites?

Data from study SI6004 (in target age population) indicated that silodosin C_{trough} reached a plateau on Day 7 (C_{trough} concentrations of 4.6 ± 3.02 , 4.8 ± 2.61 , 5.7 ± 3.69 and 5.7 ± 4.69 on Day 5, 6, 7, and 8 [end of 7th dose interval], respectively), suggesting that steady state was likely reached at Day 7 for silodosin.

Calculated time to steady state based on 5 times the estimated $t_{1/2}$ supported this conclusion. Data across several studies in Caucasians and Blacks (table 6) showed mean silodosin $t_{1/2}$ of 7.6 to 15.3 hours, suggesting steady state should be reached in about 3 days. Additionally, data were available from study KMD-207, where Japanese subjects (n=12) were administered silodosin 6 mg twice daily for 6 days and predose samplings were obtained prior to each morning dose. These results indicated that steady state was reached in about 3 days for silodosin. Overall, data from studies SI06004 and KMD-207 indicate that steady state was reached within 7 days.

Steady state PK for the metabolite KMD-3213G was reached on Day 5 (study SI6004). The trough concentrations of KMD-3293 continually increased with each dose up to the last dose measured on Day 8 (Table 7), suggesting that steady state was not reached after 7 daily doses. The concentration data is variable and it is not clear if there was an increase as suggested by the trend increase in the mean concentration. Based on calculated $t_{1/2}$ of about 13 hours, it is likely that it was close to steady state by day 7 for KMD-3293.

Table 7: Trough concentrations (ng/mL) measured in the morning of indicated days.

Moiety	Day 5	Day 6	Day 7	Day 8
KMD-3213G	56.4 (25.59)	50.4 (25.57)	50.1 (23.67)	52.3 (29.25)
KMD-3293	6.7 (3.70)	6.9 (3.79)	7.2 (3.93)	7.6 (4.70)

2.2.4 What is the absolute bioavailability of silodosin?

Study KMD-308 evaluated the bioavailability of silodosin given as 4 mg oral dose and 2 mg iv infusion over 4 hours (n=11) in a single sequence crossover design. The dose normalized silodosin oral bioavailability relative to intravenous (IV) administration was $32 \pm 11\%$ when both routes were given under fasting conditions. The bioavailability based on AUC of metabolites KMD-3213G and KMD-3293 following oral versus IV administration of silodosin was about 47% and 45%, respectively. The higher oral bioavailability (45 – 47%) of the metabolites compared to the bioavailability of the parent silodosin (32%) suggests the presence of first pass metabolism. The fraction absorbed following oral dose of silodosin is 33.5% based urinary excretion data. The metabolite bioavailability data suggests that the fraction absorbed may be higher than 33.5%, potentially as high as 47%.

2.2.5 What are the protein binding and distribution properties of silodosin?

The volume of distribution after a single IV administration of 2 mg silodosin to healthy adult males was 49.5 L (Study KMD-308). In blood, most of silodosin is present in the plasma. Silodosin and its major metabolites KMD-3213G and KMD-3293 are highly protein bound in human plasma, with most being bound to α 1-glycoprotein. Details of protein binding and blood to plasma ratio are presented below.

Following silodosin oral administration (study KMD-309, n=7) the percent of protein binding of silodosin was $96.6 \pm 1.7\%$ (range 92.9 – 98.0%). The in vitro binding of silodosin to human plasma protein ranged from $94.6 \pm 0.4\%$ to $95.8 \pm 0.2\%$ at incubation concentrations of 100 to 500 ng/mL. Separate binding study with human serum albumin, gamma-globulins, and α 1-acid glycoprotein indicated that most of silodosin in plasma was bound to α 1-acid glycoprotein (study PK10153). The protein binding result from in vitro incubation was consistent with the observed binding in vivo.

KMD-3213G and KMD-3293 were also highly bound to human plasma. Following silodosin oral administration (study KMD-309, n=7) the percent of protein binding of KMD-3213G was $90.2 \pm 4.9\%$ (range 79.4 – 92.9%). KMD-3213G in vitro binding rate in human plasma was 91.2 ± 0.6 to 92.0 ± 0.9 at incubation concentration of 200 to 500 ng/mL. KMD-3213G binding to rat and dog plasma was lower at

approximately 70% and 60%, respectively. As with KMD-3213 parent compound, KMD-3213G in plasma also bound mainly to α 1-glycoprotein (study DMPK2003-0053).

KMD-3293 in vitro binding to human plasma was $91.9 \pm 0.4\%$ and $90.2 \pm 1.2\%$ at concentrations of 200 ng/mL and 500 ng/mL, respectively. KMD-3293 in plasma was also bound mainly to α 1-glycoprotein (study DMPK2004-0033).

Within the systemic circulation (i.e., blood), most of silodosin is present in the plasma. In vitro human blood to plasma ratio (R_B) of silodosin were 0.51 ± 0.04 and 0.55 ± 0.03 at the [14C]-silodosin concentrations of 24 ng equivalent/mL and 121 ng equivalent/mL, respectively ($n=3$ each). After taking into account the hematocrit value of each sample, the percentage of silodosin associated with blood cells was $2.2 \pm 3.8\%$ (range 0.0 – 6.6%) and $3.7 \pm 3.4\%$ (range 0.4 – 7.2%) at the [14C]-silodosin concentrations of 24 ng equivalent/mL and 121 ng equivalent/mL, respectively (Study PK10091). This is supported by data from mass balance study KMD3213-US012-99, which administered a single dose of 8 mg [14C]-silodosin, showing silodosin $AUC_{0-\infty}$ of total radioactivity from blood and plasma to be $1.27 \pm 0.318 \mu\text{g equivalent}\cdot\text{h/g}$ and $3.56 \pm 0.406 \mu\text{g equivalent}\cdot\text{h/g}$, respectively. Considering a normal hematocrit range of 36 – 50%, this in vivo data suggests there was little association of radioactivity in the blood with the cellular fraction of blood.

2.2.6 What are the metabolic pathways for silodosin?

Silodosin has 2 main plasma metabolites, KMD-3213G and KMD-3293. In vitro studies using human liver microsome and selective CYP inhibitors (furafylline (CYP1A1/2), coumarin (CYP2A6), sulfafenazole (CYP2C9), S-mephenytoin (CYP2C19), quinidine (CYP2D6), diethylthiocarbamate (CYP2E1), and ketoconazole (CYP3A4)) indicated that CYP3A4 is important in the metabolism of silodosin. Inhibitors of CYP2C8 were not evaluated. In vitro incubation with 2 μM ketoconazole, an inhibitor of CYP3A4, inhibited the metabolism of silodosin in human liver microsomes by 71% (Study KMD-OIR001). In vivo drug interaction study with ketoconazole showed increased exposure to silodosin, consistent with the in vitro observation. However, CYP enzymes do not appear to play a role in the formation of the major metabolites KMD-3213G and KMD-3293.

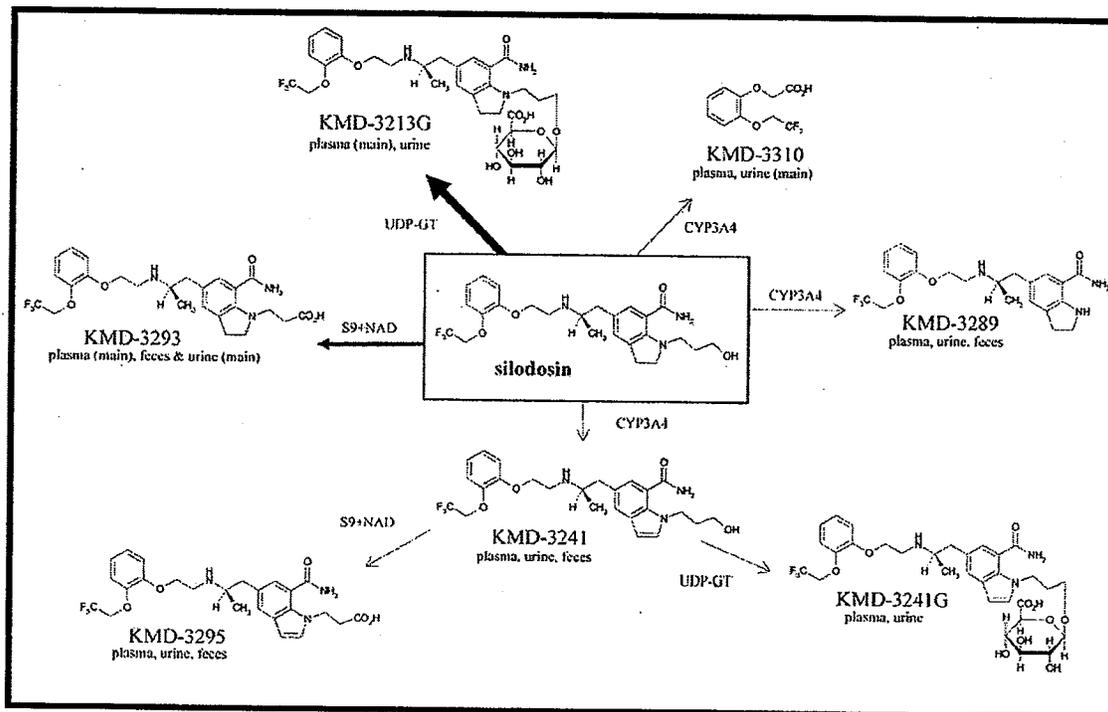
KMD-3213G is a glucuronide conjugate which was noted in the presence of UGT2B7 among a series of UGT isoforms (cDNA expressed _____ or human UGT1A1, 1A3, 1A6, 1A9, 1A10, 2B7, 2B15, and control microsomes) tested in vitro. [14C]KMD-3123G was formed only in the samples incubated with UGT2B7. The mean % of peak of KMD-3123G relative to total radioactivity was $1.69 \pm 0.22\%$, $5.08 \pm 0.33\%$, and $8.49 \pm 0.59\%$ after incubation ($n=3$) for 10, 30, and 60 min, respectively, indicating linear increase of formation up to 60 min (Study AE-3348).

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Metabolism to KMD-3293 appears to be mediated by alcohol dehydrogenase and aldehyde dehydrogenase. Incubations with S9 fraction and dehydrogenase substrates and inhibitors suggested that alcohol dehydrogenase and aldehyde dehydrogenase were involved in the formation of KMD-3293 from KMD-3213. Formation of KMD-3293 was not detected (LOQ = 0.1 μM) following incubation of silodosin in human liver microsomes (30 minutes, 100 μM silodosin), indicating CYP enzymes do not metabolize silodosin to KMD-3293 (Study PK10126).

Silodosin also metabolizes into a number of minor metabolites, including KMD-3295, KMD-3241, KMD-3289, KMD-3250, and KMD-3310. In vitro studies indicate metabolism to KMD-3241, KMD-3289, KMD-3250, and KMD-3310 is mediated by CYP3A4 since incubation with 2 μM ketoconazole significantly inhibited their formation. The proposed metabolic pathway is presented in Figure 9.

Figure 9: Proposed human metabolic pathway of silodosin and metabolites



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After oral dosing, KMD-3213G reaches exposure levels that are approximately 4.4 times (in mass unit) those of silodosin, while KMD-3293 exposure is similar to that of silodosin (study SI06004). Based on IC₅₀ values (molar unit), the binding affinity of KMD-3213G for the α 1A adrenergic receptor (AR) in rats is about 1/4 of silodosin's (study AL-2232-G). KMD-3213G has approximately half of the antagonistic effect on noradrenaline-induced contraction in isolated rat prostate tissue (Study KMD-1104). The binding affinity to human α 1-AR for KMD-3213G is 1/8 that of silodosin's. Based on this information, the effect of KMD-3213G in humans may be approximately 1/16 to 1/8 of silodosin's. Because the molecular weights are different for KMD-3213G (709.75) and silodosin (495.53), the 4.4 times higher KMD-3213G exposure based on mass unit is equivalent to 3.1 times in molar unit for purpose of comparing relative activity. Therefore, taking into account the approximately 3-fold higher exposure (molar unit) to KMD-3213G, the effect of KMD-3213G may be about 3/16 (19%) to 3/8 (38%) of the parent silodosin's or 16 – 28% of the total activity (from silodosin and KMD-3213G).

Less is known about KMD-3293. The binding affinity to human α 1A-AR subtype of KMD-3293 is 1/42 of silodosin's, suggesting that KMD-3293 does not significantly contribute to efficacy since exposure to KMD-3293 is similar to silodosin.

2.2.7 Is silodosin a P-glycoprotein (P-gp) substrate and/or inhibitor?

Silodosin is a P-gp substrate. The effect of P-gp inhibition on the PK of silodosin is not well understood. Silodosin at a dose of 4 mg twice daily did not affect the exposure of digoxin, a P-gp substrate. The following section provides additional details.

Study PK-03-002 evaluated the P-gp to membrane permeation of silodosin using vinblastine-treated P-gp over-expressed Caco-2 cell monolayers. The results indicated that there is directionality in the membrane

permeation of KMD- 3213 across Caco-2 cell monolayers with a basolateral to apical/apical to basolateral permeability ratio of 8.4. It was shown that the directionality was due to P-gp since it was abolished by increasing concentration of verapamil, a P-gp inhibitor. These data indicate a potential for P-gp inhibitors to increase the bioavailability of silodosin.

The effect of P-gp inhibition on the PK of silodosin is not completely understood. The sponsor conducted an in vivo drug interaction study with ketoconazole. Ketoconazole has the potential to inhibit P-gp in addition to CYP3A4. There was significant increase in silodosin AUC (3.2-fold) and C_{max} (3.8-fold) with concomitant administration of ketoconazole (see section 2.4.2). However, it is not known to what extent P-gp inhibition contributed to the observed increased silodosin concentration. Since strong P-gp inhibitors have the potential to increase silodosin's exposure and a 2-fold increase in silodosin exposure from the standard dose of 8 mg dose may predispose some patients to large drops in blood pressure and brief loss of consciousness, this reviewer recommends that strong P-gp inhibitors (e.g., cyclosporine, and itraconazole) should not be used concomitantly with silodosin.

The effect of silodosin on P-gp activity was not evaluated in vitro. However, sponsor conducted an in vivo drug interaction study with digoxin, a P-gp substrate with narrow therapeutic index. The results indicated that silodosin does not affect the PK of digoxin. See section 2.4.5 for more details.

Description of in vitro P-gp study:

The following is a brief description of the methods and results of the in vitro P-gp assessment (Study PK-03-002). Membrane permeation of [¹⁴C]-silodosin (10 μM) across Caco-2 cell monolayers were evaluated in both "Apical (A) to Basolateral (B)" direction and "B to A" direction after 21 day-culture period following inoculation or insert. Caco-2 cells were cultured in the medium added with vinblastine at 10 nM. Digoxin was used as positive control for the Caco-2 system.

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Apparent membrane permeation coefficient (P_{app}) of [¹⁴C]-silodosin in "B to A" direction (25.205×10^{-6} cm/s) was 8.4 times higher than that in "A to B" direction (3.007×10^{-6} cm/s), which suggests directionality of silodosin permeation across Caco-2 cell monolayers. In a separate experiment, this directionality was modified by the addition of verapamil, a known P-gp inhibitor. Without verapamil P_{app} in "B to A" direction (25.783×10^{-6} cm/s) was 10.4 times higher than that in "A to B" direction (2.477×10^{-6} cm/s). In the presence of verapamil, P_{app} in "B to A" direction decreased to 19.697×10^{-6} cm/s (with 10 μM verapamil), 11.734×10^{-6} cm/s (60 μM verapamil), or 11.356×10^{-6} cm/s (100 μM verapamil) dependent on verapamil concentration while "A to B" increased to 8.754×10^{-6} cm/s (10 μM), 15.613×10^{-6} cm/s (60 μM), or 14.001×10^{-6} cm/s (100 μM). As the verapamil concentration increased the difference between "B to A" and "A to B" disappeared. At 10 μM, same concentration of [¹⁴C]-silodosin, the difference was 2.2 times, and it was completely disappeared (0.8 times) at verapamil concentration over 60 μM.

Table 8: Effect of verapamil on [¹⁴C]-silodosin (noted as ¹⁴C-KMD-3213) permeation across P-gp over-expressed Caco-2 cell monolayers

Verapamil conc. (μM)	P_{app} ($\times 10^{-6}$ cm/s)		
	A to B direction	B to A direction	(B to A) / (A to B)
0 (control)	2.477 ± 0.160	25.783 ± 1.250	10.4
10	8.754 ± 0.752	19.697 ± 0.551	2.2
60	15.613 ± 0.810	11.734 ± 0.651	0.8
100	14.001 ± 0.357	11.356 ± 0.417	0.8

Values are mean ± S.D. of three monolayers.

A; Apical side, B; Basolateral side

Added ¹⁴C-KMD-3213 concentration was 11 μM.

Verapamil was added in both A and B sides.

2.2.8 What are the routes of excretion for silodosin?

Following oral administration of 8 mg [¹⁴C]-silodosin, the main route of excretion (based on measurement of radioactivity in study KMD3213-US012-99) was via the feces, with a mean of 54.9% excreted via this route through 240 hours post-dose. Excretion in the urine accounted for a mean of 33.5% of the administered activity through 240 hours post dose. The mean 0 – 240 hours recovery of radioactivity in excreta was 88.4%. After IV administration (4-hour infusion of 2 mg silodosin), the total body clearance of silodosin was 167 ± 33.8 ml/min (or 10.0 ± 2.03 L/hour) in Japanese males (Study KMD-308, n=12). {Review note: The sponsor's summary indicated a CL value of 167 L/hour. This was apparently due to an erroneous assumption by Watson that the CL results reported by Kissei were in the same L/hour unit used by Watson. The Kissei report used CL unit of ml/min}

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Results from study KMD3213-US012-99 showed 2.87 (±0.68) % of the administered dose was excreted in the urine as unchanged drug, indicating that silodosin was extensively metabolized. The mean (SD) 48 hour unchanged silodosin excretion rate was 1.68 (0.86) % following a single 8 mg dose in healthy Caucasian males (healthy controls in hepatic impairment study SI05010), consistent with the results from the above [¹⁴C]-silodosin study. Similarly, in Japanese subjects the mean 48 hours silodosin urinary excretion rate ranged from 2.1 to 4.3% following single dose and 2.7 to 4.0% after 7-day repeated oral dosing in Japanese subjects (Studies 95283, 98363, 95284, and 98364). {Review note: the sponsor's calculation of the fraction excreted in urine in the report for study SI05010 was off by 1 order of magnitude higher, i.e., 16.8% instead of 1.68%}

2.2.9 What design features of PK and clinical efficacy trials are used to support dosing?

The safety and efficacy of silodosin was supported primarily by two phase 3 studies (studies SI04009 and SI04010). Both studies had a similar design. They were multi-center, double-blind, parallel-group, placebo-controlled studies. Approximately 230 patients per treatment group were randomized to each treatment (silodosin or placebo). Each study was comprised of two periods, a 4-week placebo run-in period and a 12-week dosing period. Patients were randomized to receive either 8 mg silodosin or placebo once daily. They were instructed to take each dose with food, same as that being proposed for clinical use.

The results of the phase 3 studies indicated that silodosin was effective in decreasing the primary Clinical endpoint of international prostate symptom score (IPSS). Tables 9 and 10 (provided by the Clinical reviewer, Dr. Olivia Easley) show that a statistically significant decrease in IPSS was achieved in both phase 3 studies SI04009 and SI04010.

