2.4.2.7.1.6 Given the *in vitro* finding that febuxostat is a weak inhibitor of CYP 2D6, is there a significant drug-drug interaction between desiparmine (a CYP2D6 substrate) and febuxostat?

While the desipramine 90% CI's for AUC were outside the upper limit of 125%, the metabolite showed no change in its pharmacokinetics. While the magnitude of the change in desipramine AUC is low, this information should be included in the labeling.

Desipramine Interaction Study-C02-005

This was an open-label, randomized, double-blind, single-center, placebo-controlled, two-period crossover study to evaluate the effect of febuxostat on the pharmacokinetics of desipramine (a CYP2D6 substrate) in healthy subjects. A total of 22 subjects were enrolled in the trial, 2 discontinued for personal reasons and were replaced while 2 were dropped after the samples were analyzed as it was determined from the data that they were poor metabolizers. Febuxostat levels were not determined in this study. The subjects were randomly assigned to receive in a random order either once daily 120 mg oral doses of febuxostat (administered as six 20 mg tablets) for 9 days with a single 25 mg oral dose of desipramine on Day 6, or once daily febuxostat placebo for 9 days with a single 25 mg oral dose of desipramine on Day 6.

The co-administration of febuxostat with desipramine increased the mean desipramine Cmax, AUCt and AUC∞ by 16%, 24%, and 22%, respectively, in comparison to the desipramine alone regimen. This is also reflected in a 22% decrease in the apparent clearance of desipramine (Cl/F).

		Desipramine				2-Hydroxydesipramine			
		Desipramine with Febuxostat		Desipramine Alone		Desipramine with Febuxostat		Desipramine Alone	
Parameter	Units	Mean	SD	Mean	SD	Mean	SD	Mean	SD
t_{max}	(h)	6.6	1.3	6.0	1.0	4.2	1.5	4.0	1.2
C_{max}	(ng/mL)	9.62	3.46	8.35	3.24	6.19	1.96	6.57	2.31
AUC_t	(ng·h/mL)	267.57	148.36	223.56	150.25	149.33	30.36	141.44	30.26
AUC_∞	(ng·h/mL)	295.43	193.65	262.67	248.86	163.15	30.25	166.04	62.19
$t_{1/2}$[a]	(h)	21.1 (18.9)	8.3	21.5 (17.8)	14.2	23.4 (20.0)	10.8	27.3 (18.5)	34.3
λ_z	(1/h)	0.0367	0.0116	0.0390	0.0140	0.0346	0.0132	0.0374	0.0158
Cl/F	(L/h)	124.4	101.7	157.4	137.2	-	-	-	-
AUC_∞ Ratio[b]		0.7362	0.4046	0.8832	0.4918	-	-	-	-

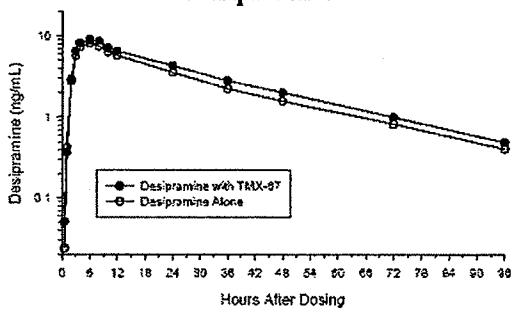
a Arithmetic mean (harmonic mean)

b AUC ratio means 2-hydroxydesipramine AUC_∞ to desipramine AUC_∞

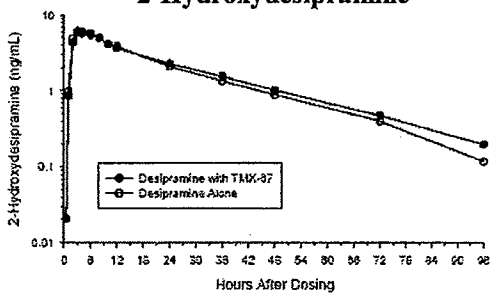
N=18.

As for the metabolite 2-hydroxydesipramine, there was no apparent difference in the pharmacokinetic parameters of the metabolite, with or without febuxostat. There is, however, an approximately 17% difference in the AUC ratio of parent to metabolite in the presence of febuxostat, suggesting the presence of some degree of formation rate reduction, presumably through CYP2D6 inhibition.

Desipramine



2-Hydroxydesipramine



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With regards to the 90% CIs, the desipramine Cmax was within the 0.80-1.25 range, but the upper bound of the 90% CIs for AUCt and AUC∞ of desipramine extended above the 0.80-1.25 range. Indicating that this is not an absorption phenomena but is related to the metabolism of desipramine resulting in an increased mean plasma exposure of approximately 24%.

The 90% CIs for the metabolite 2-hydroxydesipramine Cmax, AUCt, and AUC∞ parameters were all within the 0.80-1.25 range. This finding, in conjunction with the parent desipramine data suggests that the impact of the interaction of febuxostat on desipramine AUC is gradual in nature and does not appreciably affect the formation of the metabolite.

Parameter	Point Estimate	90% Confidence Interval
Desipramine		
C_{max}	1.163	(1.0967- 1.2324)
AUC_t	1.242	(1.1369 - 1.3570)
AUC_∞	1.220	(1.1059 - 1.3459)
AUC Ratio[a]	0.832	(0.7629 - 0.9069)
2-Hydroxydesipramine		
C_{max}	0.959	(0.9026 - 1.0183)
AUC_t	1.059	(1.0089 - 1.1122)
AUC_∞	1.015	(0.9277 - 1.1102)

a AUC ratio means 2-hydroxydesipramine AUC_∞ to desipramine AUC_∞

As to the significance of this interaction, it is likely to be minimal as the changes seen are much less than those seen with more potent inhibitors of CYP2D6. Nevertheless, these results should be incorporated into the package insert as in combination with other weak inhibitors or a narrow therapeutic range CYP2D6 substrate these differences may be exacerbated.

2.4.2.7.1.7 Is there a pharmacokinetic or pharmacodynamic interaction between warfarin and febuxostat?

The results from the formal drug interaction between warfarin and febuxostat are inconclusive as 9 of the 22 patients were removed from the treatment portion of the study due to an increase in their INR values. Coupled with the fact that in the clinical database there are reports of hemorrhage and bleeding in patients on warfarin, strongly suggests that the conclusion that there

is no interaction is unwarranted at this time. Until additional information becomes available, b(4)

Warfarin Interaction Study-C03-057

This was a randomized, double-blind, single-center, placebo-controlled, two-way, crossover study with open-label warfarin designed to evaluate the effect of febuxostat on the pharmacokinetics and pharmacodynamics of warfarin. Subjects received 5 mg of warfarin on Days 1 and 2. On Days 3-9, subjects received the appropriate dose of warfarin to maintain an International Normalized Ratio (INR) between 1.2-1.8. On Day 9 of the warfarin lead-in, subjects with INR values within or closest to the range of 1.5-1.8 were randomized to receive 120 mg febuxostat or placebo for febuxostat with concomitant warfarin administration for 14 days in each of two crossover periods without a washout between the crossover periods. A total of 22 healthy volunteers were enrolled in the study and 21 were randomized to therapy. A total of 8 subjects were dropped from the trial for high INR values and were given vitamin K (4 patients received warfarin alone, and 4 received warfarin & febuxostat). A ninth subject received vitamin K at the end of the study due to increased INR values (febuxostat arm). A total of 13 subjects completed all phases of the study (see section entitled Discontinuations for INR below).

Following administration of warfarin with febuxostat, co-administration of febuxostat with warfarin increased the estimated Cmax and AUC24 central values by less than 3% for (R)-warfarin and less than 5% for (S)-warfarin. Febuxostat concentrations were not determined.

Analyte	Regimen		t_{max} (h)	C_{max} (ng/mL)	AUC_{24}[a] (ng·h/mL)	λ_z (h^{-1})	$t_{1/2z}$[b] (h)	V_z/F (L)	CL/F (L/h)
R-warfarin	Warfarin QD + Febuxostat QD	N	13	13	13	8	8	8	13
		Mean	2.4	1182	20770	0.0230	33.4(30.2)	8.03	0.162
		SD	3.2	438	8070	0.0072	12.5	2.65	0.024
	Warfarin QD + Placebo QD	N	13	13	13	8	8	8	13
		Mean	2.2	1206	20728	0.0246	35.8(28.1)	8.76	0.165
		SD	3.0	519	9159	0.0104	22.2	4.40	0.026
S-warfarin	Warfarin QD + Febuxostat QD	N	13	13	13	12	12	12	13
		Mean	0.7	834	12516	0.0317	23.8(21.9)	9.40	0.272
		SD	0.3	270	4770	0.0087	7.8	2.51	0.054
	Warfarin QD + Placebo QD	N	13	13	13	12	12	12	13
		Mean	0.7	853	12237	0.0351	20.7(19.7)	8.82	0.283
		SD	0.3	345	5421	0.0078	5.1	2.84	0.058

a AUC_{24} and AUC_t were equal in all subjects in both periods.
b Arithmetic mean (harmonic mean).

The 90% CIs for Cmax and AUC24 with respect to (R)- and (S)-warfarin were within the acceptance interval of 0.8-1.25.

Analyte	Parameter	Point Estimates	90% Confidence Interval
R-warfarin	C_{max}	1.008	0.9320 - 1.0909
	AUC_{24}[a]	1.022	0.9792 - 1.0670
S-warfarin	C_{max}	1.011	0.9073 - 1.1261
	AUC_{24}[a]	1.048	1.0053 - 1.0928

a AUC_{24} and AUC_t were equal in all subjects in both periods.

The pharmacodynamics of warfarin when co-administered with febuxostat [the time to reach maximum international normalized ratio (INRmax), the 24-hour mean international normalized

ratio (INRmean,24), and the 24-hour mean Factor VII (F-VIImean,24)] were within 7% of those for warfarin alone. The slight increases in mean INRmax and F-VIImean,24 values seen are not of the magnitude that would be considered likely to be clinically significant (see below) and not statistically significant (p>0.05).

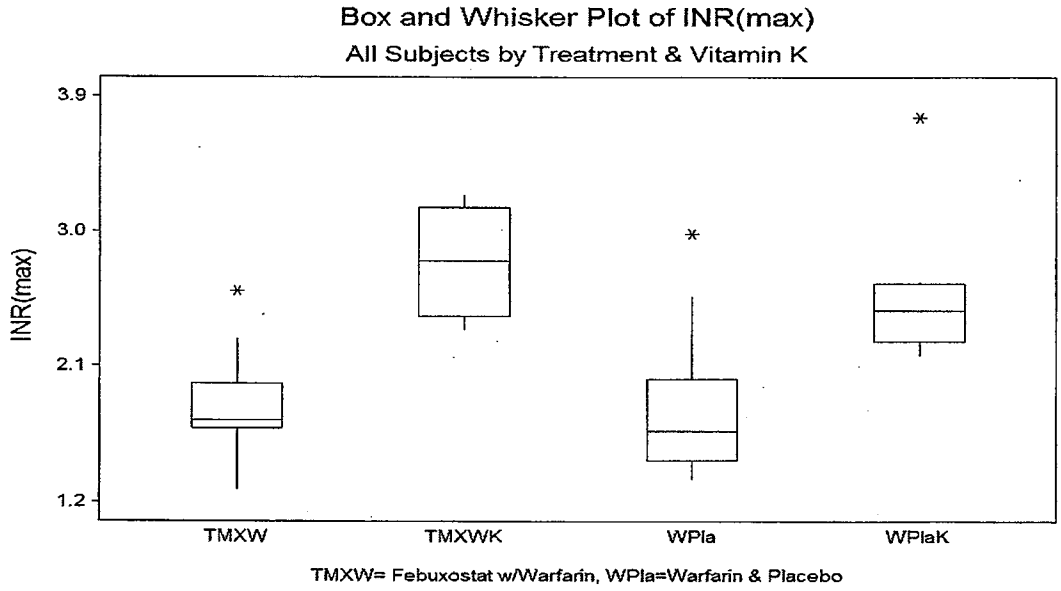
Regimen		INR_{max} (N=13)[a]	$INR_{mean,24}$ (N=13)[a]	$F\text{-}VII_{mean,24}$ (%) (N=13)[a]
Warfarin QD + Febuxostat QD	Mean	1.87	1.70	39.60
	SD	0.408	0.372	12.501
Warfarin QD + Placebo QD	Mean	1.80	1.71	37.16
	SD	0.493	0.468	12.063
P-value[b]		0.4582	0.7482	0.2912

a Included only subjects with data from both crossover periods.
b P-value for testing febuxostat effect, from ANOVA with terms for sequence, subject (sequence), period and regimen.