Table 9: Change from baseline in IPSS total score by modified intent to treat (mITT) population, study 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	

Table 10: Summary of Change from Baseline in IPSS Total Score by Treatment Group and Visit (mITT), SI04010

Visit	Statistic	Placebo N=229	Silodosin N=233
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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	

Pharmacokinetic studies indicated that the 8 mg dose is bioavailable. Food decreased silodosin's C_{max} (see section 2.4.1) and potentially minimizing the risk of orthostatic hypotension. All phase 2 and 3 studies administered silodosin with food, thus the safety of the increase silodosin C_{max} when patients take silodosin on an empty stomach may not be captured in these studies. Additionally, the maximum food effect using a standard high fat, high calorie meal was not evaluated and therefore the maximum increase in C_{max} due to administration on an empty stomach is not known. Because the proposed dosage and administration instruction is identical to that used in the phase 3 trials, the proposed administration with food is acceptable. However, the patients should be informed of the potential increased risk of hypotension and fainting due to an increase exposure to silodosin if they don't take silodosin with food.

2.2.10 What are the characteristics of dose-response relationship? Was there an evaluation of dose-response?

A phase 2 dose finding study (study US021-99) evaluated doses of 4 mg (n=88 patients) and 8 mg (n=90 patients) on a once daily schedule. The results indicated that there was slightly greater change in American Urologic Association (AUA) symptom index at end of study in the 8 mg group vs. 4 mg group (mean (SD) change from baseline of -6.8 (5.8) and -5.7 (5.5), respectively). No apparent difference was observed between the dose groups at earlier time points. Slightly higher baseline subtracted peak urine flow rate was observed in the 8 mg dose group compared to 4 mg dose group.

In this study, the incidence of retrograde ejaculation (15.6% and 11.4%), ejaculation failure (11.1% and 9.1%), and erectile disturbance (3.3% and 2.3%) were higher in the 8 mg dose group compared to the 4 mg dose group. No patient in the placebo arm reported these adverse events. These results suggest an apparent dose-response relationship for efficacy and safety. However, this is a small phase 2 study and the data is not considered conclusive. Separately, the limited availability of PK data (n=3 for 8 mg group and n=4 for 4 mg group) did not permit assessment of exposure-response.

The two phase 3 studies (studies SI04009 and SI04010) administered only a single dose level of 8 mg once daily and do not permit an evaluation of dose-response relationships. For assessment of exposure-response, sparse PK sampling was performed in Phase 3 study SI4009. However, the data collected (a single PK sampling at 2 – 6 hours post dose after the 1st dose and at week 4) was not useful for assessment of exposure response due to the large collection window. No population PK model was developed by sponsor. Sponsor indicated that a linear regression analysis of plasma silodosin (using this set of data) did not show a correlation with change in IPSS. There was an apparent trend of increasing drug concentration with mild and moderate renal impairment. This is consistent with the increase in silodosin concentration in patients with moderate renal impairment observed in study KMD-309. However, the magnitude of change in this study is difficult to interpret due to the uncontrolled collection time within a large time window.

2.2.11 What is the dose-concentration relationship for silodosin immediate release capsules?

This section addresses the dose proportionality between the proposed dose ranges of 4 mg to 8 mg once daily. Additional discussion is provided to address the Sponsor's claims of linear PK over the range of 0.1 – 48 mg.

Dose proportionality of 4 and 8 mg silodosin once daily was evaluated in study SI7004 using a crossover design. The ratio of dose normalized AUC₀₋₂₄ and C_{max} geometric means on Day 1 and Day 7 were similar for silodosin, KMD-3213G, and KMD-3293 (see Table 11), indicating dose proportionality in the range of 4 – 8 mg/day.

Table 11: Ratio of dose normalized geometric means (8 mg vs. 4 mg) for AUC₀₋₂₄ and C_{max} following administration of 8 mg and 4 mg capsules of Silodosin once a day for 7 days (Study SI7004).

	Ratio of dose normalized AUC ₀₋₂₄		Ratio of dose normalized C _{max}	
	Day 1	Day 7	Day 1	Day 7
Silodosin	1.05	0.96	0.96	0.93
KMD-3213G	1.27	1.12	1.03	0.99
KMD-3293	1.12	1.00	0.95	0.95

The thorough QT study SI05014 obtained PK data on 8 and 24 mg silodosin (total daily dose) after 5 days of dosing. This study used a parallel group design but has a large sample size of n=47 for the 8 mg dose and n=44 for the 24 mg dose. The mean (SD) AUC_{0-tlqc} values were 259.4 (111.8) and 801.5 (266.4) ng*h/mL for the 8 mg and 24 mg doses, respectively. The mean silodosin AUC increased 3.1-fold with a 3-fold increase in dose from 8 mg to 24 mg. Mean C_{max} values increased 3.4-fold. The exposure to silodosin appears to be dose proportional in the range of 8 – 24 mg.

Study SI05008 evaluated PK in small parallel groups (n=5/group) of subjects receiving doses of 16, 24, 32, 40, or 48 mg silodosin following a specific titration scheme (Table 12). Limited PK samplings were obtained at predose, 1, 2, 3, 4, 5, 6, and 24 hours postdose relative to the last dose given. Because of the small sample size and the titration scheme, the sponsor indicated that quantitative analysis was not performed on the PK data. The sponsor provided the mean PK profiles for each dose group and suggested that the profiles appear to demonstrate linear PK over the range of 16 – 48 mg. No PK parameters were calculated. This reviewer does not concur that linear PK has been demonstrated over this range. The study has small sample size and used a parallel study design and a conclusive assessment of dose proportionality can not be made.

Table 12: Dosing schedule for study SI05008

	D1		D2		D3		D4		D5		D6		D7		D8		D9		D10		
	AM	PM	AM	PM																	
16 mg Group	8	8	16	8	16	8	16	8	24	8	24	8	24	8	24	8	24	8	24	8	24
24 mg Group	8	8	16	8	24	8	24	8	24	8	24	8	24	8	24	8	24	8	24	8	24
32 mg Group	8	8	16	8	24	8	32	8	32	8	32	8	32	8	32	8	32	8	32	8	32
40 mg Group	8	8	16	8	24	8	32	8	40	8	40	8	40	8	40	8	40	8	40	8	40
48 mg Group	8	8	16	8	24	8	32	8	40	8	48	8	48	8	48	8	48	8	48	8	48
56 mg Group	8	8	16	8	24	8	32	8	40	8	48	8	56	8	56	8	56	8	56	8	56
64 mg Group	8	8	16	8	24	8	32	8	40	8	48	8	56	8	64	8	64	8	64	8	64

Overall, dose proportionality was demonstrated for 4 and 8 mg silodosin once daily. Silodosin appears to exhibit linear PK at doses up to 24 mg. Linearity at higher doses has not been demonstrated.

2.2.12 What is the effect of silodosin on QT interval prolongation?

The effect of silodosin on QT interval prolongation was evaluated in study SI05014 using silodosin 8 mg silodosin 24 mg (total daily dose) or placebo for 5 days according to the schedule below. The 8 mg dose group was given as once daily with breakfast while the 24 mg dose group was initially given in two equally divided doses and gradually shifted to just a once daily with breakfast regimen on Day 4.

Table 13: Dosing schedule for study SI05014

Regimen	Day 1		Day 2		Day 3		Day 4		Day 5	
	AM	PM								
Silodosin 8 mg	2S, 1P	3P	2S, 2P	2P	2S, 3P	1P	2S, 4P	NA	2S, 4P	NA
Silodosin 24 mg	3S	3S	4S	2S	5S	1S	6S	NA	6S	NA
Placebo	3P	3P	4P	2P	5P	1P	6P	NA	6P	NA
Moxifloxacin 400mg	NA	NA	NA	NA	NA	NA	NA	NA	1M	NA

S=silodosin 4 mg capsule

P=placebo capsule

M=moxifloxacin 400 mg tablet

Moxifloxacin 400 mg was administered as a single dose on day 5 to establish assay sensitivity. The final study report was reviewed by the interdisciplinary review team for QT (IRT-QT) (see review in DFS was signed off on 4/16/2008). The following conclusions were provided by the IRT-QT team:

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

The following findings were reported by the IRT-QT team:

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

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

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

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

The IRT-QT review also reported the following PK parameters (mean \pm standard deviation) following daily doses of silodosin for 5 days.

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

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

2.3 Intrinsic Factors

Review Note: the effect of gender was not considered since BPH only occurs in males and all PK studies were conducted in males.

2.3.1 What are the effects of age on silodosin PK?

The effect of age on silodosin PK was evaluated in study KMD 105. This study administered a single dose of silodosin 4 mg at 30 minutes after breakfast to 2 groups of Japanese male subjects, namely young and elderly. The young male group included 9 men with mean (±SD) age of 24.2 ± 3.1 years and CLcr (creatinine clearance) of 102.1 ± 12.3 mL/min. the elderly male group included 12 men with mean (±SD) age of 69.3 ± 3.7 years and CLcr of 79.7 ± 9.7 mL/min.

Table 14 shows the silodosin PK parameters in young and elderly Japanese males. The AUC₀₋₂₄ (111.5 ± 35.7 ng*h/mL) and C_{max} (20.49 ± 6.52 ng/mL) values in the young Japanese males in study KMD-105 were 23% and 29%, respectively, lower than that observed following a single 4 mg silodosin dose in young Caucasian and Black males (see section 2.2.1). However, considering the high inter-subject variability and variability among studies using subjects from the same race, the slightly lower values observed in this study of Japanese subjects should not exclude it from being used to assess the effect of age on silodosin PK in this study.

Table 14: Mean (SD) silodosin PK parameters following administration of a single dose silodosin 4 mg to elderly and young males

Parameter	Elderly	Young
AUC ₀₋₄₈ (ng*h/mL)	138.17 (52.48)	120.79 (38.55)
C _{max} (ng/mL)	21.80 (11.57)	20.49 (6.52)
T _{1/2} (h)	10.51 (4.00)	8.74 (3.06)

There were little differences in the silodosin PK between young and elderly groups. There were slight increases in AUC (15.3% increase) and t_{1/2} (21% increase). There was no change in C_{max} (1.2% decrease).

For metabolite KMD 3213G, there was no difference in C_{max} (42.74 ± 13.15 ng/mL in elderly compared to 42.54 ± 18.93 ng/mL in young males). KMD-3213G AUC_{0-48hrs} increased by about 44% (973 ± 445 ng*h/mL vs. 675 ± 340 ng*h/mL) and t_{1/2} increased by about 58% (16.76 ± 8.72 hours vs. 10.58 ± 4.28 hours) in the elderly. The higher exposure observed in elderly men may not significantly affect the safety and efficacy profile of silodosin in this population since KMD-3213G is estimated to contribute only about 16 to 28% of the total activity. Furthermore, safety data for US phase 2 and 3 trials (phase 2 double blind study KMD3213-US021-99, phase 3 double blinds studies SI04009 and SI04010, and phase 3 open-label safety study SI04011) included 42.8% of patients (384 out of 897 that were dose at 8 mg once daily) that were ≥ 65 years of age and 10.7% (96 out of 897) that were ≥ 75 years of age, indicating that the elderly population was well represented in the safety population.

Based on the above data, this reviewer recommends no dosage adjustment for age.

2.3.2 What are the effects of hepatic impairment on silodosin PK?

Study SI05010 evaluated the effect of moderate hepatic impairment (Child-Pugh score of 7-9) on silodosin PK. This study enrolled 18 males (9 normal control and 9 subjects with moderate impairment). The control group was matched for age, weight, sex (all males), race (all Whites), and smoking status. Each subject was given a single dose of silodosin 4 mg after breakfast in period 1 and intensive PK samplings were obtained for 7 days post dose. All patients tolerated the 4 mg dose and were given a single dose of silodosin 8 mg after breakfast in period 2.

Small differences in PK were observed between normal subjects and subjects with moderate hepatic impairment. The ratio of the AUC geometric means from subjects with hepatic impairment versus controls was 0.74 for both 4 and 8 mg doses. The ratios of the C_{max} geometric means were 0.63 and 0.74 for the 4 mg and 8 mg doses, respectively (Table 15). The data indicate that there was a slight decrease in silodosin AUC and C_{max} in subjects with moderate hepatic impairment. Renal clearance appeared to be higher in subjects with hepatic impairment compared to controls (724 ± 188 mL/h versus 414 ± 230 mL/h) and may have partly contributed to the overall lack of change in silodosin exposure in subjects with moderate hepatic impairment. No dosage adjustment is recommended for patients with mild or moderate hepatic impairment.

The sponsor also provided ratios of the arithmetic means for unbound silodosin concentration and total and unbound metabolites KMD-3213G and KMD-3293 concentration. These data are consistent with the conclusion that there was not a large increase in exposure to silodosin or its major metabolite in patients with moderate hepatic impairment. Tables 16 and 17 show the ratio of the arithmetic means of the total and unbound plasma concentrations in subjects with moderate hepatic impairment versus normal controls. The data indicated a trend of slight decrease in total silodosin but a slight increase in unbound silodosin in subjects with moderate hepatic impairment. Exposure of metabolites KMD-3213G and KMD-3293 were lower in subjects with hepatic impairment.

Table 15: Mean (SD) total silodosin PK parameters in patients with moderate hepatic impairment and controls and the calculated ratio of geometric mean and/or ratio of arithmetic means (study SI05010).

Silodosin dose	Silodosin PK parameter	Moderate hepatic impairment (H)	Normal control SILODOSIN	Ratio of geometric means (H vs. C)	Ratio of arithmetic means (H vs. C)
4 mg	AUC _{0-∞} (ng*h/mL)	151.4 (54.42)	194.0 (35.38)	0.74	0.78
	C _{max} (n/mL)	24.8 (12.16)	35.0 (12.33)	0.63	0.71
	T _{max} (h)	1.8 (0.83)	2.0 (0.87)	NC	0.9
	T _{1/2} (h)	8.2 (2.28)	9.3 (2.31)	NC	0.9
8 mg	AUC _{0-∞} (ng*h/mL)	249.6 (66.92)	327.8 (37.34)	0.74	0.76
	C _{max} (n/mL)	36.8 (16.97)	46.8 (10.29)	0.74	0.79
	T _{max} (h)	2.6 (0.88)	2.7 (0.87)	NC	1.0
	T _{1/2} (h)	11.0 (3.63)	9.0 (1.63)	NC	1.2

NC=not calculated; sample size were 8 – 9 for all parameters

Table 16: ratios of plasma PK parameters (total concentrations) between moderate liver impairment subjects and controls.

Total drug concentration		4 mg Ratio	8 mg Ratio
KMD-3213G	AUC _{0-∞}	0.8	0.8
	C _{max}	0.7	0.6
	T _{max}	1.0	0.9
	T _{1/2}	0.9	1.4
KMD-3293	AUC _{0-∞}	0.7	0.6
	C _{max}	0.6	0.6
	T _{max}	1.0	0.9
	T _{1/2}	1.1	1.1

Table 17: Ratios of plasma PK parameters (unbound concentrations) between moderate liver impairment subjects and controls.

Unbound drug concentration		4 mg Ratio	8 mg Ratio
Silodosin	AUC _{0-∞}	1.3*	1.2
	C _{max}	1.0	1.1
	T _{max}	0.8	1.3
	T _{1/2}	Insufficient data	1.2
KMD-3213G	AUC _{0-∞}	0.20*	0.5
	C _{max}	0.3	0.9
	T _{max}	1.5	1.3
	T _{1/2}	Insufficient data	0.6
KMD-3293	AUC _{0-∞}	0.7	0.8
	C _{max}	0.8	0.9
	T _{max}	0.8	1.1
	T _{1/2}	0.7	0.7

* = AUC_{0-72 hours}

The sponsor did not evaluate the effect of severe hepatic impairment on the PK of silodosin. Inference of the effect of severe hepatic impairment can not be made with the available data from subjects with moderate hepatic impairment. Therefore the effect of severe hepatic impairment on the PK of silodosin is not known.

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2.3.3 What are the effects of renal impairment on silodosin PK?

The effect of moderate renal impairment (n=6, subjects had CLcr of 27, 32, 33, 46, 48, and 49 ml/min, respectively) on silodosin PK was evaluated in study KMD 309. This was a single-dose (4 mg) study in Japanese men under fasting conditions. Relative to normal controls (n=7), total (bound + unbound) AUC_{0-48h} in subjects with moderate renal impairment (n=6) were higher by 3.13- and 3.77-fold for silodosin and KMD 3213G, respectively. C_{max} values were higher by 3.11- and 1.92-fold for silodosin and KMD 3213G, respectively, in subjects with moderate renal impairment (Table 19). Slightly lower magnitude of difference was observed for unbound concentrations. Unbound AUC_{0-∞} values were higher by 2.01- and 2.67-fold while C_{max} values were higher by 1.49- and 1.31-fold for silodosin and KMD 3213G, respectively (Table 20). No serious adverse events were reported in this study.

There were several confounding factors in this study. One confounding factor was that the control subjects were not matched for body weight or age. Enrolled subjects with moderate renal impairment were older and had slightly lower body weight (Table 18). Results from study KMD-105 (see section 2.3.1) indicated that the age difference should not contribute to the observed higher exposure in subjects with moderate renal impairment in this study. The effect of the difference in body weight is not known. However, it is unlikely that the slightly lower mean body weight would significantly contribute to the difference observed in this study.

Another confounding factor of this study was that it was conducted in Japanese and its applicability to the US population is not clear. Cross-study comparison indicated Japanese subjects generally have lower silodosin AUC and C_{max} and shorter $t_{1/2}$ than Caucasians, but the ranges of observed PK values for the races overlapped each other (see section 2.3.4). The ratio of exposure to metabolite KMD-3213G versus silodosin was generally slightly higher in Japanese subjects, but the ranges also overlapped. Comparisons to other races are not available. Since the objective of this study is to evaluate the relative change in exposure (as opposed to absolute differences), this reviewer believes that this study is acceptable for the evaluation of the relative PK of silodosin in subjects with moderate renal impairment and normal controls.

A review of the safety of patients enrolled in phase 2 and phase 3 trials who had moderate renal impairment (n=21) by the Clinical reviewer showed a higher incidence of dizziness and orthostatic hypotension (see Clinical review by Medical Officer, Dr. Olivia Easley). One patient with moderate renal impairment experienced the serious adverse event of syncope on the second day of treatment with the 8 mg once a day dose. He was discontinued from the trial. Based on the safety data in patients with moderate renal impairment from this Phase 1 study as well as the Phase 2 and Phase 3 studies and the observed pharmacokinetic changes for both total and unbound parameters as listed above, a dose of 4 mg once daily is recommended for patients with moderate renal impairment.

The effect of mild renal impairment on the PK of silodosin was not evaluated. A review of the safety of patients enrolled in phase 2 and phase 3 trials who had mild renal impairment (n=245) by the Clinical reviewer indicated that they did not experience greater rates of adverse events (see Clinical review by Medical Officer, Dr. Olivia Easley). This reviewer concurs with the Clinical reviewer that no dose adjustment is needed for patients with mild renal impairment.

The effect of severe renal impairment on the PK of silodosin was not evaluated. However, it is likely that the effect of severe renal impairment is \geq those observed in subjects with moderate renal impairment. Since there is an alternative pharmacologic treatment option (e.g. Flomax) for treatment of signs and symptoms of BPH in this population, this reviewer recommends that silodosin should not be used in patients with severe renal impairment.

Table 18: Patient demographics (mean \pm SD)

Group	Creatinine clearance (mL/min)	Body weight (kg)	Age (year)
Moderate renal impairment* (n=6)	39.2 \pm 9.6 (range 27 – 49)	61.5 \pm 5.96	65.7 \pm 7.3
Normal control (n=7)	138.7 \pm 17.3 (range 125 – 176)	70.21 \pm 9.23	31.6 \pm 7.4

* Sponsor indicated that this was a severe renally impaired population. However, the subjects enrolled in this study were consistent with moderate renal impairment and has been classified as such by this reviewer.