Discontinuations for INR

A total of eight subjects were removed from the trial due to high INR values. An additional subject was given vitamin K at the end of the trial due to a high INR value at study close-out. Additional information regarding these subjects was requested and supplied by the sponsor in an amendment dated 7/13/05 (Amendment 20).

A box-whisker plot of the data reveals that while there were as many patients removed from the trial on the placebo arm as on the febuxostat arm the mean increase in INR values in the febuxostat patients was higher than that of any other group. It should be noted that the highest absolute INR value was in the placebo phase of the trial. If this subject was removed from the database, the resulting INR values for the placebo arm would be markedly reduced.



Because these subjects were removed from the study prior to the PK analysis portion of the study, no PK data is available to determine whether or not the cause of the increased INR value was due to a PK or PD alone interaction.

At best this trial is inconclusive, in that the removal of subjects with high INR values without obtaining (at a minimum) a plasma level for warfarin does not remove the possibility that this interaction has a pharmacokinetic basis. Coupled with the fact that in the clinical database there are reports of an increased INR, resulting in hemorrhage and bleeding in patients on warfarin, strongly suggests that the conclusion that there is no interaction is unwarranted at this time. Until additional information becomes available. b(4)

2.5 General Biopharmaceutics

2.5.1 What is formulation (quantitative composition) of febuxostat 80 and 120 mg tablets?

The compositions of the drug products (80 and 120 mg) are listed in Tables 2.5.1.1 and 2.5.1.2. b(4)

Table 2.5.1.1. Quantitative Composition of 80 mg Febuxostat Tablet.

Component	Compendial Reference	Role	Abbott Material Code	Unit Formula (mg/tablet)
Febuxostat (TEI-6720, A-319198.0)	In-house	Active		80.00
Lactose, Monohydrate,	NF			
Cellulose, Microcrystalline,	NF			
Hydroxypropyl Cellulose,	NF			
Croscarmellose, Sodium	NF			
Silicon Dioxide	NF			
Magnesium Stearate,	NF			
Total Core Tablets				
Color Coating				
Opadry II, Green,	In-house	Color coating		
Total Coated Tablets				520.84

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Table 2.5.2.2. Quantitative Composition of 120 mg Febuxostat Tablet.

Component	Compendial Reference	Role	Abbott Material Code	Unit Formula (mg/tablet)
Febuxostat (TEI-6720, A-319198.0)	In-house	Active		120.00
Lactose, Monohydrate,	NF			
Cellulose, Microcrystalline,	NF			
Hydroxypropyl Cellulose,	NF			
Croscarmellose, Sodium	NF			
Silicon Dioxide	NF			
Magnesium Stearate,	NF			
Total Core Tablets				
Color Coating				
Opadry II, Green,	In-house	Color coating		
Total Coated Tablets				769.23

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2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?

The food effect was evaluated in Study C03-054 with the 120 mg tablet (the highest dosage strength tablet), single dose. An FDA high fat meal decreases the rate and the extent of absorption of febuxostat (C_{max} decreased 38%, AUC decreased 16%, and T_{max} delayed by 0.5 hr) (Tables 2.5.2.1 and 2.5.2.2).

Table 2.5.2.1. Summary of Pharmacokinetic Parameter Estimates for Febuxostat Following Administration of a Single 120 mg Oral Dose of Febuxostat to Healthy Subjects Under Fasting and Non-fasting Conditions.

Regimen		t_{max} (h)	C_{max} (µg/mL)	AUC_t (µg·h/mL)	AUC_∞ (µg·h/mL)	$t_{1/2z}$[a] (h)	Cl/F (h)	MRT (h)	V_{ss}/F (L)
A	n	19	19	19	19	19	19	19	19
Fasting	Mean	1.74	5.273	15.468	15.636	4.4 (4.2)	8.20	4.0	33.2
	SD	1.05	1.781	3.941	3.948	0.9	2.30	0.7	12.0
B	n	19	19	19	19	19	19	19	19
Non-fasting	Mean	2.26	3.437	13.064	13.281	5.1 (4.8)	9.88	5.5	56.1
	SD	1.23	1.489	3.624	3.674	1.4	3.37	1.7	36.9

[a] Harmonic mean is in the parentheses.

Table 2.5.2.2. Bioavailability of Febuxostat Under Non-fasting Conditions, Relative to Fasting Conditions.

Parameter	Point Estimate	90% Confidence Interval
Cmax	0.617	(0.515 - 0.738)
AUCt	0.838	(0.782 - 0.898)
AUC∞	0.843	(0.787 - 0.902)

The Sponsor has also conducted a multiple dose study (Study C02-036) to assess the effect of food not only on pharmacokinetics but also on pharmacodynamics of febuxostat at steady-state. In Study C02-036, the 80 mg tablet was studied. Consistent with what was found in the single-dose study, the administration of febuxostat under non-fasting conditions resulted in respective mean C_{max} and AUC_{24} values 49% and 18% lower than those under fasting conditions (Table 2.5.2.3). However, uric acid reduction in serum was slightly higher under fed conditions than fast conditions after multiple dosing (58% vs. 51%) (Table 2.5.2.4).

Table 2.5.2.3. Bioavailability of Febuxostat Under Non-fasting Conditions, Relative to Fasting Conditions.

Parameter	Point Estimate	90% Confidence Interval
Cmax	0.512	(0.440 - 0.595)
AUC24	0.824	(0.782 - 0.870)

Table 2.5.2.4. Summary of Mean Serum Urate Cmean,24 Values on Days -1 and 6 and Percent Change from Baseline in Serum Urate $C_{mean,24}$ on Day 6 Following Once Daily Multiple Oral Dosing with 80 mg of Febuxostat Under Fasting or Non-Fasting Conditions in Healthy Subjects.

		$C_{mean,24}$ (mg/dL)		% Change from Baseline
Treatment		Day -1	Day 6	Day 6
Fasting	N	23	23	23
	Mean	5.110	2.606	-51.16
	SD	1.592	1.291	14.34
Non-Fasting	N	23	23	23
	Mean	5.255	2.235	-58.49
	SD	1.512	1.005	12.00

Based on these results, febuxostat tablets may be given without regard to food as the observed pharmacokinetic changes are not translated into a meaningful change in pharmacodynamics.

2.5.3 What is the relative bioavailability of the proposed to-be-marketed formulation to the formulations used in the pivotal clinical trials?

Table 2.5.3.1 listed formulations used in the pivotal Phase 3 trials, the on-going clinical long-term safety studies and pivotal clinical pharmacology studies.

Table 2.5.3.1. Formulations Used in Clinical Trials.

Study	Content	Teijin 20 mg (Formulation A3)	Abbott 20 mg (Formulation B1, pilot scale)	Abbott 20 mg (Formulation B1, production scale)	Abbott 40 mg (Formulation B1, production scale)	To-be-Marketed Dosage Strength	
						Abbott 80 mg (Formulation B1, production scale)	Abbott 120 mg (Formulation B1, production scale)
TMX-99-001	SD and MD PK study	X					
TMX-01-008	Renal impairment	X					
TMX-01-012	Hepatic impairment	X					
TMX-01-016	Age and Gender	X					
C02-036	80 mg MD food effect					X	
C03-054	120 mg SD food effect						X
C02-023	QTc			X		X	
TMX-01-005	Phase 2 POP-PK	X		X			
C02-009	Phase 3 POP-PK				X	X	
TMX-01-014	Antiacid	X					
TMX-00-006	Colchicine (effect on TMX-67)	X					
TMX-02-017	Indomethacin		X				
C02-013	Naproxen	X					
C03-059	Hydrochlorothiazide					X	
C02-006	Clochicine (effect on colchicine)	X					
C02-005	Desipramine		X				
C03-057	Warfarin				X	X	
C02-009	Pivotal Phase 3 trial				X	X	
C02-010	Pivotal Phase 3 trial		X	X			
C02-021	long-term safety (ongoing)				X	X	X
TMX-00-004	long-term safety (ongoing)	X					

The pivotal clinical trials used the to-be-marketed formulation, Abott Formulation B1. 80 and 120 mg are the to-be-marketed dosage strengths. 20 mg and 40 mg tablets of Formulation B1 used in some of the clinical trials [redacted] Because of the dose-proportional PK in the range of 10-120 mg for febuxostat, it is expected that these tablets would be bioequivalent.

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Teijin's formulation, Formulation A3, was used in many PK studies. Results from the bioequivalence study (Study TMX-02-018) demonstrated that 20 mg tablet of Formulation B1 was bioequivalent to 20 mg tablet of Teijin Formulation A3 (Table 2.5.3.2). In addition, the Abbott B1 80 mg tablet was bioequivalent to four Abbott B1 20 mg tablets.

Table 2.5.3.2. Bioavailability of Febuxostat Following Single Oral Doses of the Test Regimens (Abbott B1 20 mg Tablet, Abbott 80 mg Tablet), Relative to the Reference Regimens (Teijin 20 mg Tablet, 4 of Abbott B1 20 mg Tablets).

Comparison (Test Regimen vs. Reference Regimen)	Pharmacokinetic Parameter	Relative Bioavailability	
		Point Estimate	90% Confidence Interval
Abbott B1 20 mg Tablet vs. Teijin 20 mg Tablet	C_{max}	0.955	0.8434 – 1.0818
	AUC_t	0.968	0.9189 – 1.0194
	AUC_∞	0.983	0.9359 – 1.0323
Abbott B1 80 mg Tablet vs. 4 of Abbott B1 20 mg Tablets	C_{max}	1.085	0.9583 – 1.2291
	AUC_t	1.022	0.9707 – 1.0769
	AUC_∞	1.022	0.9734 – 1.0737

2.5.4 Does the to-be-marketed tablets demonstrate dosage form equivalent?

Yes. Results from Study C03-044 demonstrated that one febuxostat 120 mg Formulation B1 tablet was bioequivalent to 1 febuxostat 80 mg Formulation B1 tablet plus 1 febuxostat 40 mg Formulation B1 tablet (Table 2.5.4.1). Therefore, 1 febuxostat 120 mg tablet and the combination of 1 febuxostat 80 mg tablet plus 1 febuxostat 40 mg tablet can be used interchangeably.

Table 2.5.4.1. Relative Bioavailability of 1 Febuxostat 120 mg Tablet to 1 Febuxostat 80 mg Tablet plus 1 Febuxostat 40 mg Tablet in Healthy Subjects.

Parameter	Point Estimate[a]	90% Confidence Interval
C_{max}	0.998	0.9010-1.1056
AUC_t	0.988	0.9531-1.0233
AUC_∞	0.988	0.9542-1.0228

a N=35

2.5.5 Has the Sponsor developed an appropriate dissolution method and specifications that will ensure in vivo performance and quality of the product?

No. The proposed dissolution method and acceptance criterion for febuxostat tablets (Table 2.5.5.1) are not acceptable because the conditions, as proposed are, such that the tablets would pass the acceptance criterion even at 10 min (Figures 2.5.5.1 and 2.5.5.2 and Table 2.5.5.2). Drug release was essentially complete at 20 minutes.

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✓ Trade Secret / Confidential (b4)

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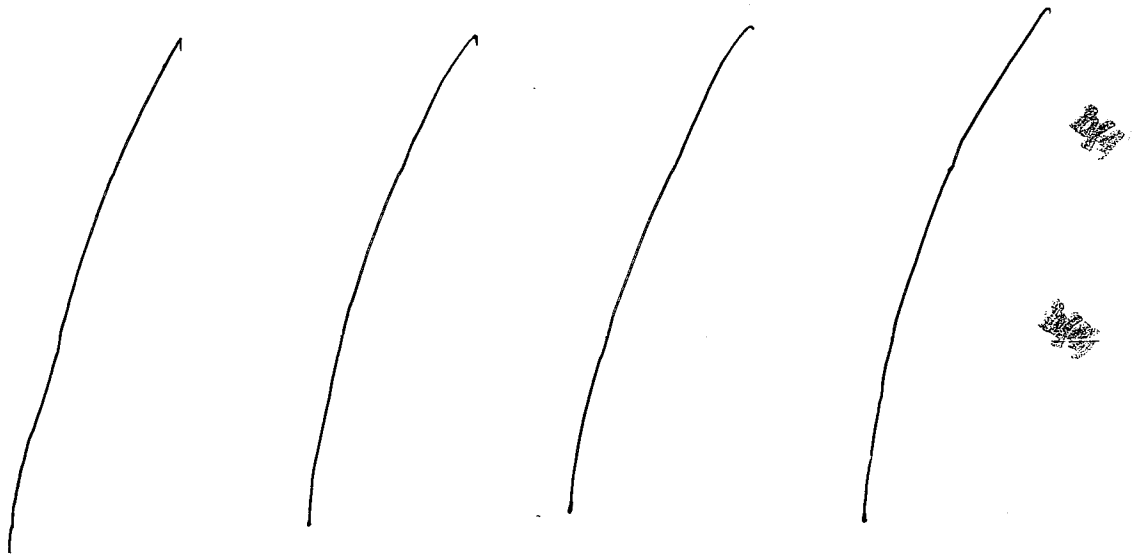

Therefore, based on the totality of the dissolution data, the following dissolution method and acceptance criterion for the 80 and 120 mg tablets were reached with the chemistry review team:

Drug Release Parameters	**Value**
Apparatus	Automated USP Dissolution Apparatus #2 (Paddle)
Dissolution medium	0.05 M Potassium Phosphate Buffer, pH 6.8 ± 0.05
Dissolution medium volume	900 mL
Dissolution medium temperature	37.0 ± 0.5°C
Rotation speed	75 rpm
Analytical finish	UV Spectrophotometry using absorbance at 316 nm
Acceptance criteria	Q= — at 15 min

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If lower dose strength tablets will be developed for future clinical studies (e.g., 40 and 60 mg tablets), the current dissolution method and acceptance criterion will be revisited. A different pH medium may be used if solubility allows.

2.6 Analytical

2.6.1 How are the active moieties identified and measured in the plasma and other biological fluids in the clinical pharmacology and biopharmaceutics studies?

Febuxostat:

Febuxostat was quantified in the U.S. at [redacted] Unchanged febuxostat concentrations were determined in both human plasma and urine by HPLC with

b(4)

fluorescence detection (320 nm excitation, 380 nm emission). Total febuxostat (unchanged plus conjugated derivatives) concentrations were determined in human urine by HPLC with fluorescence detection.

67M-1, 67M-2 and 67M-4:
These metabolites were quantified in the U.S. at [redacted] b(4)
Unchanged metabolite concentrations were determined in both human plasma and urine by LC/MS/MS method. Total metabolite (unchanged plus conjugated derivatives) concentrations were determined in human urine by validated LC/MS/MS methods.

Human Serum (Uric Acid, Xanthine, and Hypoxanthine):
Quantitation of uric acid, xanthine and hypoxanthine in human serum was conducted using an HPLC method with UV detection (260 nm).

Human Urine (Uric Acid, Xanthine, and Hypoxanthine):
Uric acid, xanthine and hypoxanthine urine concentrations were determined by HPLC and UV detection (250 nm) and LC-MS/MS methods in the U.S.

2.6.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods measured total concentrations of febuxostat and its metabolites in human plasma. These moieties are highly protein bound, so free concentrations may be more appropriate. However, it is standard to measure only total concentrations. The protein binding of febuxostat was measured in the PK studies. Free concentrations were calculated for each patient based on individual protein binding data.

2.6.3 What bioanalytical methods are used to assess concentrations?

Individual method information, including linear range, sensitivity, quality control concentrations, precision and accuracy, is presented in the following tables. Overall, the analytical methods adequately determined the concentrations of the compounds of interest.

Table 2.6.3.1. Summary of Analytical Methods.

Analyte	Matrix	Analytical Method	Internal Standard	Limit of Quantitation (Linear Range)
Febuxostat	Human EDTA Plasma	HPLC-Fluorescence Detection [redacted] PS 23150_1)	[redacted]	0.01µg/mL (0.01-20 µg/mL)

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Total Febuxostat (Intact plus conjugates)	Human Urine (Urine samples were hydrolyzed with 2 N NaOH prior to extraction)	HPLC-Fluorescence Detection — PS 23150_3)		0.05 µg/mL (0.05-100 µg/mL)
Intact Febuxostat	Human Urine	HPLC-Fluorescence Detection — PS 23150_2)		0.02 µg/mL (0.02-20 µg/mL)
67M-1, 67M-2, and 67M-4	Human EDTA Plasma	LC/MS/MS — PS 23150_4)		0.5 ng/mL (0.5-100 ng/mL)
Total 67M-1, 67M-2, and 67M-4 (Intact plus conjugates)	Human Urine (Urine samples were hydrolyzed with 2 N NaOH prior to extraction)	LC/MS/MS — PS 23150_6)		5 ng/mL (5-500 ng/mL)
Intact 67M-1, 67M-2, and 67M-4	Human Urine	LC/MS/MS — PS 23150_5)		0.5 ng/mL (0.5-100 ng/mL)
Urate	Human Serum	HPLC-UV Detection — PS 23151_1)		10 µM (10-1000 µM)
Uric Acid	Human Urine	HPLC-UV Detection — PS 23151_2)		10 µM (10-4500 µM)
		LC/MS/S — PS 23151_5)		100 µM (100-4500 µM)
Xanthine	Human Serum	HPLC-UV Detection — PS 23151_1)		0.2 µM (0.2-20 µM)
	Human Urine	HPLC-UV Detection — PS 23151_2)		10 µM (10-1000 µM)
		LC/MS/S — PS 23151_5)		10 µM (10-1000 µM)
Hypoxanthine	Human Serum	HPLC-UV Detection — PS 23151_1)		0.2 µM (0.2-20 µM)
	Human Urine	HPLC-UV Detection — PS 23151_2)		10 µM (10-1000 µM)
		LC/MS/S — PS 23151_5)		10 µM (10-1000 µM)

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Table 2.6.3.2. Calibration Curve and Quality Control Data (U.S.).

			Calibration Curve Data			Quality Control Data		
Reference	Analyte	Matrix	Correlation Coefficient	Absolute Deviation (%)	Coefficient of Variation (%)	QC Concentrations	Absolute Deviation (%)	Coefficient of Variation (%)
PS 23150_1	Febuxostat	Plasma	≥0.99844	0.34 - 3.50	1.87 - 4.83	0.0600, 1.00 & 15.0 µg/mL	1.69 - 3.87	4.16 - 6.30
PS 23150_2	Febuxostat	Urine	≥0.99887	0.11 - 1.93	0.78 - 4.48	0.0600, 1.00 & 15.0 µg/mL	0.33 - 2.35	3.32 - 4.07
PS 23150_3	Total Febuxostat	Urine	≥0.99515	0.68 - 8.92	2.22 - 8.42	0.150, 1.50, 10.0 & 75.0 µg/mL	0.27 - 4.42	4.70 - 7.08
PS 23150_4	67M-1	Plasma	≥0.99796	0.05 - 5.98	2.65 - 5.19	0.0015, 0.015 & 0.075 µg/mL	1.31 - 5.44	2.06 - 5.16
	67M-2	Plasma	≥0.99732	0.78 - 6.77	2.20 - 7.61	0.0015, 0.015 & 0.075 µg/mL	0.67 - 5.12	1.72 - 5.56
	67M-4	Plasma	≥0.99768	0.27 - 5.29	3.56 - 10.08	0.0015, 0.015 & 0.075 µg/mL	4.64 - 8.77	1.85 - 7.61
PS 23150_5	67M-1	Urine	≥0.99947	0.13 - 2.86	1.38 - 6.53	0.0015, 0.015 & 0.075 µg/mL	1.53 - 2.74	3.23 - 4.91
	67M-2	Urine	≥0.99966	0.18 - 1.90	1.19 - 9.64	0.0015, 0.015 & 0.075 µg/mL	1.60 - 4.60	2.38 - 5.08
	67M-4	Urine	≥0.99957	0.10 - 3.29	1.22 - 7.95	0.0015, 0.015 & 0.075 µg/mL	3.92 - 7.53	4.59 - 6.26
PS 23150_6	Total 67M-1	Urine	≥0.99943	0.30 - 11.40	1.39 - 4.07	0.015, 0.045, 0.375 & 1.500 µg/mL	0.73 - 3.24	3.27 - 5.76
	Total 67M-2	Urine	≥0.99908	0.18 - 11.00	1.07 - 7.64	0.015, 0.045, 0.375 & 1.500 µg/mL	0.47 - 4.09	3.32 - 5.18
	Total 67M-4	Urine	≥0.99954	0.22 - 4.14	0.90 - 5.49	0.015, 0.045, 0.375 & 1.500 µg/mL	0.12 - 2.56	3.19 - 5.18
PS 23151_1	Uric Acid	Serum	≥0.99843	0.32 - 2.01	1.38 - 4.58	29.6, 150 & 750 µM	0.83 - 3.14	2.82 - 3.45
	Xanthine	Serum	≥0.99850	0.64 - 2.08	2.35 - 5.23	0.57, 3.0 & 15 µM	1.07 - 3.25	2.71 - 5.46
	Hypoxanthine	Serum	≥0.99682	0.10 - 3.63	2.56 - 7.14	0.57, 3.0 & 15 µM	0.49 - 4.44	3.62 - 9.19
PS 23151_2	Uric Acid	Urine	≥0.99839	0.20 - 9.70	1.02 - 4.32	23.6, 500, 2650 & 3375 µM	0.97 - 5.59	2.59 - 7.62
	Xanthine	Urine	≥0.99783	0.10 - 5.88	1.14 - 6.11	30, 49, 200 & 750 µM	4.27 - 7.00	1.95 - 8.70
	Hypoxanthine	Urine	≥0.99978	0.06 - 2.68	0.68 - 5.46	30, 194, 200 & 750 µM	0.64 - 8.30	2.58 - 7.73
PS 23151_3	Xanthine	Urine	≥0.99667	0.36 - 5.70	1.56 - 5.16	30.0, 51.4, 200 & 750 µM	0.21 - 5.80	4.53 - 6.69
PS 23151_4	Uric Acid	Urine	≥0.99210	0.61 - 2.60	2.02 - 8.73	300, 1250, 3375 & 4890 µM	4.21 - 6.88	4.98 - 7.17
PS 23151_5	Uric Acid	Urine	≥0.99824	0.0 - 3.0	2.0 - 8.8	300, 1250, 2820 & 3375 µM	0.3 - 5.3	3.3 - 7.4
	Xanthine	Urine	≥0.99923	0.3 - 4.3	0.8 - 4.1	30, 39, 200 & 750 µM	0.3 - 1.7	2.9 - 3.4
	Hypoxanthine	Urine	≥0.99780	0.0 - 3.0	4.2 - 8.5	30, 64, 200 & 750 µM	0.0 - 2.5	5.1 - 7.3

b(4)

3 LABELING RECOMMENDATIONS

The labeling recommendations are deferred pending the completion of a successful clinical development program. The following items need to be considered at the time of future labeling:

b(4)

19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2 Individual Study Review

4.2.1. In Vivo and In Vitro Metabolism/Transport Studies

4.2.1.1 Study C03-040: The Metabolism and Excretion of Orally Administered [^{14}C]Febuxostat in Healthy Male Subjects

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Study Period: July 23, 2003 to Augugst 13, 2003
Sample Analysis Periods: August 14 to August 15, 2003 (———) and
July 23 to July 31, 2003 ——— ,
Principle Investigator: ———
Study Center:
Analytical Sites: / / / / b(4)

Objectives: To investigate the metabolism and excretion of radiolabeled [^{14}C] febuxostat in subjects receiving a single 80 mg oral dose.