Table 19: Mean (SD) PK parameters of total (bound + unbound) drug concentration in subjects with moderate renal impairment and normal control given a single dose of 4 mg silodosin (study KMD 309).

Moiety	PK parameter	Moderate renal impairment	Normal control	Ratio of geometric means (impaired/control)
Silodosin	AUC _{0-∞} (ng*h/mL)	305.77 (115.38)	94.75 (41.28)	3.22
	C _{max} (n/mL)	72.22 (44.12)	21.51 (8.52)	3.11
	T _{max} (h)	0.67 (0.26)	0.86 (0.56)	0.85
	T _{1/2} (h)	7.55 (1.50)	3.94 (1.57)	2.02
KMD-3213G	AUC _{0-∞} (ng*h/mL)	1971.41 (1136.67)	463.71 (160.91)	3.77
	C _{max} (n/mL)	44.19 (18.18)	22.22 (5.62)	1.92
	T _{max} (h)	7.17 (4.31)	5.86 (1.86)	1.06
	T _{1/2} (h)	25.18 (12.30)	10.73 (2.44)	2.15

Table 20: Mean (SD) PK parameters of unbound drug concentration in subjects with moderate renal impairment and normal control given a single dose of 4 mg silodosin (study KMD 309).

Moiety	PK parameter	Moderate renal impairment	Normal control	Ratio of geometric means (impaired/control)
Silodosin	AUC _{0-∞} (ng*h/mL)	6.34 (3.43)	2.96 (1.10)	2.01
	C _{max} (n/mL)	1.48 (1.30)	0.71 (0.13)	1.49
	T _{max} (h)	0.83 (0.26)	0.86 (0.56)	1.07
	T _{1/2} (h)	8.71 (3.94)	4.39 (1.34)	1.89
KMD-3213G	AUC _{0-∞} (ng*h/mL)	158.53 (102.81)	51.50 (22.93)	2.67
	C _{max} (n/mL)	3.68 (3.96)	2.14 (1.03)	1.31
	T _{max} (h)	10.00 (7.59)	6.43 (3.36)	1.40
	T _{1/2} (h)	25.14 (12.65)	15.27 (10.85)	1.74

2.3.4 What are the effects of race on silodosin PK?

No specific study was conducted to examine the effect of race. To provide an estimate for the potential effect of race, this reviewer compared the PK parameters for silodosin from studies using Japanese subjects to those from studies using either all or mostly Caucasian subjects. The largest set of available data in Japanese subjects involves the administration of a 4 mg silodosin dose. Additionally, it has been shown that silodosin PK is dose proportional between 4 and 8 mg doses. Therefore, a comparison of PK parameters from 4 mg single dose administration was the best option.

Table 21 lists the AUC_{0-∞}, C_{max}, and T_{1/2} following single dose of 4 mg silodosin across all studies submitted to the NDA. These studies enrolled young males and administered silodosin with food unless specified otherwise. It appears that Japanese subjects generally have lower AUC and C_{max} and shorter t_{1/2} values. The mean AUC ranges in Japanese and Caucasian are 94.8 – 143.9 ng*hr/mL and 127.6 – 194.0 ng*hr/mL, respectively. The mean T_{1/2} in these studies ranged from 3.9 – 10.5 hours in Japanese and ranged from 3.7 – 11.1 hours in Caucasians. An examination of T_{1/2} across all studies in the NDA (including those not included in Table 21 since different dose levels were used) indicates that the T_{1/2}

values in Caucasians are generally higher than those in Japanese. However, the ranges for AUC and $T_{1/2}$ values from Japanese and Caucasian overlap and bring to question whether there would be true differences between the 2 races.

The mean C_{max} ranges in Japanese and Caucasian are 20.5 – 26.8 ng/mL and 27.6 – 35.0 ng/mL (excluding those data obtained under fasting conditions, which is expected to yield higher C_{max}).

It should be noted that this is a cross-study comparison and should not be considered as conclusive evidence. Nevertheless, the data suggest that there is a difference in the exposure to silodosin between Japanese and Caucasian.

Table 21: Mean ± SD single dose PK of 4 mg silodosin in Japanese and Caucasian subjects.

Race	AUC _{0-∞} ng*hr/mL	C _{max} ng/mL	T _{1/2} hr	Source ^a
Japanese	112.4±13.9	32.1±8.3	4.7±2.7	98363, fasting (n=6)
	143.9±57.1	26.8±9.2	6.9±3.1	98364 (n=6)
	133.7±57.8	28.0±9.6	4.7±3.7	KMD-308, fasting (n=12)
	128.0±65.7	23.0±10.8	6.0±4.8	KMD-308 (n=12)
	121.5±38.1	20.5±6.5	8.7±3.1	KMD-105, young (n=9)
	142.4±54.7	21.8±11.6	10.5±4.0	KMD-105, elderly (n=12)
	94.8±41.3	21.5±8.5	3.9±1.6	KMD 309, fasting (n=7)
Caucasian	127.7±62.0	39.0±28.7	3.7±1.6	UK01-97, fasting (n=9)
	127.6±59.5	27.7±15.04	5.5±2.7	UK01-97 (n=9)
	169±48.4	27.6±11.5	10.7±2.0	US011-98 (n=9)
	144.7±65.7	28.7±13.3	11.1±5.2	SI07004 (n=22)
	194.0±35.4	35.0±12.3	9.3±2.3	SI05010, mean age 58 years old (n=9)
	146.0±48.6	31.9±8.8	10.4±3.7	KMD-306-UK (n=9)
Data presented as arithmetic means unless specified otherwise, ^a =conducted under fed state unless specified otherwise				

A further comparison of the relative exposure of silodosin and its major active metabolite KMD-3213G indicated that the ratio of KMD-3213G to silodosin AUC in Japanese was slightly higher than in Caucasian and Black. AUC ratio of KMD-3213G to silodosin ranged from 4.9 to 8.5 in Japanese males (studies KMD-309, KMD-105), except one study that showed a ratio of 11.8 after first dose and lower to 8.0 on Day 7 (study KMD-207). The steady state AUC₀₋₂₄ ratio was 4.5 in Caucasians and Blacks of based on the primary PK study SI06004. However, a higher ratio of 6.1 in Whites and Blacks was reported in study SISI05014 (n=48 at 8 mg dose). It appears that the AUC ratio of KMD-3213G to silodosin is generally higher in Japanese subjects but the ranges overlap between the races.

2.4 Extrinsic Factors

2.4.1 What are the effects of food intake on silodosin PK?

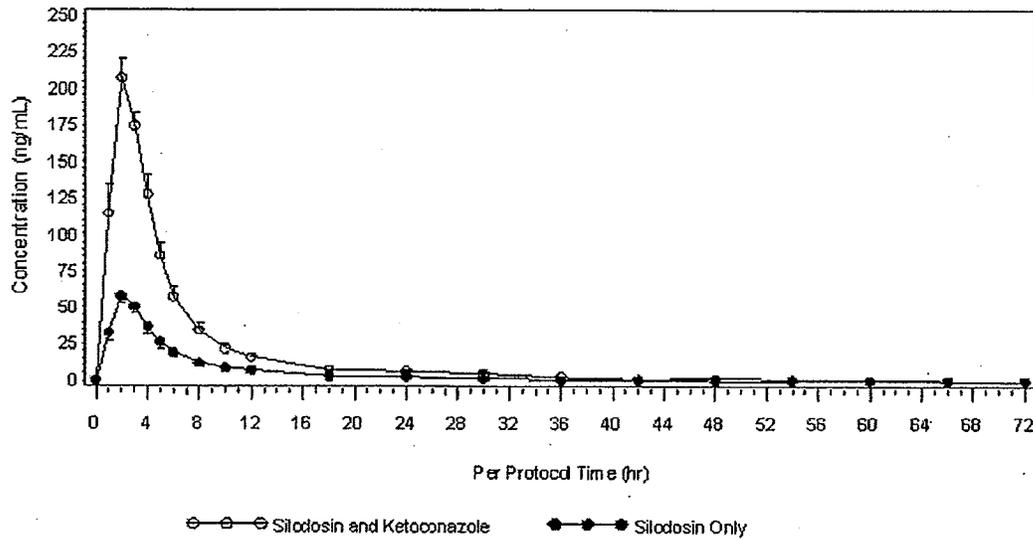
A food effect study using a high-fat (i.e., approximately 50 percent of total caloric content of the meal) and high-calorie (i.e., approximately 800 to 1000 calories) meal was not conducted for silodosin. The sponsor provided results from 3 separate studies (studies KMD-308, KMD3213-UK-01-97, and 95283) that administered single doses of silodosin with meals that were either not comparable to a high fat high calorie meal (studies KMD-308 and 95283) or the meal content was not documented (study KMD3213-UK-01-97). Table 22 provides a summary of the 3 studies.

Changes for C_{max} and AUC are listed in Table 23. Ketoconazole coadministration significantly increased the C_{max} and AUC of silodosin and its major metabolites. Terminal $T_{1/2}$ values were not altered significantly (Tables 24 and 25). The mean PK profiles for silodosin from studies SI06008 and KMD-306-UK are shown in Figures 10 and 11, respectively.

Table 23: Summary of ratios of geometric means (silodosin + ketoconazole versus silodosin alone)

Moieity	Study SI06008 (n=22) 8 mg silodosin on 2 nd day, 400 mg ketoconazole x 4 days		Study KMD-306-UK (n=16) 4 mg silodosin on 2 nd day, 200 mg ketoconazole x 4 days	
	Ratio of C_{max}	Ratio of AUC	Ratio of C_{max}	Ratio of AUC
Silodosin	3.76	3.18	3.66	2.91
KMD 3213G	3.32	3.26	2.71	2.46
KMD 3293	2.96	2.50	2.05	1.86

Figure 10: Mean (SEM) silodosin plasma concentration time profile (study SI06008)

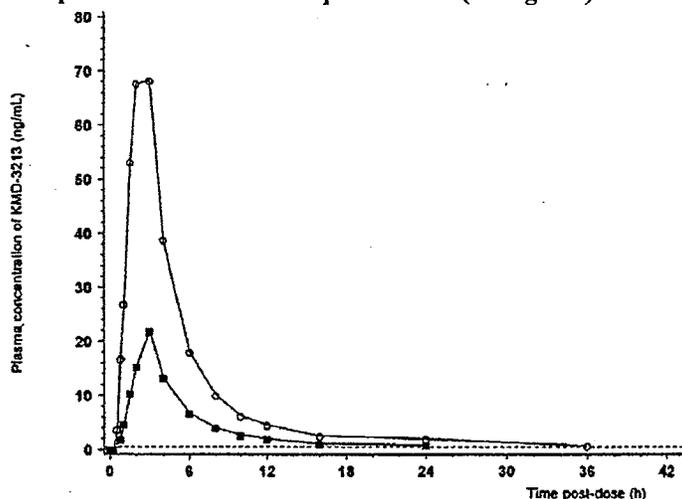


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Table 24: Summary of silodosin PK parameters (study SI06008). Data presented as arithmetic means.

Parameter	Statistic	Silodosin and Ketoconazole	Silodosin Only
		N=22	N=22
AUC[0-inf] (ng-hr/mL)	Mean (SD)	1159.1 (356.32)	378.1 (168.52)
	SEM	75.97	35.93
	CV (%)	30.7	44.6
	Min, Max	610.4, 2292.5	225.9, 888.4
	n	22	22
Cmax (ng/mL)	Mean (SD)	234.4 (62.21)	63.7 (22.78)
	SEM	13.26	4.86
	CV (%)	26.5	35.8
	Min, Max	129.0, 371.0	26.2, 133.0
	n	22	22
Kel (hr ⁻¹)	Mean (SD)	0.0770 (0.01005)	0.0948 (0.04692)
	SEM	0.00214	0.01000
	Median	0.0792	0.0825
	Min, Max	0.0566, 0.0899	0.0225, 0.2656
	n	22	22
t1/2 (hr)	Mean (SD)	9.2 (1.32)	9.1 (5.50)
	SEM	0.28	1.17
	Median	8.8	8.4
	Min, Max	7.7, 12.3	2.6, 30.8
	n	22	22
Tmax (hr)	Mean (SD)	2.1 (0.77)	2.2 (0.43)
	SEM	0.17	0.09
	Median	2.0	2.0
	Min, Max	1.0, 4.0	2.0, 3.0
	n	22	22

Figure 11: Geometric mean plasma silodosin concentration time profiles (study KMD-306-UK). Solid squares represent silodosin only and open circles represent silodosin and ketoconazole. Dotted line represents lower limit of quantitation (0.5 ng/mL).



b(4)

Therefore, this reviewer recommends that silodosin should not be used in patients taking strong CYP3A4 inhibitors. This recommendation is stronger than the recommendation to cut the dose to 4 mg in patients with moderate renal impairment. The rationales are: 1) the increase in unbound concentration in patients with moderate renal impairment was lower at about 2- to 2.7-fold for AUC and 1.3- to 1.5-fold for C_{max} , and 2) Relative ratio of C_{max} increase due to coadministration of ketoconazole (3.7- to 3.8-fold) was higher than due to moderate renal impairment (1.9- to 3.1-fold).

The effect of concomitant administration of moderate CYP3A4 inhibitors was not evaluated. Because they have the potential to increase the silodosin exposure, the need for concomitant administration with silodosin should be carefully considered.

Review note:

It should be noted that the observed effects of ketoconazole on the PK of silodosin may not be due entirely to ketoconazole's effect on CYP3A4. The interpretations are complicated by the following reasons:

1. Ketoconazole has the potential to inhibit the efflux transporter P-glycoprotein (P-gp), which silodosin is a substrate. Inhibition of P-gp efflux transporter in the gastrointestinal tract could increase drug absorption. Inhibition of P-gp related renal transport may also affect drug exposure. However, the in vivo P-gp inhibition potency of ketoconazole has not been well established.
2. In vitro studies indicated that the major metabolites were not mediated by CYP3A4.
3. The mean elimination $t_{1/2}$ was similar in the presence or absence of ketoconazole co-administration.
4. Ketoconazole has been shown in vitro to inhibit the enzyme UGT2B7, which is responsible for metabolism of silodosin to the major metabolite KMD-3213G. It is not known if in vivo administration of 400 mg ketoconazole could inhibit UGT2B7.

A separation of the various effects or potential effects of ketoconazole is not possible at this time. Because the risk of adverse events such as hypotension and fainting may increase with increased silodosin exposure, prevention of high silodosin exposure is a priority. Therefore, a recommendation that silodosin should not be used concomitantly with strong CYP3A4 inhibitors AND strong P-gp inhibitors is entered by this reviewer.

b(4)

2.4.3 What are the effects of CYP3A4 induction on silodosin PK?

The effect of CYP3A4 induction on the PK of silodosin was not evaluated. Since silodosin is metabolized partly by CYP3A4, induction of CYP3A4 may reduce exposure to silodosin. The major metabolites KMD-3213G and KMD-3293 are not formed via CYP3A4. Their exposure will likely remain the same or decreased if silodosin exposure is reduced. Metabolites formed via CYP3A4 pathway (e.g., KMD-3310, KMD-3289, and KMD 3241) may potentially have higher exposure as a results of increased silodosin metabolism via this pathway. The known metabolites of CYP3A4 pathways are minor metabolites with low relative exposure compare to silodosin. Changes in the exposure of the minor metabolites are unlikely to significantly alter the efficacy profile of oral silodosin.

2.4.4 What are the effects of silodosin administration on the PK of other drugs?

The effect of silodosin's ability to inhibit or induce *in vitro* metabolic activities of Cytochrome P450 enzymes were evaluated in studies PK10049 (inhibition) and ZXA0002 (induction). The results indicated that at therapeutic concentration silodosin, KMD-3213G, and KMD-3293 do not inhibit the *in vitro* metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The inhibition effect on CYP2C8 was not evaluated. With respect to the potential to induce CYP activity, the *in vitro* results indicated that silodosin, KMD-3213G, and KMD-3293 did not induce the metabolic activity of CYP1A2 or CYP3A4 in human hepatocytes. Since no induction of CYP3A4 was observed, it suggests that silodosin and its metabolites KMD-3213G and KMD-3293 also do not induce metabolic activity of CYP2C8, CYP2C9, or CYP2C19. These data indicate that silodosin and its major metabolites KMD-3213G and KMD-3293 are unlikely to induce or inhibit the activity of the tested CYP isoforms *in vivo* following oral dose of 8 mg silodosin once daily.

Additional details of studies PK10049 and ZXA0002 can be found in Appendix 4.2.2.

2.4.5 What are the effects of Silodosin administration on the PK of digoxin?

Digoxin is a narrow therapeutic index drug and a substrate of the transporter P-glycoprotein (P-gp). The effect of silodosin on the PK of digoxin was examined in study KMD-307-UK. It was a multiple dose, single-sequence, crossover study in 16 subjects. Digoxin loading dose of 0.5 mg was administered twice daily for 1 day and the maintenance dose of 0.25 mg was administered once daily on Days 2 – 16. Silodosin 4 mg twice a day was administered on Days 9 – 16. The analysis of the effects of silodosin administration on the PK of digoxin was carried out by comparing the digoxin exposure on Day 8 (i.e., without silodosin) and Day 16 (i.e., with silodosin). Because this was a single sequence study, a parallel group of 8 subjects received placebo on Days 9 – 16 instead of silodosin to help assess any effects of the single-sequence design.

No significant differences in digoxin AUC and C_{max} were observed between Day 16 and Day 8 in groups treated with silodosin (Table 26). Silodosin administration also did not affect the amount of unchanged digoxin excreted in the urine (Table 26). The same comparisons in the placebo group yielded no difference in digoxin PK, indicating that there was not an effect of sequence (Table 27). These data indicate that coadministration of silodosin 4 mg twice daily does not alter the PK of digoxin.

The dose used in this study (4 mg twice daily) differs from the proposed dose of 8 mg once daily. At steady state, the silodosin 8 mg once daily regimen is expected to yield similar AUC but higher C_{max} (estimated to be approximately 30% higher based on $t_{1/2}$ of 13.3 hours) than the silodosin 4 mg twice daily regimen. Since no effect on the PK of digoxin was observed with the 4 mg twice daily regimen, it is not likely that the 8 mg once daily regimen would produce a significant PK interaction with digoxin. A repeat study with the proposed silodosin dosing regimen of 8 mg once daily is not warranted at this time.

Tables 26 and 27 show the digoxin PK parameters for groups dosed with silodosin and placebo, respectively.

Table 26: Summary of digoxin PK parameters following multiple oral doses alone (Day 8) and in combination with silodosin (Day 16). See Table 27 below for description of the superscript notations and additional notes.