Study Design: This was a single-center, open-label study. Each subject received a single 80 mg dose of [^{14}C] febuxostat under fasted conditions. Plasma samples were assayed for febuxostat concentration. Plasma, whole blood, urine, and fecal samples were assayed for total radioactivity. Metabolic patterns were determined in selected plasma, urine and fecal samples.

Subjects were to be discharged from the testing facility when whole blood/plasma radioactivity levels were <3 times background radioactivity, and when either (1) two consecutive samples of both blood and feces contained <1% of administered radioactivity OR (2) when ≥90% of the radioactive dose was accounted for in the collected urine and feces.

Six subjects were planned and 6 subjects were enrolled and included in the analysis of the study. Five subjects completed the study. Subject 101 withdrew from the study after sample collections on Day 7 because a family member was hospitalized. He returned after the end of the study for end-of-treatment sample collections and laboratory assessment.

Demographic and Baseline Characteristics:

Age (yr)	28 (20 – 45)
Weight (kg)	78 (65 – 90)
Height (cm)	180 (173 – 185)
Race N (%)	Caucasian 6 (100%)

Data presented as mean (range).

Test Article: The test product dose was an oral solution (50 g) containing an 80 mg equivalent of [^{14}C] febuxostat (Figure 1). The total radioactivity administered per dose of approximately 100 µCi was based on dosimetry calculations. The actual dose was 78.1 mg of febuxostat and 107.8 µCi of Carbon-14 (see table below).

Study Drug[a]	Manufacturer	Lot#	Nominal (mg)	Actual (mg)
Febuxostat	Abbott Laboratories	82-182-NI-00	79.5	77.6
[^{14}C] Febuxostat	[redacted]	CFQ13480	0.5[b]	0.5
Combined Total			**80.0 (100.0)[c]**	**78.1 (107.8)[c]**

b(4)

a [redacted]
b Based on dosimetry
c (µCi) Carbon-14

80 mg dose is one of the proposed clinical doses (the other one is 120 mg).

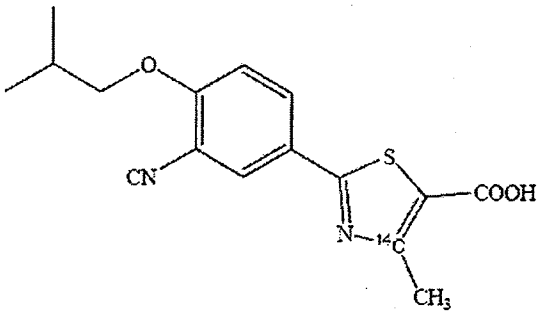


Figure 1. Structure of [^{14}C] febuxostat.

Sample Collection:

- Venous blood samples (20 mL) were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 10, 12, 16, 24, 30, 36, and 48 hours post-dose, and thereafter every 24 hours until release.
- On Day 1, pooled urine composites were collected from 0 to 6, 6 to 12, and 12 to 24 hours post-dose. Thereafter urine samples were pooled into 24-hour composite samples for each subsequent day of confinement.
- Individual fecal samples were collected on Day 1 as excreted and on Days 2 to 10 the samples were pooled into 24-hour samples.

Sample Analysis: All whole blood samples were shipped to [redacted] on wet ice for total radioactivity determination. All plasma samples were assayed for both total radioactivity and febuxostat concentrations. Plasma samples were assayed for concentrations of febuxostat concentrations by [redacted], using a validated high performance liquid chromatography (HPLC) with florescence detection method. The limit of quantitation was 0.01 µg/mL. Metabolic patterns were determined from plasma samples containing sufficient radioactivity at [redacted] using radio-HPLC.

b(4)

All composite urine and fecal samples were assayed for total radioactivity and those samples containing sufficient radioactivity were assayed for metabolic patterns at [redacted] using radio-HPLC. b(4)

The limit of quantitation (LOQ) for total radioactivity in plasma and whole blood were 46 dpm/mL and 60 dpm/g, respectively. The LOQ for total radioactivity in urine and feces were 50 dpm/mL and 64 dpm/g, respectively.

Oxidizer recovery checks were conducted under the same conditions that were used to analyze the study samples. The mean recovery for whole blood (n=3) was 96.7% and the mean recovery for feces (n=3) was 98.3%. These values were used to normalize the dpm/g values from the whole blood and feces study samples.

Pharmacokinetic/Statistical Analysis: Pharmacokinetic (PK) parameters were estimated from febuxostat plasma concentrations and total radioactivity values by standard noncompartmental methods using WinNonlin® Professional V.3.1 computer software package (Pharsight Corporation, Mountain View, California).

Concentrations of total radioactivity in plasma and whole blood were expressed as either µg equivalents/mL or µg equivalents/g. Amounts of radioactivity in excreta and total recovered radioactivity were expressed as a percentage of the administered radioactive dose. Amounts of unchanged drug and each detected metabolite in the biological samples analyzed were expressed as a percentage of the administered dose (excreta) or as a percentage of the sample radioactivity (plasma).

Subject 101 was included in the summarization of febuxostat plasma concentration and total radioactivity in both plasma and whole blood since these concentrations were below the lower limit of quantitation at 48 hours post-dose for all 6 subjects. However, since incomplete urine and fecal radioactivity data was collected for Subject 101 due to early withdrawal from the study, this subject was not included in the summarization of total radioactivity and urine and fecal radioactivity.

Pharmacokinetic Results:

Plasma/Blood:

Table 1. Summary of Descriptive Statistics for Febuxostat and Total Radioactivity Pharmacokinetic Parameter Estimates.

Regimen		t_{max} (h)	C_{max} (µg/mL)	AUC_t (µg·h/mL)	AUC_∞ (µg·h/mL)	AUC_∞ % Extrp	$t_{1/2z}$[a] (h)	λ_z (h^{-1})	Cl/F (L/h)	V_z/F (L)
Febuxostat	N	6	6	6	6	6	6	6	6	6
	Mean	0.50	3.953	8.278	8.480	3	10.8 (9.7)	0.071	9.86	52.3
	SD	0.00	1.584	2.202	2.186	1	3.5	0.029	3.10	28.3
Total Radioactivity[b]	N	6	6	6	6	6	6	6	NA	NA
	Mean	0.58	4.197	10.034	10.259	2	6.5 (6.2)	0.112		
	SD	0.20	1.673	2.694	2.762	1	1.9	0.024		

N number of subjects

a Arithmetic mean (harmonic mean)

b Cmax and AUC values expressed as µg equivalents/mL and µg equivalents h/mL, respectively.

Extrp extrapolated
NA not applicable

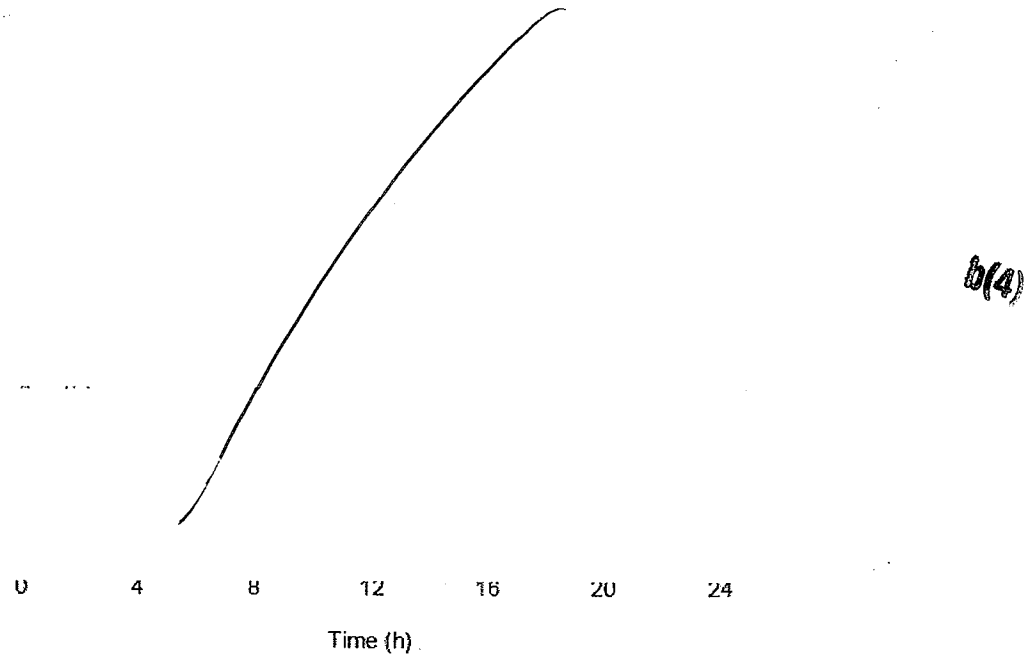


Figure 2. Plasma Concentration-Time Profiles of Febuxostat and Total Radioactivity

The pharmacokinetic parameter estimates for the single 80 mg dose of febuxostat were consistent with those obtained from a previous study (Study TMX-99-001). The mean T_{max} value was approximately 0.5 hour earlier than what was seen in Study TMX-99-001, suggesting that dosing as an oral solution is absorbed more quickly.

A comparison of the mean C_{max} values for total radioactivity versus febuxostat in this study indicated that febuxostat accounted for 94.2% of the total radioactivity observed for C_{max}. A similar comparison using mean AUC_t and AUC_∞ values indicated that febuxostat was 82.5% and 82.7% of the total radioactivity AUC, respectively (Table 1 and Figure 2). These comparisons indicate that the majority of exposure in the plasma was febuxostat.

The above results were confirmed by metabolic profiling for the plasma samples. A summary of the mean metabolite profile in plasma is presented in Table 2. The major peak was febuxostat, which accounted for an average of 95.8% at 0.25-hour post dose. The major peak in the plasma chromatograms at the 4-hour timepoint averaged 84.7% for febuxostat (P14), 4.4% and 5.5% for 67M-1 (P9) and 67M-2 (P8) metabolites, respectively, 3.8% for the regio-isomers of the acyl-glucuronide of febuxostat (P10, 12, 13), 1.3% for the 67M-4 (P3) and 0.5% for the sulfate conjugate of 67M-1 (P5).

Table 2. Mean Metabolite Profile in Plasma, Data Presented as % Region of Integration of Total Radioactivity in Chromatogram.

Time (hours)	P3	P5	P8	P9	P10	P12	P13	P14 (Febuxostat)
0.25	0.00	0.00	0.80	1.06	0.25	0.78	1.31	95.80
0.5	0.00	0.00	1.69	2.62	1.06	1.74	2.82	90.55
1	1.14	0.17	3.07	3.22	1.22	1.70	3.34	86.13
1.5	0.85	0.69	3.58	4.08	0.83	2.10	3.83	84.21
2	1.01	0.80	3.34	4.32	0.83	2.04	3.82	83.84
3	1.10	0.40	5.05	3.51	0.32	0.91	2.56	85.98
4	1.25	0.51	5.45	4.36	0.22	0.90	2.63	84.70

P3 67M-4 metabolite
P5 sulfate conjugate of 67M-1 metabolite
P8 67M-2 metabolite
P9 67M-1 metabolite
P10, P12, P13 regio-isomers of the acyl-glucuronide of febuxostat
P14 febuxostat.

The whole blood radioactivity comparison with plasma radioactivity showed that there was no preferential binding with red blood cells (Table 3). At 36 hours post-dose, the radioactivity was below the limit of quantitation in plasma and whole blood for all subjects.

Table 3. Mean Radioactivity Concentrations Expressed as µg Equivalents/Gram in Plasma, Whole Blood, and Red Blood Cells.