Parameter	Day 8 ^a (N=16)	Day 16 ^b (N=16)	Ratio of geometric LS means (Day 16: Day 8)	90% CI for ratio of geometric LS means (Day 16: Day 8)
AUC(0- τ) (ng.h/mL)	14.7 (20.1)	14.4 (16.0)	0.984	0.936, 1.03
C _{max} (ng/mL)	1.26 (21.2)	1.25 (14.0)	0.992	0.912, 1.08
t _{max} ^c (h)	1.88 (0.738)	1.92 (0.811)	NC	NC
CL _{ss} /F (mL/min)	284 (20.1)	289 (16.0)	NC	NC
Ae _r (μ g)	144 (16.1)	137 (33.9)	0.953	0.848, 1.07
CL _R (mL/min)	163 (15.5)	158 (32.9)	NC	NC

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Table 27: Summary of digoxin PK parameters following multiple oral doses alone (Day 8) and in combination with placebo (Day 16)

Parameter	Day 8 ^a (N=8)	Day 16 ^b (N=8)	Ratio of geometric LS means (Day 16: Day 8)	90% CI for ratio of geometric LS means (Day 16: Day 8)
AUC(0- τ) (ng.h/mL)	15.0 (18.3)	14.5 (19.7)	0.968	0.903, 1.04
C _{max} (ng/mL)	1.22 (26.7)	1.15 (16.3)	0.942	0.837, 1.06
t _{max} ^c (h)	1.88 (0.991)	1.82 (0.921)	NC	NC
CL _{ss} /F (mL/min)	277 (18.3)	286 (19.7)	NC	NC
Ae _{τ} (μ g)	161 (20.4)	156 (11.6)	0.970	0.822, 1.14
CL _R (mL/min)	178 (21.7)	178 (19.6)	NC	NC

^a Digoxin administered alone, ^b Digoxin administered with KMD-3213 or placebo
Geometric mean (CV%) data are presented; ^c Arithmetic mean (SD)

N = Number of subjects studied

τ = 24 hours

NC = Not calculated

Review note on formulation: The formulation used in this study (produced by — was not bridged to the to-be-marketed formulation. However, the same formulation was used in study KMD-306-UK where single dose PK of silodosin 4 mg is available. The AUC_{0- ∞} was 140 (32.6%CV) ng*h/mL and C_{max} was 30.7 (29%CV) (geometric means). These were similar to the exposure following administration of 4 mg silodosin once daily using the to-be-marketed formulation (Single dose: Mean \pm SD AUC₀₋₂₄ = 145 \pm 66 ng*h/mL and C_{max} = 29 \pm 13 ng/mL; Steady state: AUC₀₋₂₄ = 159 \pm 70 ng*h/ml, C_{max} = 28 \pm 12 ng/mL, study S107004), indicating that the — formulation was similarly bioavailable and its use in this study would not be an issue for purpose of interpreting the interaction between silodosin and digoxin.

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2.5 General Biopharmaceutics

2.5.1 What is the process of formulation development?

Silodosin is formulated as immediate release capsules. The formulation is robust with rapid dissolution (>85% in 15 minutes). The compositions of the capsules are listed in table 28. The to-be-marketed (TBM) 4 mg capsule is the 4C formulation manufactured by Watson (Watson 4C). The TBM 8 mg capsule (Watson 8C) is also produced by Watson and contains exactly twice the mass of each component in a size #1 gelatin capsule.

There were 3 manufacturing methods (denoted as A, B and C in Table 28) and 3 manufacturers, namely Kissei, — and Watson. Available data from representative batches (using same manufacturing method and similar time frame but may not be same batch used in clinical trial, Table 29 as provided by sponsor and concurred by the Chemistry reviewer, Dr. Yichun Sun) indicate that capsules

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produced by Kissei and Watson had rapid dissolution (in vitro dissolution of >85% in 15 minutes in at least 3 media). Therefore these products are considered to have similar performance to the to-be-marketed product manufactured by Watson. Produced 2 formulations, namely 4 mg produced by method B (4B) and 4 mg produced by method C (4C). had >85% dissolution in 0.1N HCl but slower in pH 4.5 and pH 7.4 buffers. There was no dissolution data available for 4C formulation. The 4B formulation was used in study KMD3213-US011-98 (Phase 1 PK study) and the 4C formulation was used in studies KMD-306-UK (drug interaction study with 200 mg ketoconazole), KMD-307-UK (drug interaction study with digoxin), and KMD3213-US021-99 (Phase 2 dose finding study). Silodosin's PK for the 4C formulation was available from study KMD-306-UK.

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Table 28: List of clinical formulations

Formula Number	0.1A	0.5A	1A	1.5A	2A1	2A2	2.5A	4A	2B	4B	2C	4C
Manufacturing Method	Method A								Method B		Method C	
Ingredient	Quantity in milligrams/capsule											
Silodosin	0.1	0.5	1	1.5	2	2	2.5	4	2	4	2	4
D-Mannitol												
Pregelatinized starch (PCS)												
Pregelatinized starch												
Magnesium stearate												
Sodium lauryl sulfate												
Total (mg)	50	50	50	50	50	100	50	100	185	185	175	175
Capsule size No.												

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Table 29: Summary of in vitro dissolution studies

Formula	Manufacturing/ Testing Performed By	Studies Where Used	Representative Batch	Conditions	Media	Collection Times	No. of Dosage Units	Results
2A1	Kissei	95283 KMD3213-UK01-97 KMD-201	RJ222	50 rpm paddles	900 mL water, pH 1.2, 5, and 6.8 buffers	10, 15, 20, 30 minutes	12	> 85% in 15 minutes in all media
2A2	Kissei	98364	RL011	50 rpm paddles	900 mL water, pH 1.2, 5, and 6.8 buffers	10, 15, 20, 30 minutes	12	> 85% in 15 minutes in all media
4A	Kissei	98363 98364 KMD3213-UK01-97	KN051	50 rpm paddles	900 mL water, pH 1.2, 3, 5, and 6.8 buffers	5, 10, 15, 20, 30 minutes	6	> 85% in 15 minutes in all media
4B	—	KMD3213-US011-98	98127B	50 rpm paddles	500 mL water, 0.1 N HCl, pH 4.5 and 7.4 buffers	5, 10, 20, 30 minutes	3	>85% in 15 min. in 0.1 N HCl, slower in other media
2C	Kissei	KMD-202, KMD-203 KMD-207, KMD-305	9104	50 rpm paddles	900 mL water, pH 1.2, 5, and 6.8 buffers	10, 15, 20, 30 minutes	12	> 85% in 15 minutes in all media
4C	Kissei	KMD-105, KMD-303 KMD-309, KMD-202 KMD-203, KMD-206 KMD-303, KMD-305	PR201	50 rpm paddles	900 mL water, pH 1.2, 5, and 6.8 buffers	5, 10, 15, 30 minutes	12	> 85% in 15 minutes in all media
4C	Watson	SI05008, SI06004 SI05014, SI05010 SI06008, SI06002 SI07004, SI04009 SI04010, SI04011	XC5C015	50 rpm paddles	900 mL water, 0.1 N HCl, pH 4.5 and 6.8 buffers	3, 5, 10, 15, 20, 30 minutes	Water N=6, Other media N=12	> 85% in 15 minutes in all media

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Table 31: Drug product used in phase 2 and phase 3 studies

Study ID	Site of manufacture	Method of Manufacture	Formulation ¹	Clinical Supply Batch Number(s)
KMD-201	Kissei	A	0.1A	HZ051
			1A	HZ061
			2A1	HZ071
KMD-202	Kissei	C	2C	LH251
			4C	LJ021
KMD-203	Kissei	C	2C	LH251, LV131
			4C	LJ021, LV201
KMD-206	Kissei	C	4C	LV201
KMD3213-US021-99	—	C	4C	99443
KMD-303	Kissei	C	4C	X106
KMD-305	Kissei	C	2C	X003
			4C	MR071, MR091, MR181
SI04009	Watson	C	4C	XC5C015
SI04010	Watson	C	4C	XC5C015
SI04011	Watson	C	4C	XC5C015,
				XC5C016

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2.5.2 Is the to-be-marketed (TBM) formulation identical to the one used for the phase 3 efficacy trials? No. The Phase 3 clinical trials (SI04009, SI04010, and SI04011) used 2 capsules of the 4 mg strength together for a total dose of 8 mg instead of a single 8 mg TBM formulation. However, the composition of the — used in the two strengths is identical except that twice the amount — is encapsulated into a larger capsule shell for the 8 mg capsule compared to the 4 mg capsule. Dissolution in 0.1 N HCl, buffer pH 4.5, and buffer pH 6.8 showed that both strengths had greater than 85% dissolution within 15 minutes. The Division has previously agreed with sponsor that the in vitro dissolution comparison was adequate and that no in vivo bioequivalence study was needed (see meeting minutes for teleconference on 10/13/2006). The 4 mg TBM formulation being proposed for use in specific populations is identical to the phase 3 clinical formulation. Drug products used in phase 3 clinical trials and the TBM products are both manufactured by Watson. The drug formulation used in phase 3 trials was adequately bridged to the TBM formulation.

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2.5.3 Were formulations changes before phase 2 adequately linked to the TBM formulation? No. Two formulations manufactured by — namely 4 mg capsule produced by method B (— 4B) and 4 mg capsule produced by method C (— 4C). — 4B had >85% dissolution in 0.1N HCl but slower dissolution in pH 4.5 and 7.4 buffers. There was no dissolution data available for — 4C formulation. The — 4B formulation was used in study KMD3213-US011-98 (Phase 1 PK study) and the — 4C formulation was used in studies KMD-306-UK (drug interaction study with 200 mg ketoconazole), KMD-307-UK (drug interaction study with digoxin), and KMD3213-US021-99 (Phase 2 dose finding study). Silodosin's PK for the — 4C formulation was available from study KMD-306-UK and was inline with results from other formulations (see discussion in section 2.4.5).

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Drug products manufactured by Kissei were considered adequately bridged to the TBM formulation. This was based on available dissolution data from representative batches (using same manufacturing method and similar time frame but may not be same batch used in clinical trial) showing rapid dissolution of all representative batches. Please see section 2.1.5 for additional details.

7. ~~_____~~
8. Co-administration of silodosin did not significantly affect the PK of digoxin, a P-gp substrate with narrow therapeutic index.
9. In vitro studies indicated that silodosin administration is not likely to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 or induce the activity of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and P-gp.

4 Appendices

4.1 Proposed labeling

Please see file in the FDA Electronic Document Room.

4.2 Individual Study Reviews

4.2.1 Bioanalytical methods review summary, page 41

4.2.2 Selected Preclinical study reviews, page 51.

4.2.3 Selected Clinical study reviews, page 64.

4.3 Consult Review

- Review of QT study SI05014 by the IRT-QT team was signed off in DFS on 4/16/2008 and is not included here.

4.4 Office of Clinical Pharmacology GRMP Filing Checklist, page 83

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Appendix 4.2.1: NDA 22-206 Bioanalytical methods review summary

Silodosin development was carried out initially by Kissei and subsequently by Watson. Each company developed its own bioanalytical methods to measure silodosin and its metabolites. The methods were validated and are acceptable. Most methods met the FDA recommended acceptance criteria of $\leq 20\%$ for precision (CV) and within $\pm 20\%$ for accuracy (RE, relative to nominal value) at the lower limit of quantitation (LLOQ) and $\leq 15\%$ or within $\pm 15\%$, respectively, at all other concentrations. However, several assays were validated with expanded acceptance criteria of $\leq 20\%$ and $\pm 20\%$ for precision and accuracy, respectively, at all concentrations instead of just at the LLOQ. These were evaluated on a case-by-case basis and they were accepted because it is felt that the additional variability and assay errors would not significantly affect the clinical interpretation of the PK results. The methods that deviated from the recommended acceptance criteria are listed below:

1. 05-8753b: validation for KMD-3213G and KMD-3293 in plasma had precision intra-assay variability of 11.9 – 18.9% and 11.8 – 19.0%, respectively, exceeding the 15% recommended threshold. The acceptance criteria for precision and accuracy were expanded to $\leq 20\%$ and $\pm 20\%$, respectively, at all concentrations by sponsor. This assay was used to measure KMD-3213G and KMD-3293 in plasma samples from all clinical studies conducted Watson, namely studies SI05008, SI06004, SI07004, SI04009, SI05010, SI06008, and SI05014. The expanded acceptance criteria are less than ideal and may introduce additional variability and error into the PK data for KMD-3213G and KMD-3293. However, since these metabolites only contribute a minor part of the activity of oral silodosin, the extension of acceptance criteria from 15% to 20% threshold should not significantly alter the interpretation of the data with respect to clinical implications.
2. 06-8879b: validation for KMD-3213G and KMD-3293 in urine resulted in some precision and accuracy variability outside of $\leq 15\%$ or $\pm 15\%$ range but within $\leq 20\%$ or $\pm 20\%$ range. This assay was used in study SI05010 evaluating the effect of moderate hepatic impairment on the PK of silodosin.
3. 0608881b: validation for KMD-3310 in urine resulted in some precision and accuracy variability outside of $\leq 15\%$ or $\pm 15\%$ range but within $\leq 15\%$ or $\pm 20\%$ range. This assay was used in study SI05010 evaluating the effect of moderate hepatic impairment on the PK of silodosin. KMD-3310 is a minor metabolite and the expanded acceptance criteria to 20% should not affect the clinical interpretation of the results of study SI05010.

This appendix provides a summary of the bioanalytical methods used in the development of silodosin by Kissei and Watson.

Kissei's development

For determination of the concentrations of silodosin and its metabolites in human plasma and urine, HPLC fluorescence / _____ and LC/MS/MS methods were used. Pretreatment by _____ was used for the LC/MS/MS method, while pretreatment using either _____ was used for the HPLC fluorescence method depending on the substance to be determined. Table 32 lists the methods used by Kissei together with the range of calibration curve.

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Cross validation of selected Kissei's assays:

For cross-validation of 2 HPLC fluorescence methods and a LC/MS/MS method, some plasma samples were determined by both types of assay in studies KMD-105 and KMD-207. The sponsor provided the results of the analyses but did not provide the raw data.

Selected plasma samples from study KMD-105 were analyzed for silodosin using both an HPLC method and a LC/MS/MS method (method PK20009). The sponsor reported that the LC/MS/MS method yielded about 12% lower calculated concentration than those obtained using the HPLC method (mean 88%, 95% CI 85 – 92%).

In a subsequent study (study KMD-207), plasma samples were analyzed for silodosin using a modified HPLC method (method JCL017021) and the previous LC/MS/MS method (method PK20009). The sponsor reported that the ratio (mean) of resulted concentration values obtained by LC/MS/MS to those obtained by HPLC fluorescent method was 1.0 (95% CI 0.94 – 1.06).

These results indicate that there may be small differences in the reported concentration values across these assays.

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Table 32: Summary of Kissei's bioanalytical methods

Study No.	Method	Sample (mL)	Target substance	Range of calibration curve (ng/mL)	Limit of quantification (lower limit) (ng/mL)	Study site
KMD-YA-1	HPLC fluorescence method	Plasma (1)	silodosin	0.33-33	0.33	Kissei
			KMD-3241	0.44-44	0.44	
			KMD-3289	0.11-11	0.11	
KMD-YA-12	HPLC fluorescence method	Plasma (1)	silodosin	0.495-99	0.495	Kissei
			KMD-3241	0.315-31.5	0.315	
			KMD-3289	0.101-10.1	0.101	
7014-101	HPLC fluorescence method	Plasma (1)	silodosin	0.5-100	0.5	—
			KMD-3241	0.3-30	0.3	
			KMD-3289	0.1-10	0.1	
PK20009	LC/MS/MS	Plasma (0.2)	silodosin	0.1-20	0.1	Kissei
			KMD-3241	0.1-20	0.1	
			KMD-3289	0.1-20	0.1	
			KMD-3293	0.1-20	0.1	
PK20005	HPLC fluorescence method	Plasma (0.5)	KMD-3213G	2-100	2	Kissei
JCL017021	HPLC fluorescence method	Plasma (0.5)	silodosin	0.5-50	0.5	—
			KMD-3293	0.5-50	0.5	
			KMD-3213G	2-200	2	
JCL022111	LC/MS/MS	Plasma filtrate (0.2)	silodosin	0.01-2.5	0.01	—
			KMD-3213G	0.5-125	0.5	
KMD-YA-2	HPLC fluorescence method	Urine (1)	silodosin	0.33-33	0.33	Kissei
			KMD-3241	0.44-44	0.44	
			KMD-3289	0.11-11	0.11	
KMD-YA-13	HPLC fluorescence method	Urine (0.25)	silodosin	1.98-396	1.98	Kissei
			KMD-3241	1.26-126	1.26	
			KMD-3289	0.404-40.4	0.404	
KSI106	HPLC fluorescence method	Urine (0.5)	silodosin	2-400	2	—
			KMD-3241	1.25-125	1.25	
			KMD-3289	0.4-40	0.4	

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Table 34 summarizes the stability results from Kissei and table 35 summarizes the stability results from Watson.

Freeze-thaw stability has been demonstrated for 4 freeze-thaw cycles for silodosin, KMD-3293 (study PK20009), and 5 cycles for KMD-3213G (study PK20005) in plasma. Silodosin, KMD-3213G, and KMD-3293 in plasma filtrate (i.e., unbound plasma samples) were demonstrated to be stable following 4 freeze-thaw cycles (study 06-8877a). Silodosin, KMD-3213G, and KMD-3293 in urine was demonstrated to be stable following 3 freeze-thaw cycles (study 06-8879b). Freeze-thaw stability for other metabolite is summarized in tables 34 and 35.

Storage stability has been demonstrated for silodosin and KMD-3293 in plasma for 1 year at -20 °C and -80 °C (study PK20009) and KMD-3213G in plasma for 13.8 months at -20 °C (study PK20019). Storage stability for other metabolites and matrices is summarized in tables 34 and 35.

Table 34: Summary of stability data for Kissei's bioanalytical methods

Study No.	Test item	Sample	Target substance	Results ^{b)}	Study site
PK20009	Stability in freeze-thawing	Plasma	silodosin KMD-3241 KMD-3289 KMD-3293 KMD-3295	4 times	Kissei
PK20005	Stability in freeze-thawing	Plasma	KMD-3213G	5 times	Kissei
PK20008	Stability in freeze-thawing	Urine	silodosin KMD-3241 KMD-3289 KMD-3293 KMD-3295 KMD-3213G	3 times	Kissei
JCL022111	Stability in freeze-thawing	Plasma filtrate	silodosin KMD-3213G	3 times	—

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Table 34: Summary of stability data for Kissei's bioanalytical methods (continued)

Study No.	Test item	Sample	Target substance	Results ^{b)}	Study site
KMD-YA-18	Stability in freeze-thawing	Plasma	KMD-3290 ^{a)}	5 times	Kissei
KMD-YA-19	Stability in freeze-thawing	Urine	KMD-3290 ^{a)}	5 times	Kissei
KMD-YA-12	Stability in storage	Plasma	silodosin KMD-3241 KMD-3289	-40 °C, 1 year	Kissei
PK20006	Stability in storage	Plasma	KMD-3213G	-40 °C, 13 months	Kissei
PK20019	Stability in storage	Plasma	KMD-3213G	-20 °C, 13.8 months	Kissei
PK20009	Stability in storage	Plasma	silodosin KMD-3241 KMD-3289 KMD-3293 KMD-3295	-20 °C, 1 year -80 °C, 1 year	Kissei
JCL022111	Stability in storage	Plasma filtrate	silodosin KMD-3213-G	-20 °C, 3 months	—
KMD-YA-13	Stability in storage	Urine	silodosin KMD-3241 KMD-3289	-40 °C, 1 year	Kissei
PK20008	Stability in storage	Urine	silodosin KMD-3241 KMD-3289 KMD-3293 KMD-3295 KMD-3213G	-20 °C, 6 months	Kissei
KMD-YA-18	Stability in storage	Plasma	KMD-3290 ^{a)}	-40 °C, 6 months	Kissei
KMD-YA-19	Stability in storage	Urine	KMD-3290 ^{a)}	-40 °C, 6 months	Kissei

a) Optical isomer of silodosin (S-silodosin)

b) Data are the longest results for each sample in the storing condition.

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Table 35: Summary of stability data for Watson's bioanalytical methods

Study No.	Test item	Sample	Target substance	Results	Study site
05-8753b	Room temperature Reconstitution solution In autosampler Freeze-thaw cycles In storage @ -80 degrees	Plasma	Sildenafil KMD-3213G KMD-3293	5 hr, 17 min 43 hr, 8 min 5 hr, 47 min 4 cycles 56 days	✓
06-8920	Room temperature Reconstitution solution In autosampler Freeze-thaw cycles In storage @ -80 degrees	Plasma	KMD-3295	4 hr, 40 min 121 hr, 23 min 9 hr 5 cycles 22 days	✓
06-9207	Room temperature Reconstitution solution In autosampler Freeze-thaw cycles In storage @ -80 degrees	Plasma	KMD-3310	4 hr, 10 min 8 hr, 51 min 116 hr, 32 min 4 cycles 15 days	✓
06-8877a	Room temperature Reconstitution solution In autosampler Freeze-thaw cycles In storage @ -80 degrees	Unbound Plasma	Sildenafil KMD-3213G KMD-3293	4 hr, 21 min 21 hr, 40 min 5 hr, 21 min 4 cycles 32 days	✓

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Table 35: Summary of stability data for Watson's bioanalytical methods (continued)

Study No.	Test item	Sample	Target substance	Results	Study site
06-8879b	Room temperature Reconstitution solution In autosampler Freeze-thaw cycles In storage @ -80 degrees	Urine	Sildenafil KMD-3213G KMD-3293	4 hr, 6 min 146 hr, 7 min 9 hr, 12 min 3 cycles 15 days	✓
06-8881b	Room temperature Reconstitution solution In autosampler Freeze-thaw cycles In storage @ -80 degrees	Urine	KMD-3310	4 hr, 25 min 139 hr, 25 min 9 hr, 6 min 4 cycles 14 days	✓

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Validation results for bioanalytical methods from Kissei and Watson:

Table 36 provides a summary of the method validation results for the bioanalytical methods used in studies submitted in the NDA. The methods were validated and are acceptable. Most methods met the FDA recommended acceptance criteria of $\leq 20\%$ for precision (CV) and within $\pm 20\%$ for accuracy (RE, relative to nominal value) at the lower limit of quantitation (LLOQ) and $\leq 15\%$ or within $\pm 15\%$, respectively, at all other concentrations. However, several assays were validated with expanded acceptance criteria of $\leq 20\%$ and $\pm 20\%$ for precision and accuracy, respectively, at all concentrations instead of just at the LLOQ. The methods that deviated from the recommended acceptance criteria are listed below:

- 05-8753b: validation for KMD-3213G and KMD-3293 in plasma had precision intra-assay variability of 11.9 – 18.9% and 11.8 – 19.0%, respectively, exceeding the 15% recommended threshold. The acceptance criteria for precision and accuracy were expanded to $\leq 20\%$ and $\pm 20\%$, respectively, at all concentrations by sponsor. This assay was used to measure KMD-3213G and KMD-3293 in plasma samples from all clinical studies conducted Watson, namely studies

- SI05008, SI06004, SI07004, SI04009, SI05010, SI06008, and SI05014. The expanded acceptance criteria are less than ideal and may introduce additional variability and error into the PK data for KMD-3213G and KMD-3293. However, since these metabolites only contribute a minor part of the activity of oral silodosin, the extension of acceptance criteria from 15% to 20% threshold should not significantly alter the interpretation of the data with respect to clinical implications.
- 06-8879b: validation for KMD-3213G and KMD-3293 in urine resulted in some precision and accuracy variability outside of $\leq 15\%$ or $\pm 15\%$ range but within $\leq 20\%$ or $\pm 20\%$ range. This assay was used in study SI05010 evaluating the effect of moderate hepatic impairment on the PK of silodosin.
 - 0608881b: validation for KMD-3310 in urine resulted in some precision and accuracy variability outside of $\leq 15\%$ or $\pm 15\%$ range but within $\leq 15\%$ or $\pm 20\%$ range. This assay was used in study SI05010 evaluating the effect of moderate hepatic impairment on the PK of silodosin. KMD-3310 is a minor metabolite and the expanded acceptance criteria to 20% should not affect the clinical interpretation of the results of study SI05010.

Table 36: Summary of bioanalytical methods and corresponding PK studies

Study No.	Method	Sample (mL)	Target substance	Intra-assay Variability		Inter-Assay Variability		PK Study in which Method was Used	Study site
				Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)		
KMD-YA-1	HPLC fluorescence method	Plasma (1)	silodosin	2.31 - 14.35	-1.60 - 9.10	0.28 - 7.56	-0.14 - 5.49	95283	Kissei
			KMD-3241	0.75 - 5.42	-0.79 - 10.89	0.29 - 8.23	-2.96 - 6.88	95284	
			KMD-3289	2.22 - 4.14	-13.81 - -0.52	0.05 - 8.25	-3.31 - 4.36	KMD-201	
KMD-YA-2	HPLC fluorescence method	Urine (1)	silodosin	2.24 - 10.42	2.48 - 5.55	0.21 - 11.36	-0.54 - 9.00	95283	Kissei
			KMD-3241	1.77 - 7.70	-12.21 - 8.57	0.38 - 9.68	-4.48 - 7.42	95284	
			KMD-3289	2.58 - 5.58	-4.97 - 4.97	0.18 - 5.41	-1.78 - 2.52	KMD-201	
KMD-YA-12	HPLC fluorescence method	Plasma (1)	silodosin	1.9 - 3.1	-3.8 - 10.4	2.3 - 5.9	-1.3 - 5.8	98363	Kissei
			KMD-3241	1.1 - 2.4	-2.1 - 9.7	1.1 - 2.7	-1.2 - 11.4	98364	
			KMD-3289	0.6 - 8.3	-6.5 - -2.8	2.5 - 2.8	-3.7 - -1.2		
KMD-YA-13	HPLC fluorescence method	Urine (0.25)	silodosin	1.9 - 5.3	-5.1 - 10.5	1.1 - 3.3	-2.7 - 8.2	98363	Kissei
			KMD-3241	1.1 - 3.1	-5.2 - 10.5	1.6 - 3.2	-3.5 - 8.3	98364	
			KMD-3289	2.3 - 5.5	-5.9 - 1.5	2.9 - 5.1	-4.6 - -1.1		
KMD-YA-18	HPLC fluorescence method	Plasma (1)	KMD-3290 ^{a)}	1.3 - 6.1	-2.6 - 3.1	0.4 - 3.9	1.9 - 3.4	98364	Kissei
KMD-YA-19	HPLC fluorescence method	Urine (1)	KMD-3290 ^{a)}	2.1 - 10.4	-1.7 - -0.1	1.5 - 5.8	-3.4 - -1.7	98364	Kissei

a) Optical isomer of silodosin (S-silodosin).

Kissei: Kissei Pharmaceutical Company, LTD.

Table 36: Summary of bioanalytical methods and corresponding PK studies (continued)

Study No.	Method	Sample (mL)	Target substance	Intra-assay Variability		Inter-Assay Variability		PK Study in which Method was Used	Study site
				Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)		
KSI 76	HPLC fluorescence method	Plasma (1)	KMD-3213	1.2 - 11.0	-6.2 - 8.2	3.7 - 7.7	-2.5 - 3.5	KMD3213-UK01-97 KMD3213-UK02-97	K
KSI 77	HPLC fluorescence method	Urine (0.5)	KMD-3213	1.2 - 11.0	-9.4 - 12.2	3.2 - 11.2	-4.3 - 4.8	KMD3213-UK01-97 KMD3213-UK02-97	
KSI 105	HPLC fluorescence method	Plasma (1)	silodosin	1.2 - 11.2	-6.9 - 7.4	3.3 - 9.1	-2.8 - 3.5	KMD3213-US011-98	
			KMD-3241	1.3 - 5.5	-14.3 - 8.7	2.4 - 5.3	-12.1 - 2.9		
			KMD-3249	1.0 - 3.7	-7.9 - 2.5	2.5 - 3.8	-4.9 - 1.2		
KSI 106	HPLC fluorescence method	Urine (0.5)	silodosin	0.9 - 6.4	-0.6 - 14.8	2.5 - 7.4	4.7 - 8.7	KMD3213-US011-98 KMD3213-US012-99	
			KMD-3241	2.1 - 8.4	-13.1 - 19.2 ^{b)}	6.2 - 9.7	-6.9 - 16.7 ^{b)}		
			KMD-3289	1.5 - 8.5	-2.7 - 13.0	6.1 - 8.8	6.0 - 7.4		
7014-101	HPLC fluorescence method	Plasma (1)	silodosin	4.5 - 11.1	-7.9 - 11.4	5.9 - 10.9	-1.0 - 8.8	KMD3213-US012-99	
			KMD-3241	4.2 - 11.5	-7.0 - 12.0	5.6 - 10.5	0.1 - 4.1		
			KMD-3289	5.2 - 12.5	-9.0 - 10.4	7.2 - 12.1	0.1 - 5.4		

b) Values at lower limit of quantification.

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Table 36: Summary of bioanalytical methods and corresponding PK studies (continued)

Study No.	Method	Sample (mL)	Target substance	Intra-assay Variability		Inter-Assay Variability		PK Study in which Method was Used	Study site
				Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)		
PK20005	HPLC fluorescence method	Plasma (0.5)	KMD-3213G	0.8 – 4.4	1.2 – 7.7	1.5 – 4.7	-1.5 – 2.2	KMD-105	Kiscei
PK20008	LC/MS/MS	Urine (0.2)	silodosin	1.6 – 6.7	-8.3 – 5.3	2.1 – 11.6	-6.0 – 4.0	KMD-105	Kiscei
			KMD-3241	3.9 – 11.3	-12.2 – -4.6	5.7 – 14.1	-17.3 ^{b)} – 7.5		
			KMD-3289	2.7 – 4.8	-0.9 – 2.3	3.4 – 11.0	-9.8 – 2.4		
			KMD-3293	4.2 – 10.8	-0.7 – 7.7	3.7 – 6.9	-1.1 – 6.8		
			KMD-3295	5.2 – 8.3	4.0 – 7.5	4.3 – 10.1	-3.1 – 3.2		
PK20009	LC/MS/MS	Plasma (0.2)	silodosin	2.6 – 9.2	-15.9 – -7.9	3.5 – 14.2	-1.7 – 3.1	KMD-105	Kiscei
			KMD-3241	2.2 – 13.3	-12.6 – -5.5	6.1 – 6.8	-6.3 – 0.5		
			KMD-3289	5.6 – 8.1	-12.0 – 0.3	7.0 – 8.3	-1.5 – 6.6		
			KMD-3293	2.5 – 13.8	-13.0 – -2.7	6.0 – 8.2	-3.1 – 3.5		
			KMD-3295	2.6 – 11.3	-10.5 – -4.3	2.7 – 9.4	-6.7 – -0.6		
JCL017021	HPLC fluorescence method	Plasma (0.5)	silodosin	0.6 – 5.3	-0.7 – 4.8	1.0 – 2.7	-0.8 – 2.8	KMD3213-US021-99 KMD-207 KMD-305 KMD-306-UK KMD-307-UK KMD-308 KMD-309	—
			KMD-3293	0.2 – 8.8	-5.7 – 10.8	0.4 – 5.1	-6.4 – 9.0		
			KMD-3213G	0.9 – 1.5	-5.9 – 8.0	0.3 – 3.7	-6.6 – 10.4		

b) Values at lower limit of quantification.

^{j)} was added to the plasma and urine samples. However, it was not added in JCL022111.

, Kiscei: Kiscei Pharmaceutical Company, LTD.

Note: for study PK2009, the intra-assay accuracy was within the acceptable range. The -15.9% relative error occurred at the LLOQ.

Table 36: Summary of bioanalytical methods and corresponding PK studies (continued)

Study No.	Method	Sample (mL)	Target substance	Intra-assay Variability		Inter-Assay Variability		PK Study in which Method was Used	Study site
				Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)		
JCL022111	LC/MS/MS	Plasma filtrate (0.2)	silodosin	1.9 – 12.6	-6.0 – 3.8	4.1 – 10.9	-1.0 – 1.0	KMD-309	—
			KMD-3213G	1.4 – 11.9	-6.0 – 14.6	3.9 – 8.6	-0.1 – 14.2		
JCL027251	HPLC fluorescence method	Urine (1)	silodosin	0.7 – 17.3 ^{b)}	-5.0 – 6.7	3.3 – 11.0	0.0 – 2.8	KMD-309	—
05-8753b	LC-MS/MS	Plasma (0.200)	Silodosin	1.6 – 4.8	-5.7 – 7.2	3.9 – 4.9	-1.0 – 3.2	S105008 S106004 S107004 S104009 S105010 S106008 S105014	—
			KMD-3213G	2.2 – 6.3	-5.5 – -3.3	11.9 – 18.9	-7.0 – -4.7		
			KMD-3293	1.1 – 6.5	-4.4 – 12.0	11.8 – 19.0	-6.9 – 0.4		
06-8920	LC-MS/MS	Plasma (0.200)	KMD-3295	4.1 – 15.0	-12.0 – 1.04	7.7 – 12.7	-5.1 – 0.8	S106004	—
06-9207	LC-MS/MS	Plasma (0.100)	KMD-3310	2.0 – 7.0	-8.8 – 7.0	5.5 – 7.1	-4.3 – 1.0	S106004	—

b) Values at lower limit of quantification.

^{j)} was added to the plasma and urine samples. However, it was not added in JCL022111.

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Table 36: Summary of bioanalytical methods and corresponding PK studies (continued)

Table 2.7.1-14 Summary of Bioanalytical Methods and Corresponding Pharmacokinetic Studies (continued)

Study No.	Method	Sample (mL)	Target substance	Intra-assay Variability		Inter-Assay Variability		PK Study in which Method was Used	Study site
				Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)		
06-8877a	LC-MS/MS	Unbound Plasma (0.050)	Sildenafil	2.2 - 6.0	-9.7 - 2.0	4.3 - 6.4	-5.4 - -3.2	SI05010	—
			KMD-3213G	3.0 - 9.7	-7.0 - 10.0	6.4 - 8.7	0.0 - 3.3		
			KMD-3293	1.8 - 8.7	-9.3 - 10.0	4.7 - 8.7	0.5 - 3.7		
06-8879b	LC-MS/MS	Urine (0.200)	Sildenafil	1.1 - 7.5	-0.5 - 12.0	2.7 - 6.3	3.2 - 7.3	SI05010	—
			KMD-3213G	6.6 - 14.3	-18.0 - 14.0	11.3 - 16.1	-5.7 - -1.7		
			KMD-3293	2.3 - 12.9	-16.0 - 10.0	7.8 - 10.8	-8.4 - 2.4		
06-8881b	LC-MS/MS	Urine (0.100)	KMD-3310	2.2 - 13.7	-12.8 - 15.6	10.1 - 16.2	1.0 - 5.6	SI05010	—

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Appendix 4.2.2

Review notes on selected preclinical studies

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Study PK10049: CYP inhibition potential

This study evaluated the effects of KMD-3213, KMD-3293 and KMD-3213G on the metabolic activities of Cytochrome P450 in an in-vitro test system with pooled human liver microsomes. Each metabolic activity was investigated using the substrate for each CYP isoform and estimated by measuring the produced metabolite by the LC/MS/MS method. The following substrates (and their respective activities) were used: 7-ethoxyresorufin (CYP1A2), coumarin (CYP2A6), tolbutamide (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), chlorzoxazone (CYP2E1) and midazolam (CYP3A4).

The IC₅₀ values of KMD-3213 against the metabolic activities of CYP2D6 and CYP3A4 were 21.7 and 100.3 μM, respectively. The IC₅₀ values against other CYP activities were greater than at least 200 μM.

The IC₅₀ values of KMD-3293 were higher than 300 μM against all the activities of CYP isoforms. The IC₅₀ values of KMD-3213G were higher than at least 150 μM against all the CYP activities.

Based on primary PK study SI6004, the mean C_{max} for KMD-3213, KMD-3213G, and KMD-3293 were 61.6 ng/mL (0.124 μM), 102.4 ng/mL (0.144 μM), and 34.3 ng/mL (0.067 μM), respectively. Since the IC₅₀ values of KMD-3293 and KMD-3213G were greater than at least 150 μM, it was considered that these compounds also have low potential for causing drug-drug interactions due to inhibition of CYP-mediated metabolism. IC₅₀ values of KMD-3213 against CYP2D6 and CYP3A4 were 21.7 μM and 100.3 μM, respectively. K_i was estimated based on equation $K_i = \frac{1}{2} IC_{50}$ assuming competitive inhibition or $K_i = IC_{50}$ assuming non-competitive inhibition. The resulting KMD-3213 [I]/K_i ratios for CYP2D6 were 0.011 and 0.006 assuming competitive or non-competitive inhibition, respectively. The data suggests that at therapeutic concentration, KMD-3213 is unlikely to inhibit CYP2D6 activity ([I]/K_i < 0.1). KMD-3213 [I]/K_i ratios (where [I] = maximum steady state plasma total concentration (bound + unbound)) for CYP3A4 were <0.005 regardless of competitive or non-competitive inhibition assumptions. It was noted that 2C8 was not tested. Accuracy of calibration curves for the substrates metabolites were acceptable.

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Study ZXA0002: CYP induction potential.

This evaluated the potential of silodosin and metabolites KMD-3213G and KMD-3293 to induce the metabolic activity of CYP enzymes in cultured human hepatocytes. Concentrations up to 1950 ng/ml were used for silodosin and KMD-3293 and up to 3150 ng/mL of KMD-3213G.

Effect on 7-ethoxyresoruffin O-deethylase (CYP1A2) or midazolam 1'-hydroxylase (CYP3A4/5) activities showed no evidence of >2-fold or a concentration-dependent induction by KMD-3213, KMD-3213G, or KMD-3293. Positive controls for CYP1A2 (100 µM omeprazole) and CYP3A4/5 (20 µM rifampicin) induced >2-fold increase in all incubations with one exception. Hepatocytes from one donor (donor — showed only a 1.14-fold increase in CYP1A2 activity with omeprazole but did showed a 2.91 fold increase in concentration of resoruffin produced. Maximum relative potency (to the active control) was 2% for CYP1A2 and 23% for CYP3A4/5 (less than the 40% general cut-off for positive induction signal). It was noted that hepatocytes from donor — did not show adequate CYP1A2 activity and was not used for assessment of CYP1A2 induction. Hepatocytes from a fourth donor (donor — were used to give n=3 for the evaluation of CYP1A2.

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Current FDA draft guidance on in vivo drug interaction studies indicates that CYP3A4 is sensitive to all known co-inducers of CYP3A4, CYP2C8, CYP2C9, and CYP2C19. Since no induction of CYP3A4 was observed, it suggests that silodosin and its metabolites KMD-3213G and KMD-3293 do not induce metabolic activity of CYP2C8, CYP2C9, or CYP2C19.

Table 37: Effect of silodosin, KMD-3213G, and KMD-3293 treatment on CYP1A2 and CYP3A4/5 activity in cultured human hepatocytes.

Donor	CYP1A2 ^a						CYP3A4/5 ^a					
	KMD-3213		KMD3213G		KMD3293		KMD-3213		KMD3213G		KMD3293	
	Fold induction ^b	Relative potency (%) ^c	Fold induction ^b	Relative potency (%) ^c	Fold induction ^b	Relative potency (%) ^c	Fold induction ^b	Relative potency (%) ^c	Fold induction ^b	Relative potency (%) ^c	Fold induction ^b	Relative potency (%) ^c
—	a	a	0.81	-8	a	a	1.38	5	0.85	-2	0.90	-1
—	0.89	-2	0.95	-1	0.77	-4	1.40	3	0.94	-1	1.48	4
—	0.58	-302	0.57	-73	0.43	-639	0.65	-11	1.35	16	1.48	10
—	0.46	-14	1.00	0	0.94	-1	b	e	b	b	b	b

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^a Calculated using protein normalised activity data
^b The magnitude of induction of either CYP1A2 or CYP3A4/5 by either KMD-3213 (1950 ng/mL), KMD-3213G (3150 ng/mL) or KMD-3293 (1950 ng/mL) expressed as fold incubation compared to the solvent control
^c The magnitude of induction of either CYP1A2 or CYP3A4/5 by either KMD-3213 (1950 ng/mL), KMD-3213G (3150 ng/mL) or KMD-3293 (1950 ng/mL) expressed as a % of that elicited by the respective positive control (CYP1A2: omeprazole, CYP3A4/5: rifampicin)
^d Activity data not considered sufficiently robust to use in these calculations
^e Donor not used for this assay

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Study PK10153: Protein binding of KMD-3213

In-vitro protein binding study using [C14]-KMD-3213 (study PK10153) and ultrafiltration techniques showed binding rate to plasma protein was almost constant over the concentration range of 100 – 500 ng eq./mL. The incubation condition was 5 minutes at 37 degree C in human plasma, human serum albumin (40 mg/mL), human serum globulins (10 mg/mL), or human alpha 1 acid glycoprotein (0.9 mg/mL). Each condition was tested in triplicate.