	Predose Mean (range)	0.5 hours Mean (range)	3 hours Mean (range)	12 hours Mean (range)	24 hours Mean (range)	36 hours Mean (range)
Plasma	0.00 -	4.15 (2.43-6.69)	0.93 (0.38-1.26)	0.11 (0.09-0.16)	0.03 (0.02-0.04)	0.00 -
Whole Blood	0.00 -	2.68 (1.71-4.20)	0.58 (0.26-0.82)	0.08 (0.06-0.12)	0.02 (0.00-0.03)	0.00 -
Red Blood Cells[a]	0.00 -	0.82 (0.46-1.26)	0.14 (0.09-0.27)	0.03 (0.00-0.05)	0.01 (0.00-0.04)	0.00 -

a Red blood cell binding is a calculated value from the measured whole blood and plasma in dpm/g.

Urine/Feces:

A summary of the cumulative recovery of radioactivity from 5 subjects is shown in Table 4. Subject 101 was not included in the febuxostat recovery calculations due to early withdrawal from the study before achieving exit criteria.

From urine, in the 0 to 6, 6 to 12, and the 12 to 24 hour collection intervals, recovered doses averaged 34.7%, 6.5%, and 4.6%, respectively. The first 24 hours of urine recovery accounted for approximately 46% on average of the urine recovery, which represented approximately 93% of the total fraction that was excreted in urine (49%). The 24 to 48 hour intervals had an average recovery of 2.5% of the dose. The combined 0 to 48 hour collections accounted for more than 98% of the total recovery excreted in urine. After 48 hours an average of less than 1% of the dose was excreted in any subsequent 24-hour collection interval.

Based on fecal samples in the 0 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hour collection intervals, the recovery averaged 4.5%, 29.5%, 11.6%, 9.1%, and 3.8% of the dose, respectively.

After the 96 to 120 hour collection interval, an average of less than 1% of the total dose was observed in any subsequent 24-hour interval.

Table 4. Cumulative Recovery of Radioactivity

Subject	Total Recovery in Urine (% of Dose)	Total Recovery in Feces (% of Dose)	Total Recovery (% of Dose)
102			93.6
103			94.8
104			93.2
105			94.0
106			94.7
Mean ± SD	49.1 ± 9.8	44.9 ± 10.1	94.1 ± 0.7

b(4)

Febuxostat in the 0 to 24 hour urine sample cumulatively accounted for 1.1% to 3.5% of dosed radioactivity. The major metabolite peaks observed from each subject in the 0 to 24 hour urine samples, expressed as a percentage of dose, were the dicarboxylic acid 67M-4 (0.1%-3.1%), the hydroxylated febuxostat 67M-2 (3.9%-7.3%), the hydroxylated febuxostat 67M-1 (2.5%-7.1%), the acyl-glucuronides of febuxostat isomers P10, P11, P12 (26.7%-37.5%), and the glucuronide of reduced febuxostat (0.3%-0.6%) (Table 5).

Febuxostat in the 0 to 120 hour feces cumulatively accounted for 7.8% to 15.8% of dose in Subjects 102 to 106. The major metabolite peaks observed in 0 to 120 hour fecal samples, expressed as a percentage of dose, were the dicarboxylic acid 67M-4 (7.8%-15.0%), the sulfate conjugate of the hydroxylated febuxostat (2.0%-3.1%), the hydroxylated febuxostat 67M-2 (3.7%-6.3%), and hydroxylated febuxostat 67M-1 (3.6%-7.1%) (Table 5).

Table 5. Distribution of the Prominent Radioactive Components in Human Excreta Samples Following a Single 80 mg Oral Dose of [^{14}C]Febuxostat.

	Cumulative Percent of Dose[a]	
Component(s)	**Urine (0-24 h)**	**Feces (0-120 h)[b]**
Febuxostat	1.1 - 3.5	7.8 - 15.8
67M-1	2.5 – 7.1	3.6 - 7.1
67M-2	3.9 – 7.3	3.7 - 6.7
67M-4	0.1 – 3.1	7.8 - 15.0
Febuxostat glucuronide[c]	25.9 – 37.1	0.4 -1.0
Reduced 67M-1/67M-2 glucuronide	0.3 – 0.6	0.0 - 0.02
Sulfate conjugate of 67M-1	0.0 – 0.2	2.0 - 3.1
Total Profiled	37.0 – 60.4	27.3 - 50.4

a Excluding Subject 101 who withdrew from the study prior to achieving exit criteria.
b Only fecal samples containing sufficient radioactivity were profiled and included in the mean values.
c Total of 3 isomers of the acyl-glucuronide of febuxostat.

Overall, 17 radioactive peaks (P0-P16) were observed in the chromatograms of urine and fecal samples. Febuxostat (designated as metabolite P14) contributed a combined total of 10.2% to 18.2% (1.1% to 3.5% urine and 7.8% to 15.8% feces) of the dose, indicating that febuxostat is extensively metabolized in humans. Of the urine and fecal samples, an average of 86.8% (46.2% urine and 40.6% feces) of the dose was evaluated, with the known metabolites and febuxostat accounting for 82.3% of the dose. The remaining 4.4% were unidentified peaks at concentrations too low to identify. The remaining radioactivity was not profiled because later sample collections

contained radioactivity too low to be assessed accurately. Please refer to Table A.1 in the Appendix for detailed metabolite profiles in each subject.

The proposed metabolic pathway of febuxostat is listed in Figure 3.

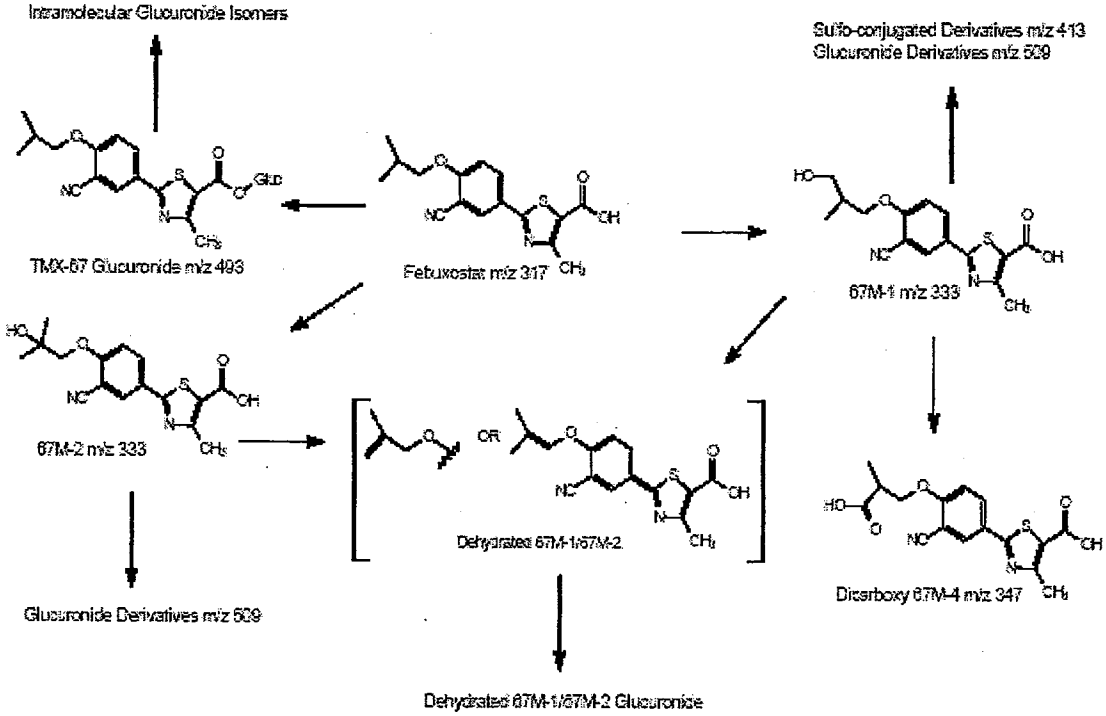


Figure 3. Proposed Metabolic Pathway of Febuxostat.

Dsicussion/Conclusion:

- The mean cumulative recovery of radioactivity in excreta was 94% at 216 hours (9 days) post-dose, mean 49% in urine and 45% in feces, indicating that febuxostat was eliminated by both renal and biliary excretion.
- Febuxostat represented a combined total of 10%-18% (1%-4% urine and 8%-16% feces) of the dose, indicating that febuxostat is extensively metabolized in humans.
- The minimum absorption of febuxostat was 49% based on total radioactivity recovered in the urine. Unchanged febuxostat in the feces was 8-16% of the dose indicated that the absorption of febuxostat could be > 84% if assuming all the feces were collected and no degradation of febuxostat in the gastrointestinal tract or feces. Some febuxostat recovered in the feces may also be generated from degradation of acyl glucuronides of febuxostat in the intestine.
- In plasma, febuxostat was the major component, accounting for an average of 94% of the total radioactivity at C_{max}, and representing 83% of total radioactivity AUC. Metabolites 67M-1, 67M-2, and 67M-4, the acyl-glucuronide of febuxostat, and the sulfate conjugate of 67M-1 were also observed in plasma, but in much lower relative amounts. The pharmacokinetic parameter estimates for the single 80 mg dose of febuxostat were consistent with those obtained from a previous study (Study TMX-99-001). The T_{max} values were approximately 0.5 hour confirm that the drug is absorbed quickly from a solution.

- In urine, the major metabolites were the acyl-glucuronides of febuxostat isomers P10, P11, P12 (26.7%-37.5%), the hydroxylated febuxostat 67M-2 (3.9%-7.3%), the hydroxylated febuxostat 67M-1 (2.5%-7.1%), febuxostat (1-4%), the dicarboxylic acid 67M-4 (0.1%-3.1%), and the glucuronide of reduced febuxostat (0.3%-0.6%) (Table 5).
- In feces, febuxostat and metabolite 67M-4 were the most prominent components, accounting for 7.8% to 16% and 7.8% to 15% of the dose, respectively. Other major metabolites were 67M-1 (3.6%-7.1%), 67M-2 (3.7%-6.7%), and the sulfate conjugate of 67M-1.
- The whole blood radioactivity comparison with plasma radioactivity showed that there was no preferential binding of febuxostat with red blood cells.
- In summary, acyl glucuronide metabolites of TMX-67 (~35% of the dose) recovered in the urine, and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4 (~14% of the dose) recovered in the urine and feces appeared to be the major metabolites *in vivo*. In addition, 67M-3, which was one of the major metabolites from *in vitro*, did not shown to be the major metabolite *in vivo*.

Appendix. (Study C03-040)

Table A.1. Summary Profile of Human Urine and Feces Following Administration of [^{14}C]Febuxostat, Data Presented As %Dose.

Subject	Matrix	P0	P1	P2	P3	P4	P5	P6	P7	P8	P9
101	Urine										
	Feces										
	Total	0.00	0.57	0.06	5.88	0.28	1.66	0.34	0.39	9.37	8.00
102	Urine										
	Feces										
	Total	0.00	0.91	0.08	10.83	0.43	2.24	0.61	0.49	10.97	10.72
103	Urine										
	Feces										
	Total	0.00	1.17	0.52	14.29	0.13	3.06	0.59	0.16	11.25	10.97
104	Urine										
	Feces										
	Total	0.00	0.92	0.12	10.62	0.28	3.01	0.70	0.43	10.73	9.30
105	Urine										
	Feces										
	Total	0.16	1.32	0.34	14.48	0.16	3.08	0.04	0.68	9.80	8.87
106	Urine										
	Feces										
	Total	0.28	0.69	0.16	17.94	0.23	2.85	0.42	0.43	11.56	11.61

b(4)

Subject	Matrix	P10	P11	P12	P13	P14 (Febuxostat)	P15	P16	Total Profiled	Total[a] Dose	Total[b] Recovery
101	Urine										
	Feces										
	Total	8.48	0.66	18.73	5.57	5.26	0.00	0.98	68.14	68.78	75.96
102	Urine										
	Feces										
	Total	7.71	0.51	18.88	10.88	11.80	0.00	0.61	87.67	89.07	93.60
103	Urine										
	Feces										
	Total	6.19	0.28	13.81	6.74	18.22	0.14	2.60	90.12	91.87	94.85
104	Urine										
	Feces										
	Total	2.12	0.47	17.87	9.84	13.46	0.03	1.23	81.13	85.69	93.25
105	Urine										
	Feces										
	Total	0.24	0.36	21.93	4.66	16.93	0.08	3.49	86.53	90.88	94.04
106	Urine										
	Feces										
	Total	0.65	0.64	21.67	7.47	10.23	0.38	1.08	88.29	92.16	94.67

b(4)

a Total dose for the intervals from the Report, Appendix 16.1.10.2.
b Total dose recovered for the 216 hours from the Report in Appendix 16.1.10.2.
The 48-hour urine data included in this table are from the DMPK Report (Appendix H, Table A12) Appendix 16.1.10.1.
NA Not applicable
P3 67M-4 metabolite
P5 sulfate conjugate of 67M-1 metabolite
P8 67M-2 metabolite
P9 67M-1 metabolite
P11 glucuronide or reduced febuxostat P11 metabolite
P10, P12, P13 regio-isomers of the acyl-glucuronide of febuxostat
P14 febuxostat

4.2.1.2 In Vitro Metabolism/Transport Study Review for TMX-67 (Febuxostat)

(Reviewer's Note: Febuxostat, TMX-67, and TEI-6720 are used interchangeably in the review.)