Table 38: Protein binding rate of [14C]-silodosin

Nominal Concentration (ng eq./mL)	Human Plasma (%)	Rat Plasma (%)	Dog Plasma (%)	Albumin (%)	γ -globulin (%)	α_1 -acid glycoprotein (%)
100	95.6±0.7	80.3±1.7	80.1±3.4	34.9±1.3	7.4±1.5	94.3±0.5
200	95.8±0.2	81.4±1.2	81.3±3.8	34.7±2.4	4.6±3.9	96.0±0.2
500	94.6±0.4	79.9±1.2	81.6±2.7	35.4±2.2	5.9±3.1	95.7±0.7

Each value represents the mean ±S.D. of three data

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Study DMPK2003-0053: Protein binding of KMD-3213G

In vitro protein binding study DMPK2003-0053 uses the same incubation conditions as study PK 10153 for KMD-3213 with respect to time, temperature, sample size (n=3), and protein concentration. KMD-3213G was measured using HPLC with UV detection with LLOQ of 10 ng/mL. KMD-3213G binding to human plasma were $92.0 \pm 0.9\%$ and $91.2 \pm 0.6\%$ at concentrations of 200 ng/mL and 500 ng/mL, respectively. Binding to rat and dog plasma were lower. KMD-3213G binds mainly to alpha1-acid glycoprotein.

Table 39: Protein binding of KMD-3213G in human, rat, and dog plasma

Concentration (ng/mL)	Protein binding (%)		
	Human	Rat	Dog
200	92.0 ± 0.9	71.5 ± 2.9	59.5 ± 4.4
500	91.2 ± 0.6	67.5 ± 1.8	63.8 ± 2.2

Each value represents the mean \pm S.D. (standard deviation) of 3 determinations.

Table 40: Protein binding of KMD-3213G to human serum proteins

Concentration (ng/mL)	Protein binding (%)		
	HSA	HSG	AGP
200	33.8 ± 3.7	20.4 ± 2.5	84.8 ± 1.7
500	35.7 ± 3.1	11.7 ± 3.8	85.9 ± 0.4

HSA: Human serum albumin

HSG: Human serum γ -globulin

AGP: α_1 -acid glycoprotein

Each value represents the mean \pm S.D. (standard deviation) of 3 determinations.

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Study DMPK2004-0033: Protein binding of KMD-3293

In vitro study DMPK2004-0033 used the same incubation conditions as study PK 10153 for KMD-3213 with respect to time, temperature, sample size (n=3), and protein concentration. KMD-3293 was measured using HPLC with UV detection with LOQ of 10 ng/mL. KMD-3293 binding to human plasma was $91.9 \pm 0.4\%$ and $90.2 \pm 1.2\%$ at concentrations of 200 ng/mL and 500 ng/mL, respectively.

Table 41: Protein binding of KMD-3293 in human plasma

Concentration (ng/mL)	Protein binding (%)
200	91.9 ± 0.4
500	90.2 ± 1.2

Each value represents the mean \pm S.D. (standard deviation) of 3 determinations.

Table 42: Protein binding of KMD-3293 to human serum proteins

Concentration (ng/mL)	Protein binding (%)		
	HSA	HSG	AGP
200	28.8 ± 0.9	7.2 ± 1.3	92.1 ± 0.6
500	31.1 ± 1.9	3.9 ± 3.7	92.1 ± 0.8

HSA: Human serum albumin

HSG: Human serum γ -globulin

AGP: α_1 -acid glycoprotein

Each value represents the mean \pm S.D. (standard deviation) of 3 determinations.

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Study PK10091: Human blood to plasma ratio (R_B) of KMD-3213

The R_B value was 0.51 ± 0.04 and 0.55 ± 0.03 at the [14C]-KMD-3213 concentrations of 24 ng eq./mL and 121 ng eq./mL, respectively (n=3 each). The percentage of associated with blood cells was $2.2 \pm 3.8\%$ (range 0.0 – 6.6%) and $3.7 \pm 3.4\%$ (range 0.4 – 7.2%) at the [14C]-KMD-3213 concentrations of 24 ng eq./mL and 121 ng eq./mL, respectively. The data indicate that most of the KMD-3213 was present in plasma.

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Study KMD-OIR001 - Identification of Cytochrome P450 isozymes involved in the metabolism of KMD-3213 and examination of Michaelis-Menten kinetics for the metabolism of KMD-3213.

In vitro experiments were performed using human liver microsomes and CYP isozyme selective inhibitors (furafylline (CYP1A1/2), coumarin (CYP2A6), sulfafenazole (CYP2C9), S-mephenytoin (CYP2C19), quinidine (CYP2D6), diethyldithiocarbamate (CYP2E1), and ketoconazole (CYP3A4)) to estimate the CYP isozymes involved in the oxidative metabolism of KMD-3213, generating major metabolites such as KMD-3241, KMD-3289, and KMD-3250. cDNA-expressed human CYP microsomes were attempted but were not used due to its use past expiration of stable period.

Reaction was conditioned at 37 °C for 10 minutes, and 100 µM KMD-3213 in duplicates.

Analyses of KMD-3213, KMD-3241, KMD-3289, and KMD-3250 in reactions were performed by HPLC.

Among the isoforms tested, CYP3A4 is the major isoform involved in the metabolism of KMD-3213. The CYP2C8 isoform was not tested. *Small sample size (n=2) and assay validation not provided.*

Table 43: Effects of CYP inhibitors on KMD-3213 metabolism

A) Effects of inhibitors on KMD-3213 decrease

Inhibitor	Conc. (µM)	CYP isozyme	Inhibition (%)
Furafylline	5	1A1/2	18.5
Coumarin	100	2A6	3.3
Sulfafenazole	20	2C9	0.0
S-mephenytoin	500	2C19	0.0
Quinidine	5	2D6	16.9
Diethyldithiocarbamate	50	2E1	0.0
Ketokonazole	2	3A4	70.6

B) Effects of inhibitors on metabolite generation

Inhibitor	Conc. (µM)	CYP isozyme	Inhibition (%)		
			KMD-3241	KMD-3289	KMD-3250
Furafylline	5	1A1/2	10.0	14.1	20.5
Coumarin	100	2A6	1.6	0.1	4.1
Sulfafenazole	20	2C9	8.5	8.7	15.6
S-mephenytoin	500	2C19	0.0	0.0	0.0
Quinidine	5	2D6	5.6	3.2	-
Diethyldithiocarbamate	50	2E1	18.4	18.6	21.8
Ketokonazole	2	3A4	75.4	85.4	96.5

-: Determination was impossible.

Study DMPK2003-0037 - Identification of the enzyme responsible for production of metabolite KMD-3310 from KMD-3213.

Incubation in human liver microsome and CYP inhibitors 1 μM a-naphthoflavone (CYP1A2), 0.5 μM tranylcypromine (CYP2A6), 20 μM sulfaphenazole (CYP2C9), 200 μM S-(+)-mephenytoin (CYP2C19), 0.5 μM quinidine (CYP2D6), 100 μM 4-methylpyrazole (CYP2E1), and 2 μM ketoconazole (CYP3A4) were used. Incubations were done in duplicates.

The KMD-3310 production activity was reduced to 5.6% of the control activity by addition of 2 μM ketoconazole. On the other hand, the production of KMD-3310 with other inhibitors ranged from 76.6 to 95.3% of the control.

With near complete inhibition by ketoconazole, it appears that CYP3A4 in the human liver microsomes is mainly responsible for the metabolism of KMD-3310 from KMD-3213. Note that KMD-3310 is a minor metabolite.

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Study PK-03-010: The effects of various drugs on the CYP3A4- mediated metabolism of KMD-3213.

Results indicated that ketoconazole is likely to inhibit the metabolism of KMD-3213. No in depth review of this report was needed since an in vivo study with strong CYP3A4 inhibitor was submitted to this NDA.

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Study PK10126: Elucidation of the enzyme responsible for the metabolism of KMD-3213 to its metabolite KMD-3293.

KMD-3293 formation was insignificant (below LOQ of 0.1 μM) with human liver microsomes (30 minutes, 100 μM KMD-3213) – suggesting little involvement of CYP450. Additional assays with S9 fraction and dehydrogenase substrates and inhibitors suggested that alcohol dehydrogenase and aldehyde dehydrogenase were involved in the formation of KMD-3293 from KMD-3213.

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Study PK-03-002: Contribution of P-glycoprotein to membrane permeation of KMD-3213.

In this study contribution of P-glycoprotein (P-gp) to membrane permeation of KMD-3213 was investigated using vinblastine-treated P-gp over-expressed Caco-2 cell monolayers.

Membrane permeation of [14C]-KMD-3213 (10 µM) across Caco-2 cell monolayers were evaluated in both "Apical (A) to Basolateral (B)" direction and "B to A" direction after 21 day-culture period following inoculation on  insert. Caco-2 cells were cultured in the medium added by vinblastine at 10 nM. Digoxin was used as positive control for the Caco-2 system. b(4)

Apparent membrane permeation coefficient (Papp) of [14C]-KMD-3213 in "B to A" direction (25.205×10^{-6} cm/s) was 8.4 times higher than that in "A to B" direction (3.007×10^{-6} cm/s), which suggests directionality of KMD-3213 permeation across Caco-2 cell monolayers. In a separate experiment, this directionality was modified by the addition of verapamil known as a P-gp inhibitor. Without verapamil Papp in "B to A" direction (25.783×10^{-6} cm/s) was 10.4 times higher than that in "A to B" direction (2.477×10^{-6} cm/s). Under the presence of verapamil, Papp in "B to A" direction decreased to 19.697×10^{-6} cm/s (with 10 µM verapamil), 11.734×10^{-6} cm/s (60 µM), or 11.356×10^{-6} cm/s (100 µM) dependent on verapamil concentration while "A to B" increased to 8.754×10^{-6} cm/s (10 µM), 15.613×10^{-6} cm/s (60 µM), or 14.001×10^{-6} cm/s (100 µM). As the increase of verapamil concentration the difference between "B to A" and "A to B" were disappeared. At 10 µM, same concentration of [14C]-KMD-3213, it was 2.2 times, though it was completely disappeared (0.8 times) over 60 µM.

These results indicated that there is directionality in the membrane permeation of KMD-3213 across Caco-2 cell monolayers and P-gp contributes this directionality.

Table 44: Effect of verapamil on [14C]KMD-3213 permeation across P-gp over-expressed Caco-2 cell monolayers

Verapamil conc. (µM)	Papp ($\times 10^{-6}$ cm/s)		
	A to B direction	B to A direction	(B to A) / (A to B)
0 (control)	2.477 ± 0.160	25.783 ± 1.250	10.4
10	8.754 ± 0.752	19.697 ± 0.551	2.2
60	15.613 ± 0.810	11.734 ± 0.651	0.8
100	14.001 ± 0.357	11.356 ± 0.417	0.8

Values are mean ± S.D. of three monolayers.

A ; Apical side, B ; Basolateral side

Added ¹⁴C-KMD-3213 concentration was 11 µM.

Verapamil was added in both A and B sides.

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Appendix 4.2.3

Individual study reviews and review notes on selected clinical studies

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Study SI7004 Individual Study Review

Title: An Investigation of the Dose Proportionality of Silodosin and Metabolites KMD- 3213G and KMD-3293 in Healthy Male Subjects after Single and Multiple doses of 4 and 8 mg.

Objectives: The primary objective was to assess the dose-proportionality of silodosin and metabolites KMD-3213G and KMD-3293 in healthy male subjects after one and seven daily doses of 4 and 8 mg. The secondary objective was to assess the safety and tolerability of silodosin.

Methods: this was a single-center, open-label, multiple dose, randomized 2-period crossover study in 22 young healthy male subjects aged 18 – 45 years. The subjects' race included 18 Whites and 4 Blacks.

The doses were one or two silodosin 4 mg capsules once daily within 30 minutes after breakfast for 7 days. The 2 periods of dosing were separated by a 7-day washout period.

Pharmacokinetic Variables: For each period on Days 1 and 7, plasma sampling for analysis of silodosin and metabolites KMD-3213G and KMD-3293 were collected pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours post-dose.

Method validation: The assay for silodosin was validated and acceptable. The assays for KMD-3213G and KMD-3293 used an expanded acceptance criteria for precision of $\pm 20\%$ at all concentrations and does not meet FDA's acceptance criteria. Therefore, the results for KMD-3213G and KMD-3293 should be interpreted with caution. Note: the study-specific bioanalytical report was not provided for this study.

Results:

Demographics: The study enrolled young healthy males, mostly of White race.

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Table 45: Summary of subjects' demographic and physical characteristics

Demographic Variable	Statistic	Sequence 1 N=11	Sequence 2 N=11	Overall N=22
Ethnicity				
Hispanic or Latino	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Hispanic or Latino	n (%)	11 (100.0%)	11 (100.0%)	22 (100.0%)
Race				
American Indian or Alaska Native	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asia	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black or African American	n (%)	2 (18.2%)	2 (18.2%)	4 (18.2%)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	n (%)	9 (81.8%)	9 (81.8%)	18 (81.8%)
Age (yrs)				
	Mean (SD)	31.2 (9.03)	28.8 (7.51)	30.0 (8.19)
	Median (25th, 75th percentile)	33.2 (23.7, 41.5)	25.7 (23.6, 35.2)	26.1 (23.7, 35.2)
	Min, Max	18.2, 45.0	21.3, 44.3	18.2, 45.0
	n	11	11	22
Weight (kg)				
	Mean (SD)	74.6 (9.53)	74.9 (11.56)	74.8 (10.34)
	Median (25th, 75th percentile)	73.0 (68.0, 84.0)	71.0 (66.0, 84.4)	73.0 (68.0, 84.0)
	Min, Max	58.4, 87.8	53.4, 89.5	53.4, 89.5
	n	11	11	22
Height (cm)				
	Mean (SD)	176.5 (4.76)	174.7 (8.03)	175.6 (6.50)
	Median (25th, 75th percentile)	176.0 (173.0, 182.0)	178.0 (167.0, 180.0)	176.5 (172.0, 180.0)
	Min, Max	168.0, 183.0	161.0, 185.0	161.0, 185.0
	n	11	11	22
BMI (kg/m²)				
	Mean (SD)	24.0 (3.23)	24.5 (3.21)	24.2 (3.15)
	Median (25th, 75th percentile)	23.3 (21.3, 26.9)	25.0 (22.2, 26.2)	24.9 (21.7, 26.2)
	Min, Max	20.1, 29.3	19.1, 29.8	19.1, 29.8
	n	11	11	22

Denominators for percentages are based on the number of subjects in the Safety population for each sequence and overall
Sequence 1 = 4 mg; 8 mg; Sequence 2 = 8 mg; 4 mg

Single-dose PK:

Table 46: Summary of silodosin PK parameters – single dose, part 1 of 2

Parameter	Statistic	4 mg N=22	8 mg N=22
AUC [0-24] (ng·hr/mL)	Mean (SD)	144.70 (65.732)	290.64 (105.426)
	SEM	14.014	22.477
	CV (%)	45.43	36.27
	Median (25th, 75th percentile)	147.38 (108.48, 164.45)	273.23 (222.87, 360.91)
	Min, Max	32.35, 311.95	106.66, 557.31
	n	22	22
	P-value ¹		0.9727
Cmax (ng/mL)	Mean (SD)	28.72 (13.248)	54.50 (25.948)
	SEM	2.825	5.532
	CV (%)	46.13	47.62
	Median (25th, 75th percentile)	28.35 (18.30, 38.00)	50.05 (36.90, 61.70)
	Min, Max	8.84, 55.30	16.20, 118.00
	n	22	22
	P-value ¹		0.7115

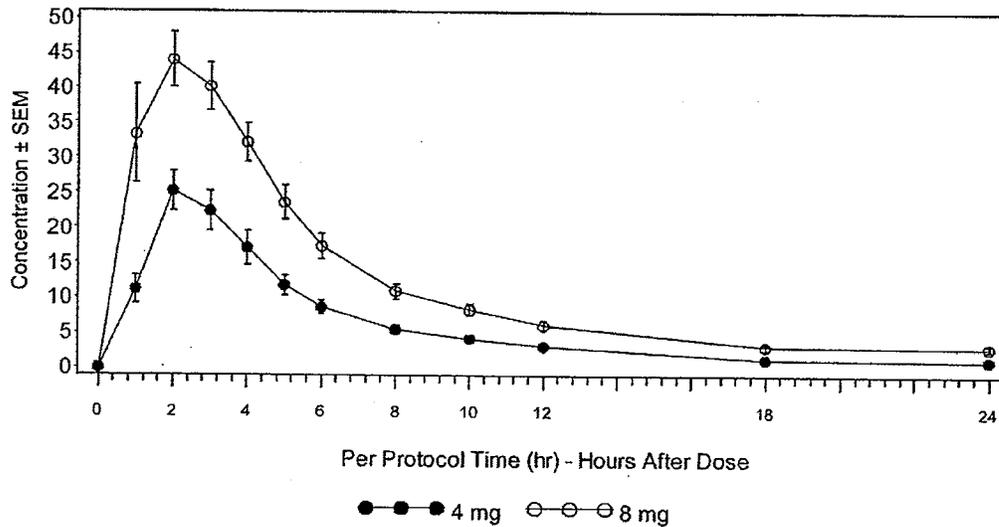
¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05
See Output 16.1.9.2-1 Part 1: Single Dose

Table 47: Summary of silodosin PK parameters – single dose, part 2 of 2

Parameter	Statistic	4 mg N=22	8 mg N=22
Tmax (hr)	Mean (SD)	2.3 (0.94)	2.4 (1.05)
	SEM	0.20	0.22
	CV (%)	41.1	44.4
	Median (25th, 75th percentile)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
	Min, Max	1.0, 5.0	1.0, 4.0
	n	22	22
kel (hr ⁻¹)	Mean (SD)	0.0736 (0.02881)	0.0724 (0.02581)
	SEM	0.00720	0.00563
	CV (%)	39.1247	35.6240
	Median (25th, 75th percentile)	0.0741 (0.0529, 0.0884)	0.0668 (0.0581, 0.0850)
	Min, Max	0.0279, 0.1357	0.0084, 0.1213
	n	16	21
t½ (hr)	Mean (SD)	11.1 (5.21)	13.3 (16.09)
	SEM	1.30	3.51
	CV (%)	46.9	120.6
	Median (25th, 75th percentile)	9.4 (7.9, 13.3)	10.4 (8.2, 11.9)
	Min, Max	5.1, 24.8	5.7, 82.6
	n	16	21

¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05
See Output 16.1.9.2-1 Part 1: Single Dose

Figure 13: Mean (SEM) silodosin plasma concentration (ng/mL) – single dose



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Table 48: Summary of KMD-3213G PK parameters – single dose, part 1 of 2

Parameter	Statistic	4 mg N=22	8 mg N=22
AUC [0-24] (ng·hr/mL)	Mean (SD)	233.73 (176.900)	513.63 (345.896)
	SEM	37.715	73.745
	CV (%)	75.69	67.34
	Median (25th, 75th percentile)	165.98 (113.00, 346.05)	367.08 (259.69, 605.04)
	Min, Max	16.01, 662.20	176.46, 1421.30
	n	22	22
	P-value ¹		0.6638
Cmax (ng/mL)	Mean (SD)	19.17 (8.486)	38.30 (16.013)
	SEM	1.809	3.414
	CV (%)	44.26	41.81
	Median (25th, 75th percentile)	17.85 (13.80, 25.00)	31.45 (29.20, 52.70)
	Min, Max	4.44, 36.30	18.60, 79.10
	n	22	22
	P-value ¹		0.9923

¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05
See Output 16.1.9.2-2 Part 1: Single Dose

Table 49: Summary of KMD-3213G PK parameters – single dose, part 2 of 2

Parameter	Statistic	4 mg N=22	8 mg N=22
Tmax (hr)	Mean (SD)	5.2 (3.35)	4.7 (1.29)
	SEM	0.71	0.27
	CV (%)	64.6	27.5
	Median (25th, 75th percentile)	4.0 (4.0, 5.0)	4.5 (4.0, 6.0)
	Min, Max	2.0, 18.0	3.0, 8.0
	n	22	22
	kel (hr ⁻¹)	Mean (SD)	0.0537 (0.03137)
	SEM	0.00946	0.00651
	CV (%)	58.4483	46.2522
	Median (25th, 75th percentile)	0.0480 (0.0371, 0.0802)	0.0623 (0.0417, 0.0807)
	Min, Max	0.0073, 0.1073	0.0200, 0.1462
	n	11	22
t _{1/2} (hr)	Mean (SD)	21.8 (24.91)	13.0 (6.86)
	SEM	7.51	1.46
	CV (%)	114.2	52.7
	Median (25th, 75th percentile)	14.4 (8.6, 18.7)	11.1 (8.6, 16.6)
	Min, Max	6.5, 94.4	4.7, 34.7
	n	11	22

¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05
See Output 16.1.9.2-2 Part 1: Single Dose

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Figure 14: Mean (SEM) KMD-3213G plasma concentration (ng/mL) – single dose

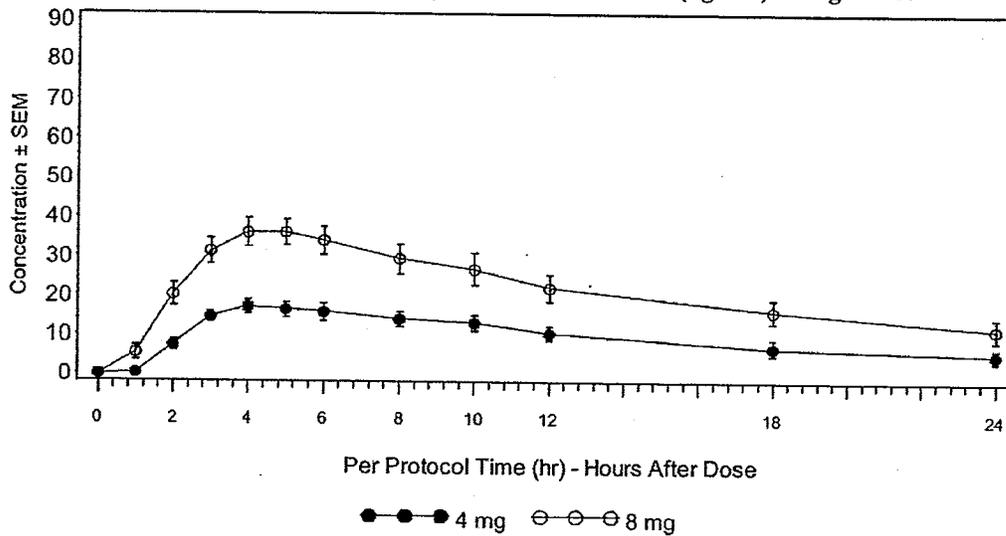


Table 50: Summary of KMD-3293 PK parameters – single dose, part 1 of 2

Parameter	Statistic	4 mg	8 mg
		N=22	N=22
AUC [0-24] (ng·hr/mL)	Mean (SD)	246.98 (215.546)	546.04 (393.687)
	SEM	45.955	83.934
	CV (%)	87.27	72.10
	Median (25th, 75th percentile)	137.51 (108.85, 293.20)	475.51 (234.97, 754.50)
	Min, Max	61.95, 743.25	48.56, 1311.55
	n	22	22
	P-value ¹		0.6778
Cmax (ng/mL)	Mean (SD)	20.75 (10.302)	39.78 (18.964)
	SEM	2.196	4.043
	CV (%)	49.66	47.68
	Median (25th, 75th percentile)	17.15 (13.20, 22.80)	36.40 (25.30, 51.50)
	Min, Max	8.38, 42.40	9.06, 86.30
	n	22	22
	P-value ¹		0.7749

¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05
See Output 16.1.9.2-3 Part 1: Single Dose

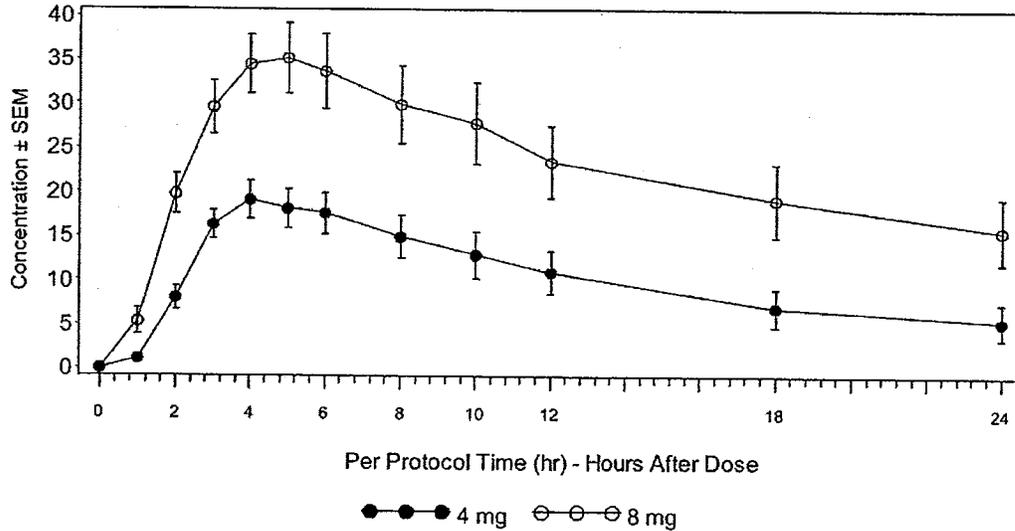
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Table 51: Summary of KMD-3293 PK parameters – single dose, part 2 of 2

Parameter	Statistic	4 mg N=22	8 mg N=22
T _{max} (hr)	Mean (SD)	4.3 (1.67)	5.3 (4.30)
	SEM	0.36	0.92
	CV (%)	39.0	81.6
	Median (25th, 75th percentile)	4.0 (4.0, 4.0)	4.0 (4.0, 5.0)
	Min, Max	2.0, 10.0	3.0, 24.0
	n	22	22
k _{el} (hr ⁻¹)	Mean (SD)	0.0591 (0.03453)	0.0656 (0.03752)
	SEM	0.00997	0.00861
	CV (%)	58.4304	57.1529
	Median (25th, 75th percentile)	0.0485 (0.0410, 0.0778)	0.0602 (0.0394, 0.0931)
	Min, Max	0.0084, 0.1384	0.0209, 0.1619
	n	12	19
t _{1/2} (hr)	Mean (SD)	19.1 (20.95)	14.5 (8.61)
	SEM	6.05	1.98
	CV (%)	109.5	59.4
	Median (25th, 75th percentile)	14.3 (8.9, 17.1)	11.5 (7.4, 17.6)
	Min, Max	5.0, 82.9	4.3, 33.2
	n	12	19

*P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05
See Output 16.1.9.2-3 Part 1: Single Dose

Figure 15: Mean (SEM) KMD-3293 plasma concentration (ng/mL) – single dose



Multiple-dose PK:

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Table 52: Summary of silodosin PK parameters – multiple doses

Parameter	Statistic	4 mg N=22	8 mg N=22
AUC [0-24] (ng-hr/mL)	Mean (SD)	159.49 (69.956)	297.34 (106.851)
	SEM	14.915	22.781
	CV (%)	43.86	35.94
	Median (25th, 75th percentile)	156.16 (115.18, 181.37)	275.92 (236.07, 361.66)
	Min, Max	63.86, 375.04	120.97, 594.14
	n	22	22
	P-value ¹		0.5676
Cmax (ng/mL)	Mean (SD)	28.36 (12.401)	51.14 (17.144)
	SEM	2.644	3.655
	CV (%)	43.73	33.52
	Median (25th, 75th percentile)	26.05 (20.30, 32.30)	50.30 (40.50, 61.00)
	Min, Max	9.85, 60.50	16.20, 88.30
	n	22	22
	P-value ¹		0.3909
Tmax (hr)	Mean (SD)	2.4 (0.73)	2.5 (0.80)
	SEM	0.16	0.17
	CV (%)	30.5	31.4
	Median (25th, 75th percentile)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
	Min, Max	1.0, 4.0	2.0, 5.0
	n	22	22
	P-value ¹		0.3909
kel (hr ⁻¹)	Mean (SD)	0.0552 (0.02419)	0.0551 (0.02086)
	SEM	0.00555	0.00455
	CV (%)	43.8605	37.8721
	Median (25th, 75th percentile)	0.0489 (0.0410, 0.0809)	0.0573 (0.0385, 0.0630)
	Min, Max	0.0191, 0.0999	0.0295, 0.0941
	n	19	21
	P-value ¹		0.3909
t _{1/2} (hr)	Mean (SD)	15.3 (7.46)	14.4 (5.44)
	SEM	1.71	1.19
	CV (%)	48.9	37.6
	Median (25th, 75th percentile)	14.2 (8.6, 16.9)	12.1 (11.0, 18.0)
	Min, Max	6.9, 36.3	7.4, 23.5
	n	19	21
	P-value ¹		0.3909

¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05

Figure 16: Mean (SEM) silodosin plasma concentration (ng/mL) – multiple dose

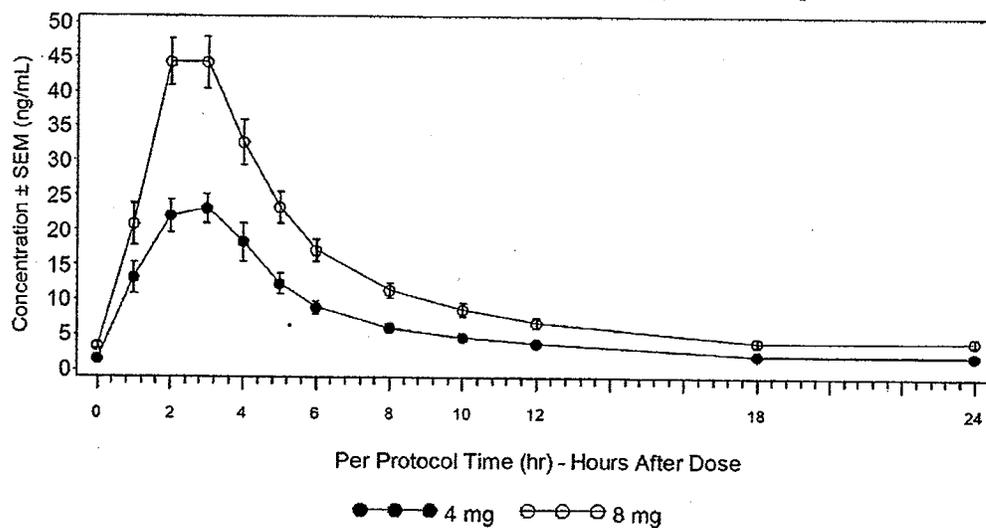


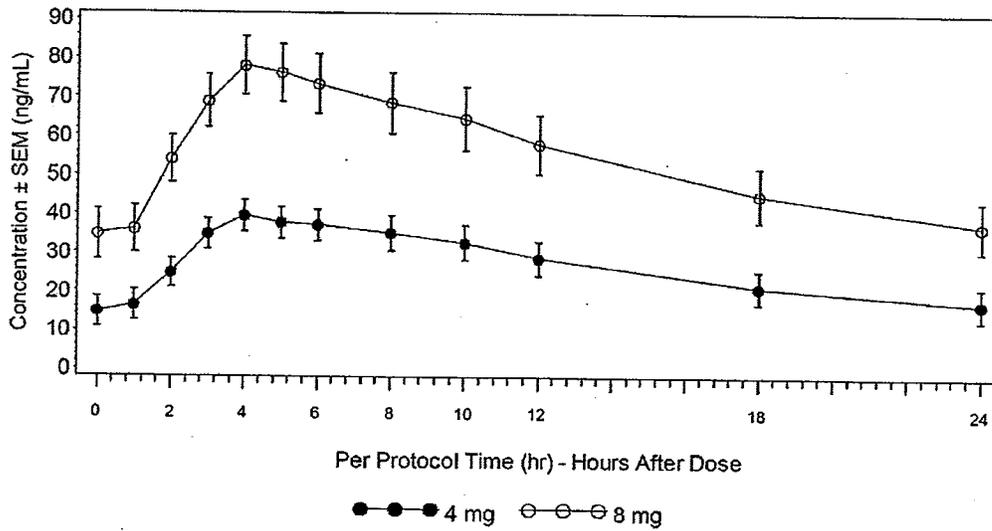
Table 53: Summary of KMD-3293G PK parameters – multiple dose

Parameter	Statistic	4 mg N=22	8 mg N=22
AUC [0-24] (ng·hr/mL)	Mean (SD)	646.41 (464.403)	1326.12 (801.113)
	SEM	99.011	170.798
	CV (%)	71.84	60.41
	Median (25th, 75th percentile)	586.68 (281.00, 906.40)	1083.78 (656.20, 2200.65)
	Min, Max	103.90, 1916.55	435.95, 3259.00
	n	22	22
	P-value ^a		0.8993
Cmax (ng/mL)	Mean (SD)	41.25 (19.952)	81.14 (36.998)
	SEM	4.254	7.888
	CV (%)	48.37	45.60
	Median (25th, 75th percentile)	38.15 (24.40, 54.50)	73.10 (53.90, 112.00)
	Min, Max	20.90, 90.80	36.60, 164.00
	n	22	22
	P-value ^a		0.9079
Tmax (hr)	Mean (SD)	4.8 (1.94)	4.5 (1.44)
	SEM	0.41	0.31
	CV (%)	40.3	32.0
	Median (25th, 75th percentile)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)
	Min, Max	3.0, 10.0	3.0, 10.0
	n	22	22
kel (hr ⁻¹)	Mean (SD)	0.0403 (0.01849)	0.0495 (0.01975)
	SEM	0.00462	0.00421
	CV (%)	45.8846	39.9026
	Median (25th, 75th percentile)	0.0371 (0.0294, 0.0496)	0.0477 (0.0311, 0.0678)
	Min, Max	0.0110, 0.0938	0.0209, 0.0820
	n	16	22
t½ (hr)	Mean (SD)	21.2 (12.47)	16.6 (7.32)
	SEM	3.12	1.56
	CV (%)	58.8	44.1
	Median (25th, 75th percentile)	18.7 (14.0, 23.9)	14.6 (10.2, 22.3)
	Min, Max	7.4, 62.9	8.4, 33.1
	n	16	22

^aP-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0.05

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Figure 17: Mean (SEM) KMD-3213G plasma concentration (ng/mL) - multiple dose



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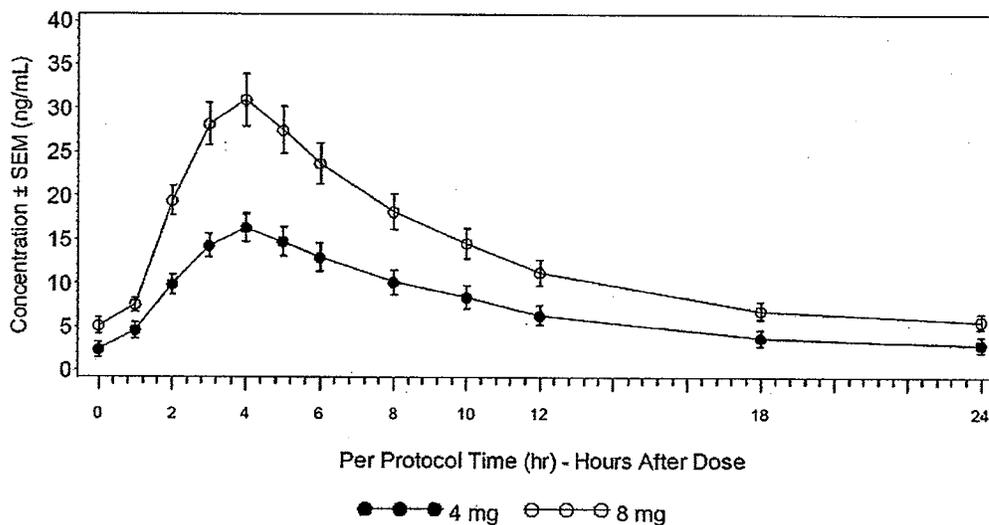
Table 54: Summary of KMD-3293 PK parameters – multiple dose

Parameter	Statistic	4 mg N=22	8 mg N=22
AUC [0-24] (ng·hr/mL)	Mean (SD)	173.64 (122.587)	321.22 (160.715)
	SEM	26.136	34.265
	CV (%)	70.60	50.03
	Median (25th, 75th percentile)	145.62 (108.25, 215.32)	282.56 (202.14, 413.64)
	Min, Max	24.48, 616.45	74.61, 769.66
	n	22	22
	P-value ¹		0.6787
Cmax (ng/mL)	Mean (SD)	17.07 (7.415)	32.32 (13.471)
	SEM	1.581	2.872
	CV (%)	43.44	41.68
	Median (25th, 75th percentile)	15.15 (12.90, 19.00)	29.00 (21.60, 37.10)
	Min, Max	6.06, 37.80	9.74, 68.50
	n	22	22
	P-value ¹		0.6724
Tmax (hr)	Mean (SD)	3.8 (0.91)	3.7 (0.83)
	SEM	0.19	0.18
	CV (%)	23.8	22.2
	Median (25th, 75th percentile)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)
	Min, Max	2.0, 6.0	3.0, 6.0
	n	22	22
kel (hr ⁻¹)	Mean (SD)	0.0643 (0.02420)	0.0711 (0.02825)
	SEM	0.00625	0.00617
	CV (%)	37.6132	39.7577
	Median (25th, 75th percentile)	0.0586 (0.0440, 0.0698)	0.0610 (0.0532, 0.0747)
	Min, Max	0.0363, 0.1269	0.0486, 0.1577
	n	15	21
t _{1/2} (hr)	Mean (SD)	12.0 (3.69)	10.8 (2.80)
	SEM	0.95	0.61
	CV (%)	30.9	26.0
	Median (25th, 75th percentile)	11.8 (9.9, 15.7)	11.4 (9.3, 13.0)
	Min, Max	5.5, 19.1	4.4, 14.3
	n	15	21

¹P-value is from the hypothesis test for dose proportionality; Dose proportionality claimed if P-value from T-test > 0,05

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Figure 18: Mean (SEM) KMD-3293 plasma concentration (ng/mL) – multiple dose



Dose proportionality:

The sponsor performed t-test comparison of dose normalized AUC and C_{max} PK parameters for single dose (Day 1) and multiple dose (Day 7). There were no significant differences detected at $p < 0.05$ level. This reviewer calculated the ratios of dose normalized geometric means and the results (see Table 55) also supported the conclusion of dose proportionality between silodosin 4 mg and 8 mg once daily.