4.2.1.2.1 In Vitro Metabolism Studies for Febuxostat (TMX-67)

Human Hepatocytes:

Study 46473: Comparative In Vitro Metabolism of [14C]TMX-67 in Male and Female Hepatocytes from Mouse, Rat, Dog and Human

The study was conducted by , from February 2001 to January 2003.

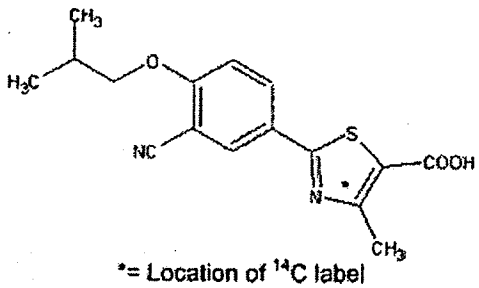
Objective: To investigate the *in vitro* metabolism (biotransformation) of ^{14}C-radiolabeled TMX-67 by hepatocytes from both genders of human, dog, rat, and mouse.

(Reviewer's Note: This review focuses on human hepatocyte results.)

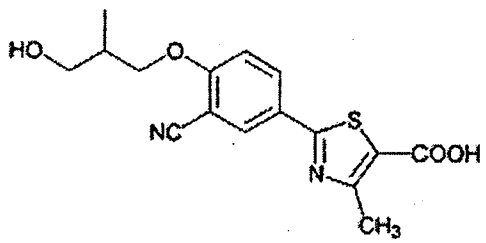
Methods: A preliminary experiment was performed with male and female human hepatocytes to determine the optimal incubation conditions to produce the greatest percentage of metabolism of [^{14}C]TMX-67. Concentrations at 5, 25 and 100 µM were incubated for 1 and 4 hr with male and female human hepatocytes at a density of 1.0×10^6 viable hepatocytes/mL at 37°C. The concentration selected for subsequent incubations was 25 µM. [^{14}C] TMX-67 (25 µM) was incubated for 4 hr at 37°C with hepatocytes from male and female human, dog, rat and mouse at 1.0×10^6 viable hepatocytes/mL. Metabolic competency of the hepatocytes from each species was evaluated by performing side by side incubations with the probe substrates (7-ethoxycoumarin and 7-hydroxycoumarin) and monitoring for cytochrome P450-mediated biotransformation and glucuronidation. Hepatocytes from all tested species were found to be metabolically competent.

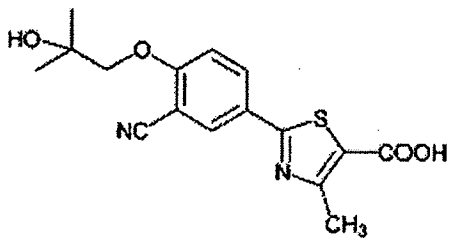
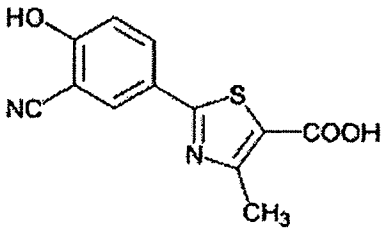
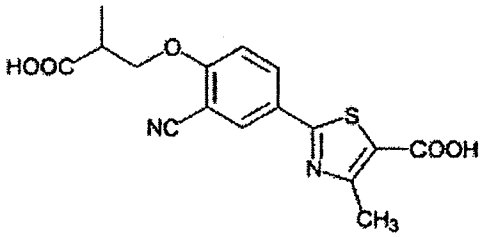
Metabolites in the hepatocyte incubations were quantitated by HPLC with radiochemical detection. Metabolites in human and dog hepatocyte incubations were tentatively identified by LC-MS/MS using the multiple reaction monitoring (MRM) technique.

Test Article:

TMX-67	 *= Location of ^{14}C label	Both radio-labeled (specific activity 58 mCi/mmol) and unradiolabeled TMX-67 were used.

Reference Materials (to confirm proposed metabolite structures):

67M-1 (M2b)	

67M-2 (M2a)	
67M-3 (M3)	
67M-4	

The radiochemical purity of [14C]TMX-67 stock solution was ~96%. In the negative control incubations, [14C]TMX-67 represented 94%-96% of the profile in the radio-chromatograms. In all species studied, the total recovery of radioactivity after incubation with hepatocytes ranged from 84% to 115%.

Results and Discussion:
All components identified in the human hepatocyte incubations were identified in at least one other animal species. The overall extent of biotransformation of TMX-67 with hepatocytes was low, especially in human hepatocyte incubations. Human male and female hepatocyte incubates after 4 hr of incubation contained 92.5% and 94.3% of the parent compound, respectively, compared to 95.5% in the concurrently performed control incubation.

Three major Phase I metabolites were identified as desbutylated TMX-67 (M3, m/z 261) and monohydroxylated TMX-67 (M2a and M2b, m/z 333). Metabolites M3 (67M-3), M2a (67M-2) and M2b (67M-1) accounted for up to 5.6% and 3.9% of the total radioactivity in male and female human hepatocyte incubations, respectively (Table 1). These three Phase I metabolites altogether accounted for 74.7% and 68.5%, respectively, of the total metabolites generated.

Three glucuronide conjugates of TMX-67 (G2b-1, G2b-2 and G2b-3) with the same mass and similar retention times were detected by LC-MS/MS. G2b-1, 2 and 3 accounted for 1.2% and 0.8% of the total radioactivity in male and female human incubations, respectively. These three

Phase II metabolites accounted for 16.0% and 14.0%, respectively, of the total metabolites generated.

Minor metabolites (<3.1% in all species) detected were another glucuronide conjugate of TMX-67, m/z 493 (G2a), two glucuronide conjugates of desbutylated TMX-67 (G1a and G1b, m/z 261) and carboxylated TMX-67 (67M-4, m/z 347). 67M-4 was only detected by MS/MS in the MRM mode.

Table 1. Percentage of Total Metabolites Generated: [14C]TMX-67 (25 µM) After 4 hr Incubations with and without Hepatocytes from Various Species.

Study System	Liver hepatocyte									
Substrate Solution	25 µM Febuxostat									
Radionuclide	^{14}C Febuxostat									
Incubation	4 hours at 37°C.									
		Percent of Total Components Generated								
			Human (n=3)		Dog (n=1)		Rat (n=1)		Mouse (n=1)	
Component	Component ID	Control[a]	Female	Male	Female	Male	Female	Male	Female	Male
U1	Unknown 1	11.3	10.5	10.7	-	2.4	8.6	6.2	3.0	5.1
G1a	Glucuronide conjugate of 67M-3	-	-	-	-	-	16.6[b]	16.6[b]	-	2.8[b]
G1b	Glucuronide conjugate of 67M-3									
M3	67M-3 (desbutylated febuxostat)	22.6	24.6	28.0	8.5	6.8	25.1	26.9	13.1	11.2
M2a	67M-2 (monohydroxylated febuxostat)	13.2[c]	28.1[c]	28.0[c]	16.0[c]	5.6[c]	24.1[c]	19.3[c]	12.3[c]	13.1[c]
67M-4	Carboxylated febuxostat									
M2b	67M-1 (monohydroxylated febuxostat)	3.8	15.8	18.7	30.2	33.5	4.8	2.8	8.5	6.5
G2a	Glucuronide conjugate of febuxostat	-	-	-	-	3.6	-	3.5	4.7	5.6
G2b-1	Glucuronide conjugate of febuxostat	-	14.0[d]	16.0[d]	26.4[d]	4.4	16.6[d]	20.7[d]	11.4	7.0
G2b-2	Glucuronide conjugate of febuxostat					25.9			29.2	24.8
G2b-3	Glucuronide conjugate of febuxostat					9.6			14.4	18.2
U2	Unknown 2	9.4	7.0	-	-	-	-	-	-	-
U3	Unknown 3	7.6	-	-	4.7	7.0	4.3	2.8	1.7	3.3
U4	Unknown 4	11.3	-	-	3.8	-	-	1.4	1.7	2.3
U5	Unknown 5	3.8	-	-	-	6.4	-	-	-	-
U6	Unknown 6	9.4	-	-	10.4	-	-	-	-	-
U7	Unknown 7	15.1	-	-	-	-	-	-	-	-
Total Identified			82.5	90.7	81.1	89.4	87.2	89.8	93.6	89.2

a Average of 5 negative controls: 1) male and female human hepatocyte incubations, 2) female dog hepatocyte incubations, 3) male dog hepatocyte incubations, 4) male and female rat hepatocyte incubations, 5) male and female mouse hepatocyte incubations.
b Quantitation is combination of G1a and G1b.
c Quantitation is combination of M2a and 67M-4.
d Quantitation is combination of G2b-1, G2b-2 and G2b-3.

Conclusions: The major *in vitro* metabolic pathways of TMX-67 (at a concentration of 25 µM) in human hepatocytes are glucuronidation and hydroxylation. Desbutylation and glucuronidation of the desbutylated metabolite are also minor biotransformation pathways. In general, gender-related differences were not detected using human hepatoctyes. *(Reviewer's Note: C_{max} of TMX-67 was approximately 15 µM at the maximum proposed dose of 120 mg, which is lower than the concentration used in this in vitro study.)*

Human Liver Microsomes:

Study 46475: In Vitro Metabolism of [^{14}C)TMX-67 by Male Liver Microsomes from Mouse, Rat, Dog and Human

The study was conducted by _____ from February 2001 to January 2003. b(4)

Objective: To investigate the *in vitro* metabolism (biotransformation) of TMX-67 by liver microsomes from male mouse, rat, dog and human and under glucuronidation conditions.

(Reviewer's Note: This review focuses on human liver microsome results.)

Methods: Conditions for TMX-67 incubation were optimized using dog liver microsomes. TMX-67 metabolism was found to be linear over concentrations of 1 μM to 100 μM when incubated for 1 hr with 1 mg/mL microsomal protein at 37°C. For all species studied, incubation media containing 25 μM [^{14}C] TMX-67 was incubated at 37°C for 30 min and 1 hour with 1 mg/mL microsomal protein. In addition, incubations were performed in the presence of UDPGA (cofactor), Brij 58 (detergent) and saccharolactone (an inhibitor of glucuronidase) in the absence and presence of NADPH. NADPH regenerating system was added last to initiate the reaction. Microsomes were incubated with a probe substrate (7-ethoxycoumarin) to confirm metabolic competency.

Metabolites in microsomal incubates were quantitated by HPLC with radiochemical detection. Dog liver microsomes were used for the generation of large quantities of metabolites, which were tentatively identified by LC-MS-MS. Metabolites in human microsomal incubates were tentatively confirmed by multiple reaction monitoring (MRM).

Test Article and Reference Materials:
Same as those used in Study 46473.

The radiochemical purity of the [14C] TMX-67 stock solution was 96%, with nine component peaks accounting for less than 4% of the remaining radioactivity. In the negative control incubations [14C] TMX-67 represented 94% of the profile in the radiochromatograms, with the nine component peaks accounting for 6% of the radioactivity. In all species studied, the total recovery of radioactivity after incubation with liver microsomes ranged from 90% to 98%.

Results and Discussion:
Very little metabolism was observed in all species, with the lowest in human. Unmetabolized TMX-67 accounted for 91.5% of total radioactivity in human compared to 94.0% in the control. Metabolites 67M-1, 67M-2, and 67M-3 were the major metabolites generated by human liver microsomes, accounting for approximately 24%, 34% and 20% of the metabolites generated, respectively (Table 2).

Table 2. *In Vitro* Metabolism by Human, Dog, Rat and Mouse Liver Microsomes.

Study System	Liver microsomes
Substrate Solution	35 µM Febuxostat
Radionuclide	^{14}C Febuxostat
Incubation	1 hour at 37°C.
Gender	Male

Component	Component ID	Percent of Total Metabolites Generated[a]							
		Human		Dog		Rat		Mouse	
		Control[b]	Microsomes	Control[b]	Microsomes	Control[b]	Microsomes	Control[b]	Microsomes
U1	Unknown 1	13.3	7.9	10.2	4.0	12.7	4.8	8.6	7.2
U2	Unknown 2	6.7	-	6.8	-	7.3	0.5	5.2	-
U3	Unknown 3	6.7	3.3	8.5	1.6	10.0	2.1	6.9	2.0
U4	Unknown 4	11.7	3.9	15.3	0.8	7.3	1.6	17.2	2.0
U6	Unknown 6	3.2	-	20.3	4.0	14.5	3.7	6.9	-
U7	Unknown 7	15.0	5.3	1.7	-	1.8	-	15.3	4.6
M3	67M-3 (desbutylated febuxostat)	25.0	19.7	31.0	11.3	29.1	24.3	24.1	30.7
M2a	67M-2 (mono-hydroxylated febuxostat)	18.3[c]	34.2[c]	13.6[c]	8.0[c]	18.2[c]	46.3[c]	13.8[c]	39.9[c]
67M-4	Carboxylated febuxostat								
M2b	67M-1 (mono-hydroxylated febuxostat)	3.3	25.7	1.7	70.4	-	16.3	1.7	15.1
Total Identified			77.6		89.6		87.3		83.7

a. Percent of total metabolites generated = Percent of total radioactivity by HPLC (sum of radioactivity from all components – [^{14}C]febuxostat % total radioactivity by HPLC) x 100.

b. Average of 4 negative controls; 1) [^{14}C] febuxostat in incubation buffer, 2) [^{14}C] febuxostat in incubation buffer + NADPH generating system, 3) [^{14}C] febuxostat in incubation buffer + microsomes without NADPH generating system, 4) [^{14}C] febuxostat in incubation buffer + microsomes + NADPH generating system, time = 0.

c. Quantitation is combination of M2a and 67M-4, but the amount of 67M-4 detected was negligible.

In the microsomal incubations performed under glucuronidation conditions, unmetabolized TMX-67 accounted for 83.6% of total radioactivity in human in the presence of NADPH, as compared to 81.7% in the absence of NADPH. In the presence of NADPH, the parent and identified metabolites accounted for 96.8% of the total radioactivity in human. The glucuronide conjugate of febuxostat was the most prominent metabolite in all species tested (Table 3).

The results suggest that the glucuronidation of [^{14}C]TMX-67 and its metabolites in liver microsomes in the presence of UDPGA is a prominent pathway. In human incubations in the absence of UDPGA, the tentatively identified Phase I metabolites represent 77.6% of the total metabolites (Table 2). In comparison, the human microsomal incubations in the presence of UDPGA, the tentatively identified Phase I metabolites only represent 13.8% of the total metabolites (Table 3). In the animal species, the Phase I metabolites represented 83.7-89.6% of the total metabolites in the absence of UDPGA and 3.5-17.3% in the presence of UDPGA. The presence of NADPH did not significantly alter the metabolic profile.

Table 3. *In Vitro* Metabolism by Human, Dog, Rat and Mouse Liver Microsomes Under Glucuronide Conditions.

Study System	Liver microsomes under glucuronide conditions.
Substrate Solution	25 µM Febuxostat
Radionuclide	^{14}C Febuxostat
Incubation	1 hour at 37°C in the presence of UDPGA
Gender	Male

		Percent of Total Metabolites Generated[a]							
		Human		Dog		Rat		Mouse	
Component	Component ID	Without NADPH	With NADPH	Without NADPH	With NADPH	Without NADPH	With NADPH	Without NADPH	With NADPH
U1	Unknown 1	1.7	2.5	2.5	0.9	2.3	1.0	1.0	0.9
U3	Unknown 3	-	5.5	2.5	1.4	2.0	1.5	1.5	1.7
U4	Unknown 4	1.7	1.9	1.9	2.3	0.3	0.3	0.5	0.4
U5	Unknown 5	5.5	8.2	8.7	4.2	2.6	1.8	3.3	2.4
U6	Unknown 6	-	-	1.2	-	-	-	-	-
U7	Unknown 7	-	-	0.6	-	-	-	0.5	-
G1a	67M-3 glucuronide	2.2	-	2.5	3.8	5.9	2.8	2.8	1.5
G1b	67M-3 glucuronide	-	-	-	-	-	1.5	-	1.7
M3	67M-3	3.3	5.0	4.3	5.6	-	-	-	0.4
M2a	67M-2	6.1[b]	5.7[b]	5.6[b]	4.2[b]	3.0[b]	3.3[b]	2.3[b]	2.2[b]
67M-4	67M-4								
M2b	67M-1	0.6	3.1	-	7.5	0.7	2.6	-	0.9
G2b	Febuxostat glucuronide	79.0	69.2	70.2	70.0	83.2	85.4	88.1	87.9
Total Identified		91.2	83.0	82.6	91.3	92.8	95.6	93.2	94.6

Additional Information: Metabolite G2b was the most prominent metabolite in all species tested, accounting for 70-80% of the metabolites generated by all species studied.

a Percent of total metabolites generated = Percent of total radioactivity by HPLC/(sum of radioactivity from all components - [^{14}C]febuxostat % total radioactivity by HPLC) x 100.

b Quantitation is combination of M2a and 67M-4, but the amount of 67M-4 detected was negligible.

Conclusions: The major *in vitro* biotransformation pathway in the microsomal incubations in human and animals seems to be the hydroxylation and desbutylation of TMX-67. However, in microsomes under glucuronidation conditions, the formation of glucuronide conjugates of TMX-67 was detected. Similar in vitro biotransformation pathway for TMX-67 was proposed as compared to hepatocyte data.

(Reviewer's Note: The initial metabolic velocity of TMX-67 (1 µM) was 1.95 pmol/min/mg protein in human liver microsomes from Study 18-A-95016. This study was not reviewed.)

4.2.1.2.2 Reaction Phenotyping for Febuxostat (TMX-67)

In vitro (liver microsomes and hepatocytes) and *in vivo* metabolism studies (Study C03-040) suggested that TMX-67 underwent both Phase 1 (oxidative) and Phase 2 (glucuronidation) metabolism. Although *in vitro* data suggested that the metabolism rate was low in human, *in vivo* data suggested that TMX-67 was extensively metabolized in humans (>70% metabolized). Major metabolites *in vivo* were acyl glucuronide metabolites of TMX-67 (~35% of the dose) recovered in the urine, and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4 (~14% of the dose) recovered in the urine and feces. 67M-3 which was one of the major metabolites from *in vitro*, did not shown to be one of the major metabolites *in vivo* (see Study C03-040). In contrast, 67M-4, which was one of the major metabolites *in vivo*, was negligibly detected in the *in vitro* incubation.

Cytochrome P450 Isoforms:

The CYP isoforms responsible for the metabolism of febuxostat were investigated in a number of *in vitro* studies, including methods of using recombinant cDNA (Study 18-A-95018 and Study 18-K-00002), correlation study (Study 18-A-95021), and anti-human CYP isozyme antibodies (Study 18-K-02001).

Recombinant cDNA Method

Study 18-A-95018: Study on the in vitro Metabolism of TEI- 6720: Preliminary Study on the Cytochrome P-450 Isozymes involved in the Metabolism of TEI- 6720 using Yeast Microsomes Expressing Specific Human Cytochromc P-450 Isozyme

The study was conducted by Teijin Ltd., in Japan in October-November 1995.

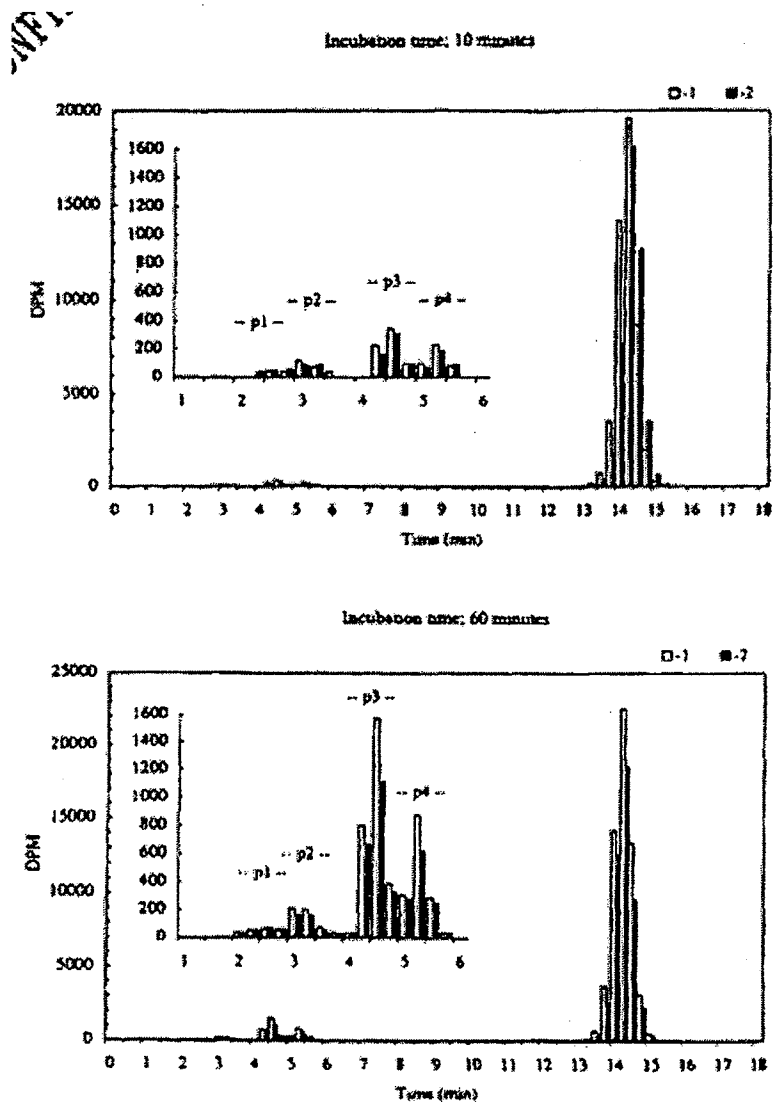
Objective: To examine what isozymes of cytochrome P-450 (CYP) could be involved in the biotransformation of TEI- 6720 in human livers using yeast microsoms expressing specific human CYP isozymes.

Methods: Yeast microsomes expressing specific human hepatic CYP isozymes (100 pmol) and negative control microsomes were mixed with a substrate solution containing [^{14}C]-TEI-6720 at a final concentration of 1 μM. CYP isozymes studied were CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1 and 3A4. The reaction was started with the addition of the reaction initiator, NADPH. The reaction was stopped 60 minutes after the initiation by the addition of acetonitrile, and metabolites produced in the reaction mixture were analyzed by HPLC.

Results and Discussion: Results from a previous study, Study 18-A-95016, showed that 4 radiolabeled peaks (potential hydrophilic metabolites), in addition to that of the radiolabeled parent drug, were detected by HPLC-radioassay (Figure 1). After 60 min incubation with cDNA expressed CYP isoforms, a similar metabolic profile was observed, although in most cases only small amounts of the metabolites were formed (Table 1).