Table 55: Ratio of dose normalized geometric means (8 mg vs. 4 mg) for AUC_{0-24} and C_{max} following administration of 8 mg and 4 mg capsules of Silodosin once a day for 7 days (Study SI7004).

	Ratio of dose normalized AUC_{0-24}		Ratio of dose normalized C_{max}	
	Day 1	Day 7	Day 1	Day 7
Silodosin	1.05	0.96	0.96	0.93
KMD-3213G	1.27	1.12	1.03	0.99
KMD-3293	1.12	1.00	0.95	0.95

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Review notes for study US021-99: Phase 2 dose finding study

Administered 4 mg (n=88), 8 mg (n=90), or placebo (n=86) once daily within 1 hour of morning meal. The study included 2 weeks lead-in adjustment and 6 weeks full dose. 24 hour PK on day 84 (end of study) in a subset of 7 patients. PK sampling at 0 (pre-dose), 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post dose. Dose was given 1 hour after breakfast.

24-hour PK in the subset of 3 patients on the 8 mg dose and 4 patients on the 4 mg dose patients were available. The dataset is too small to conduct exposure response analysis.

There were slightly greater change in American Urologic Association (AUA) symptom index at end of study in the 8 mg group vs. 4 mg group (mean (SD) change from baseline of -6.8 (5.8) and -5.7 (5.5), respectively). No apparent difference was observed between the dose groups at earlier time points. Slightly higher baseline subtracted peak urine flow rate was observed in the 8 mg dose group compared to 4 mg dose group.

Incidence of retrograde ejaculation (15.6% and 11.4%), ejaculation failure (11.1% and 9.1%), and erectile disturbance (3.3% and 2.3%) were higher in the 8 mg dose group compared to the 4 mg dose group. No patient in the placebo arm reported these adverse events.

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Review notes for study KMD-3213-UK01-97: A Double-Blind, Placebo-Controlled, Rising-Dose Study of Single, Oral Doses of KMD-3213 to Determine Safety and Tolerance in Normal Volunteers

N=9 for food effect study. Food content is not known. Design of food effect sequence is 1 mg fasted, then 4 mg fasted, then 4 mg fed as a single sequence cross over study. The dose of 4 mg is lower than the therapeutic dose of 8 mg. The group (n=9 on treatment and n=3 placebo) consisted of 9 Caucasians, 2 Blacks, and 1 of other race.

The study dosed 1 – 16 mg as single dose to 3 groups. Group A: 1 and 4 mg, Group B: 2 and 12 mg, Group C: 8 and 16 mg.

Table 56: Plasma KMD-3213 mean PK parameters by dose level

Dose (mg)	T _{MAX} (h)	C _{MAX} (ng/ml)	k _{el} (h ⁻¹)	t _{1/2} (h)	AUC _{0-t} (ng·h/ml)	AUC _{0-∞} (ng·h/ml)	AUC (ng·h/ml)	AUMC (ng·h ² /ml)	MRT (h)	V/F (L)	CL/f (ml/min)
1.0	1.0 ^a	7.16	0.2453	2.8 ^b	24.1	28.5	29.4	132	4.62	189.8	693.7
2.0	1.0 ^a	13.62	0.2189	3.2 ^b	45	50.7	52.5	308	5.72	213.0	660.2
4.0	0.5 ^a	38.96	0.2119	3.3 ^b	108.2	115.8	127.7	618	5.07	203.0	623.8
8.0	0.5 ^a	76.30	0.1327	5.2 ^b	225.0	237.0	223.7	1125	5.24	307.5	665.7
12.0	0.5 ^a	105.26	0.1043	6.6 ^b	364.8	380.6	343.7	2147	6.29	366.1	620.2
16.0	0.5 ^a	162.01	0.1061	6.5 ^b	561.4	574.2	545.5	3399	6.21	324.5	499.1

Source: Section 11.1.9, Summary Table Page 7

a Value quoted is the median

b Calculated as $\ln 2 / \text{mean } k_{el}$

* This table contains data on administration in the fasting state only

Table 57: Mean PK parameters of 4 mg KMD-3213 in fed and fasted states

State	T _{MAX} (h)	C _{MAX} (ng/ml)	k _{el} (h ⁻¹)	t _{1/2} (h)	AUC _{0-t} (ng·h/ml)	AUC _{0-∞} (ng·h/ml)	AUC (ng·h/ml)	AUMC (ng·h ² /ml)	MRT (h)	V/F (L)	CL/f (ml/min)
Fasted	0.5 ^a	38.96	0.2119	3.3 ^b	108.2	115.8	127.7	618	5.07	203.0	623.8
Fed	1.5 ^a	27.7	0.1537	4.5 ^b	103.5	109.7	127.6	939	6.81	252.0	600.7

Source: Section 11.1.9, Summary Table Page 8

a Value quoted is the median

b Calculated as $\ln 2 / \text{mean } k_{el}$

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Individual study review for study KMD-307-UK: KMD-3213 - A Phase I, Double-Blind, Randomized, Placebo-Controlled Study to Investigate the Interaction Between KMD-3213 and Digoxin in Healthy Male Subjects

Study design:

The study enrolled 24 healthy young Caucasian males. All subjects were administered 0.5 mg digoxin in the morning and evening of Day 1 (12 hour interval) and 0.25 mg digoxin on the morning of Days 2 – 16. Subjects received 4 mg silodosin (n=16, treated group) or placebo (n=6, placebo control for sequence effect group) twice daily (morning and evening at 12 hours intervals) on Days 9 – 16.

PK samplings for digoxin and silodosin (including KMD-3213G and KMD-3293) were as follows:

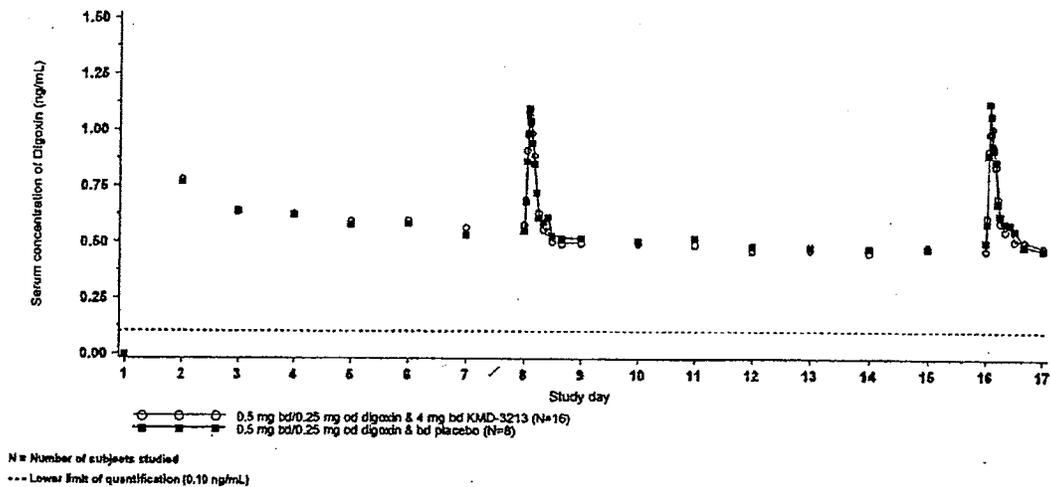
Table 58: PK sampling schedule

Pharmacokinetics:			
Blood sampling for KMD-3213			Days 9 to 16: Pre-am dose Day 17: 12 h post-last dose
Blood sampling for digoxin			Day 1: Pre-am dose Days 2 to 7: Pre-dose Days 8 and 16: Pre-am dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h post-am dose Days 10 to 15: Pre-am dose
Urine sampling for digoxin			Day 1: Pre-am dose (spot collection) Days 8 and 16: 0 to 24 h post-am dose

Results:

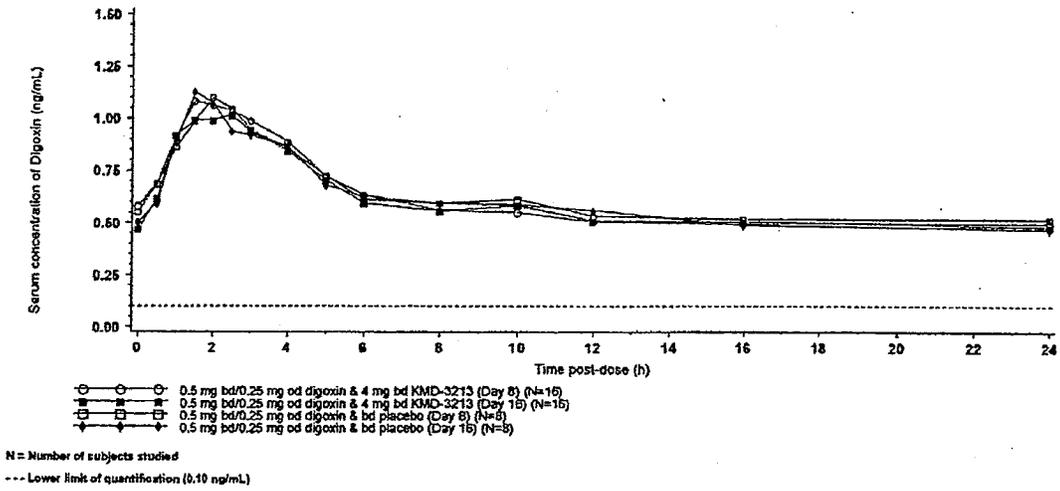
No significant differences in digoxin AUC and C_{max} were observed between Day 16 and Day 8 in groups treated with silodosin (Table 59). Silodosin administration also did not affect the amount of unchanged digoxin excreted in the urine (Table 59). The same comparisons in the placebo group also yielded a lack of difference in digoxin PK, indicating there was not an effect of sequence (Table 60). These data indicate that coadministration of silodosin 4 mg twice daily does not alter the PK of digoxin.

Figure 19: Geometric mean serum concentration of digoxin following multiple oral doses



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Figure 20: Geometric mean serum digoxin concentration on Days 8 and 16



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Table 59: Summary of digoxin PK parameters following multiple oral doses alone (Day 8) and in combination with silodosin (Day 16)

Parameter	Day 8 ^a (N=16)	Day 16 ^b (N=16)	Ratio of geometric LS means (Day 16: Day 8)	90% CI for ratio of geometric LS means (Day 16: Day 8)
AUC(0- τ) (ng.h/mL)	14.7 (20.1)	14.4 (16.0)	0.984	0.936, 1.03
C _{max} (ng/mL)	1.26 (21.2)	1.25 (14.0)	0.992	0.912, 1.08
t _{max} ^c (h)	1.88 (0.738)	1.92 (0.811)	NC	NC
C _{trough} (ng/mL)	0.500 (22.8)	0.483 (18.6)	0.965	0.903, 1.03
CL _{ss} /F (mL/min)	284 (20.1)	289 (16.0)	NC	NC
CL _{ss} /F [norm] (mL/min/kg)	3.69 (17.2)	3.76 (14.2)	NC	NC
Ae _{τ} (μ g)	144 (16.1)	137 (33.9)	0.953	0.848, 1.07
fe _{τ} (%)	57.5 (16.1)	54.8 (33.9)	NC	NC
CL _R (mL/min)	163 (15.5)	158 (32.9)	NC	NC

Source: Section 14.2 (Tables 1 and 4)

^a Digoxin administered alone

^b Digoxin administered with KMD-3213

Geometric mean (CV%) data are presented; ^c Arithmetic mean (SD)

N = Number of subjects studied

τ = 24 hours

NC = Not calculated

[norm] = Normalised for body weight (kg)

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Table 60: Summary of digoxin PK parameters following multiple oral doses alone (Day 8) and in combination with placebo (Day 16)

Parameter	Day 8 ^a (N=8)	Day 16 ^b (N=8)	Ratio of geometric LS means (Day 16: Day 8)	90% CI for ratio of geometric LS means (Day 16: Day 8)
AUC(0- τ) (ng.h/mL)	15.0 (18.3)	14.5 (19.7)	0.968	0.903, 1.04
C _{max} (ng/mL)	1.22 (26.7)	1.15 (16.3)	0.942	0.837, 1.06
t _{max} ^c (h)	1.88 (0.991)	1.82 (0.921)	NC	NC
C _{trough} (ng/mL)	0.520 (25.7)	0.472 (30.6)	0.908	0.827, 0.998
CL _{ss} /F (mL/min)	277 (18.3)	286 (19.7)	NC	NC
CL _{ss} /F [norm] (mL/min/kg)	3.36 (21.6)	3.51 (26.2)	NC	NC
Ae _{τ} (μ g)	161 (20.4)	156 (11.6)	0.970	0.822, 1.14
fe _{τ} (%)	64.2 (20.4)	62.3 (11.6)	NC	NC
CL _R (mL/min)	178 (21.7)	178 (19.6)	NC	NC

Source: Section 14.2 (Tables 1 and 4)

^a Digoxin administered alone

^b Digoxin administered with placebo

Geometric mean (CV%) data are presented; ^c Arithmetic mean (SD)

N = Number of subjects studied

τ = 24 hours

NC = Not calculated

[norm] = Normalised for body weight (kg)

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Comparisons Between Days for the Pharmacokinetic Parameters of Digoxin

Treatment	Parameter	Geometric least squares means		Ratio of geometric least squares means (Day 16:Day 8)	90% CI for the ratio (Day 16:Day 8)		95% CI for the ratio (Day 16:Day 8)	
		Day 8*	Day 16#		Lower	Upper	Lower	Upper
0.5 mg bd/0.25 mg od digoxin & 4 mg bd K2D-3213	AUC(0-t) (ng.h/mL)	14.7	14.4	0.984	0.936	1.03	0.927	1.04
	Cmax (ng/mL)	1.26	1.25	0.992	0.912	1.08	0.897	1.10
	Ctrough (ng/mL)	0.500	0.483	0.965	0.903	1.03	0.890	1.05
	Aet (µg)	144	137	0.953	0.848	1.07	0.827	1.10
0.5 mg bd/0.25 mg od digoxin & bd placebo	AUC(0-t) (ng.h/mL)	15.0	14.5	0.968	0.903	1.04	0.890	1.05
	Cmax (ng/mL)	1.22	1.15	0.942	0.837	1.06	0.817	1.09
	Ctrough (ng/mL)	0.520	0.472	0.908	0.827	0.998	0.811	1.02
	Aet (µg)	161	156	0.970	0.822	1.14	0.794	1.18
0.5 mg bd/0.25 mg od digoxin & 4 mg bd K2D-3213 (adjusted for values from the digoxin/placebo treatment)	AUC(0-t) (ng.h/mL)	0.976	0.992	1.02	0.932	1.11	0.916	1.13
	Cmax (ng/mL)	1.03	1.08	1.05	0.911	1.22	0.684	1.25
	Ctrough (ng/mL)	0.962	1.02	1.06	0.947	1.19	0.924	1.22
	Aet (µg)	0.896	0.880	0.983	0.802	1.20	0.769	1.26

* Digoxin administered alone
 # Digoxin administered with K2D-3213 or placebo
 The ratio and corresponding confidence limits are back-transformed from the difference calculated on the loge scale

Reviewer's Notes: The sponsor claimed.

Digoxin assays:

The sponsor validated the digoxin assays below based on acceptance criteria of ±25% at any quality control (QC) concentrations except for the lower limit of quantitation (LLOQ) QC, upper limit of quantitation (ULOQ) QC, and the dilution QC where the accuracy and precision can be ±30%. These acceptance criteria are higher than the FDA recommended ±15% at any QC and ±20% at LLOQ. The following will discuss where the validation exceeded the FDA recommended criteria.

Plasma digoxin concentration was measured using a radioimmunoassay (RIA). The assay had a range of 0.10 ng/mL to 10 ng/mL. The intra-assay precision had high variability (27.5%) at the lower limit of quantitation (LLOQ) of 0.10 ng/mL. Intra assay precision at other quality control (QC) concentrations (0.4, 1.5, 6.0, and 10.0 ng/mL) were ≤6.3%. Inter-assay precision was acceptable. Inter-assay and intra-assay accuracy were acceptable. Since most digoxin plasma samples had concentration ≥0.4 ng/mL, the high intra-assay precision at QC <0.4 ng/mL should not significantly alter the results.

Urine digoxin concentration was measured using a RIA. The assay had a range of 2.5 ng/mL – 100.0 ng/mL. The inter-assay precision for the low QC (7.5 ng/mL) was higher than recommended (17.7%). Inter-assay accuracy values were high for the low QC and high QC levels with relative error of -18.8% and -16.5%, respectively. The urine digoxin data should be considered more variable and be used only as supporting the plasma data.

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Appendix 4.4
Office of Clinical Pharmacology GRMP Filing Checklist

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA/BLA Number: 22-206 Applicant: Watson
Drug Name: Rapaflo NDA/BLA Type: Original
(silodosin)

Stamp Date: 12/13/2007

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

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x		The Division agreed at a teleconference with sponsor on 10/13/2006 that the in vitro dissolution comparison of 2 x 4 mg capsules and 1 x 8 mg capsule is adequate and no in vivo bioequivalence study is required.
2	Has the applicant provided metabolism and drug-drug interaction information?	x		
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	x		PK data files are available for studies conducted by Watson in the US.
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			Not applicable
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x		Phase 2 study examined 4 and 8 mg once a day dose regimens.
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?		x	The division expressed in an EOP2 meeting that it was not clear whether the 4 or 8 mg dose is the lowest effective dose.
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?		x	Only limited exposure response analysis (linear regression) was performed on the sparse PK data from phase 3 study SI04009.
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x	No specific exposure-response relationship was determined.
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			There are no pediatric studies submitted.
10	Did the applicant submit all the pediatric exclusivity			Not applicable

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

	data, as described in the WR?			
11	Is the appropriate pharmacokinetic information submitted?	x		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x		
General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	x		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	x		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	x		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x		
17	Was the translation from another language important or needed for publication?	x		Reports of studies conducted by Kissei in Japan were translated into English.

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes _____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Review comments:

1. Coadministration of a strong CYP3A4 inhibitor, ketoconazole, with silodosin increased the exposure to silodosin by about 3- to 4-fold. It is not clear if the proposed _____ is appropriate. This will be a review issue.
2. The effects of weak and moderate CYP3A4 inhibitors were not evaluated. Dosing recommendation for these populations will be a review issue.

b(4)

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

3. The effects of severe hepatic insufficiency were not evaluated. _____
-
4. The renal insufficiency study (KMD-309) enrolled patients with estimated creatinine clearance (mean \pm SD) of 39.2 ± 9.6 mL/min (range: 27 – 49 mL/min). This is consistent with moderate renal impairment instead of severe renal impairment (See Guidance For Industry, Pharmacokinetics in Patients With Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing And Labeling (May 1998)). Therefore, there was about a 3-fold increase in the exposure of silodosin in patients with moderate renal insufficiency. Dosing recommendation for renal insufficiency (mild, moderate, and severe) will be a review issue.

b(4)

Labeling comments:

1. A Drug Interaction subsection should be added under the Pharmacokinetics section to describe drug interaction studies.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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this page is the manifestation of the electronic signature.**

/s/

Doanh Tran
8/7/2008 10:50:37 AM
BIOPHARMACEUTICS

Sandhya Apparaju
8/7/2008 03:23:52 PM
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