The results indicated that significant quantities of Peak-1 were not formed by any of the CYP isoforms, with the possible exception of CYP2C18 (1.2-times control). CYP1A1 (the inducible not constitutive form of CYP1A) appeared to be involved in the formation of Peak-2; CYP1A1, CYP1A2, and CYP2C8 appeared to be involved in the formation of Peak-3; and CYP1A1, CYP1A2, CYP2C8, and CYP2C9 appeared to be involved in the formation of Peak-4 (Table 4 and Figure 2). It is noted that Peak-4 was generated in little quantity from this study compared to what obtained in human liver microsomes. It remains unclear whether Peak-4 may also be formed by NADPH-dependent, non-CYP hepatic enzymes.

The identity of the metabolites represented by the 4 peaks was not established in this study. *(Reviewer's Note: The Sponsor did not attempt to link these 4 peaks to metabolites 67M-1 to 67M-4. Such linkage was attempted by the Reviewer. Please refer to the table in the summary section.)*



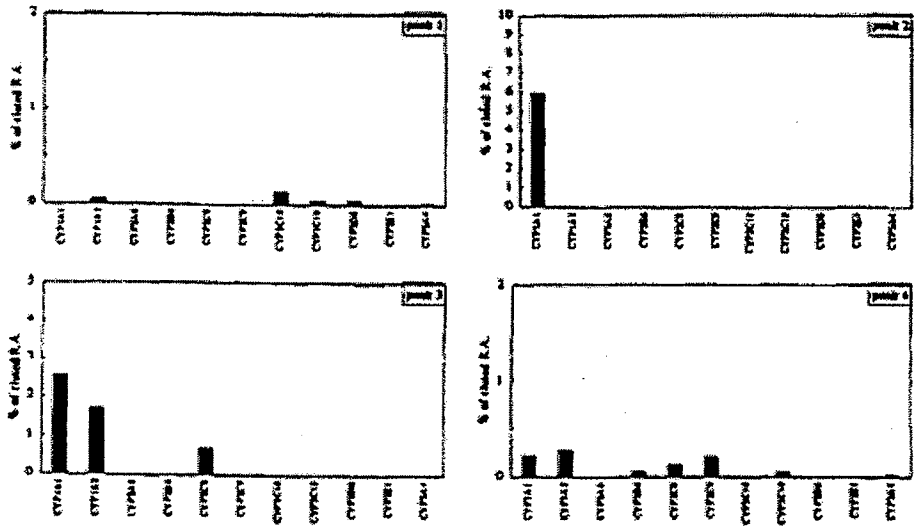
Elution profiles from 1 to 6 minutes were enhanced in each inlet figure.

Each incubation time group had 2 samples, represented as 1(□) and 2 (■)

Figure 1. HPLC elution profiles of radioactives after incubation of ^{14}C-TEI-6720 with human pooled liver microsomes.

Table 1. Ratio (%) of peak fractions to total radioactivities eluted from HPLC column.

CYP	peak 1 %	peak 2 %	peak 3 %	peak 4 %	Unchanged %
CYP1A1	0.77	6.50	2.88	0.46	89.11
CYP1A2	0.88	0.46	2.02	0.51	95.63
CYP2A6	0.84	0.37	0.11	0.23	98.15
CYP2B6	0.79	0.42	0.29	0.30	97.61
CYP2C8	0.73	0.48	1.01	0.36	97.02
CYP2C9	0.67	0.46	0.24	0.45	97.90
CYP2C18	0.96	0.51	0.21	0.18	97.64
CYP2C19	0.87	0.40	0.26	0.29	97.93
CYP2D6	0.86	0.45	0.24	0.22	97.78
CYP2E1	0.69	0.40	0.16	0.12	98.39
CYP3A4	0.84	0.52	0.31	0.25	97.64
Control	0.82	0.52	0.31	0.24	97.49



All data represented the values after deducting those of the respective control microsomes

Figure 2. Ratio (%) of peak fractions to total radioactiviies eluted from HPLC column.

Study 18-K-00002: Study on the Cytochrome P-450 Isozyrnes Responsible for the Production of TEI- 6720 Oxidative Metabolites

The study was conducted by Teijin Ltd., in Japan from October 2000 to March 2001.

Objective: To determine the cytochrome P-450 isozyrnes responsible for the production of TEI-6720 Oxidative Metabolites, using P-450 expression system microsomes prepared from cells expressing single human hepatic CYP isozyme.

Methods: An *in vitro* CYP metabolic reaction was performed for TEI- 6720 or 67M- I as a substrate. The experiment examining the formation of 67M-1, 67M-2 or 67M-3 using TEI- 6720 (30 μM) as a substrate was performed separately from the one examining the formation of 67M-4 using 67M-1 (30 μM) as a substrate. In the respective experiment, two tubes (n= 2) with or

without NADPH were prepared for each CYP isozyme. Microsomes obtained from human lymphoblast cells expressing no human CYP isozymes were used as control. Reactions for TEI-6720 were incubated for 30 min and reactions for 67M-1 were incubated for 60 min at 37°C.

Results and Discussion: The results showed that CYP2C9*1(Arg), CYP1A1, CYP1A2, CYP2C8, and CYP4A11 were shown to form metabolite 67M-1; CYP1A1, CYP1A2, CYP1B1, CYP2C8, CYP2C9*1(Arg), and CYP3A4 were shown to form metabolite 67M-2; and CYP1A1 was shown to form metabolite 67M-3. Metabolite 67M-4 was not formed by any of the CYP isozymes after incubation with metabolite 67M-1. No metabolite was generated in negative control microsomes nor in the absence of NADPH. The amounts of each metabolite generated by the CYP isozymes are summarized in Table 2 and Figure 3.

Table 2. CYP Isoform Activities by Febuxostat in Human Hepatic Microsomes.

CYP Isozyme[a]	Metabolite Generated (pmol/min/pmol CYP)			
	67M-1	67M-2	67M-3	67M-4
1A1	0.053[b]	0.377	0.484	nd
1A2	0.019[b]	0.061	nd	nd
1B1	nd	0.035[b]	nd	nd
2A6	nd	nd	nd	nd
2B6	nd	nd	nd	nd
2C8	0.032[b]	0.078[b]	nd	nd
2C9*1(Arg)	0.068	0.042[b]	nd	nd
2C9*2(Cys)	nd	nd	nd	nd
2C19	nd	nd	nd	nd
2D6 (Val)	nd	nd	nd	nd
2E1	nd	nd	nd	nd
3A4	nd	0.022[b]	nd	nd
4A11	0.111[b]	nd	nd	nd
Control	nd	nd	nd	nd

nd: Not detected.

a CYP isozymes 2A6, 2B6, 2C9*2(Cys), 2C19, 2D6(Val), and 2E1 had no measurable concentration of any of the metabolites.

b Result is an estimate because measured concentrations were less than the limit of quantitation.

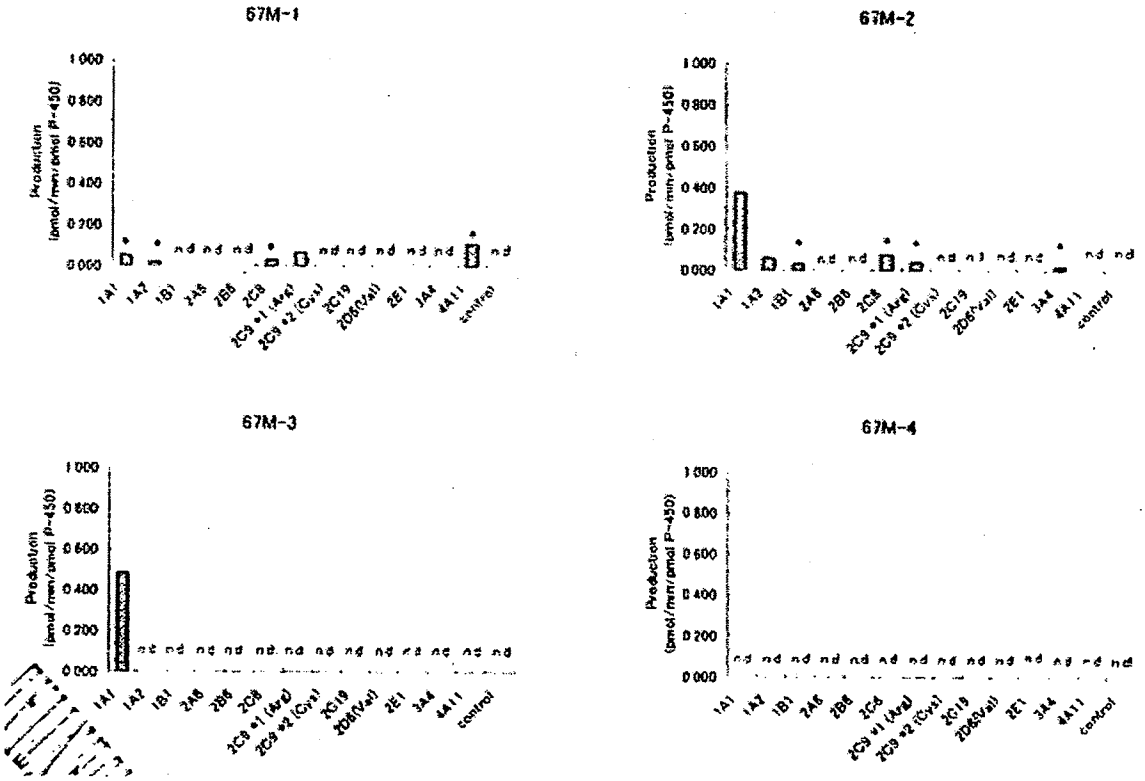


Figure 3. Profiles of metabolite formation by specific human CYP enzymes.

Reviewer's Comments:
The Sponsor did not link Peaks 1-4 identified in previous studies with 67M1-4 in this study. It is possible that 67M-4 was formed by non-CYP enzymes.

Correlation Method

Study 18-A-95021: In Vitro Cytochrome P-450 Metabolism Study for Using [redacted] Identification of Isozymes in Human b(4)

The study was conducted by Teijin Ltd., in Japan in November-December 1995.

Objective: This is a follow-up study to Study 18-A-95018 where no specific CYP isoforms could be identified for Peak-4 metabolite. The present study was performed to reveal CYP isozyme(s) responsible for producing peak 4 using 10 lots of human liver microsomes having obvious activity profiles of respective CYP isozyme.

Methods: Human liver microsomes [redacted] whose enzyme activity profiles and contents of enzymes were previously determined, were mixed with substrate solution containing ^{14}C-TEI-6720 (1 μM). Following 60 min incubation, metabolites formed were analyzed by HPLC, and their radioactivity ratio to the total eluted from the column was calculated. Pooled b(4)

human liver microsomes from HBI6 and HBI7 (at time 0) were used as control to subtract out the noise effect of non-metabolic radioactivity peaks. A comparison of the amounts of each metabolite produced with the activity profiles of each CYP isozyme over 10 lots of microsomes (HBI2, 3, 5, 6, 7, 9, 10, 11, 12, and 13) was used to identify which isozyme(s) were responsible for the production of each metabolite based on correlation analysis.

Results and Discussion: The following enzymatic activity profiles were found significantly high correlation (5%; r>0.632, 1%; r>0.765) with profiles of the ratio of each peak:

Peak 1 : No correlation was observed.
Peak 2 : 7-Ethoxyresorufin *O*-dealkylation activity (CYP1A)
Caffeine *N*3-demethylation activity (CYP1A)
Benzphetamine *N*-demethylation activity (unknown)
Peak 3 : Caffeine *N*3-demethylation activity (CYP1A)
Benzphetamine *N*-demethylation activity (unknown)
Peak 4 : Testosterone 6β-hydroxylation activity (CYP3A)

Their correlated relationships were illustrated in Figure 4. The identity of the metabolites represented by the 4 peaks was not established in this study.

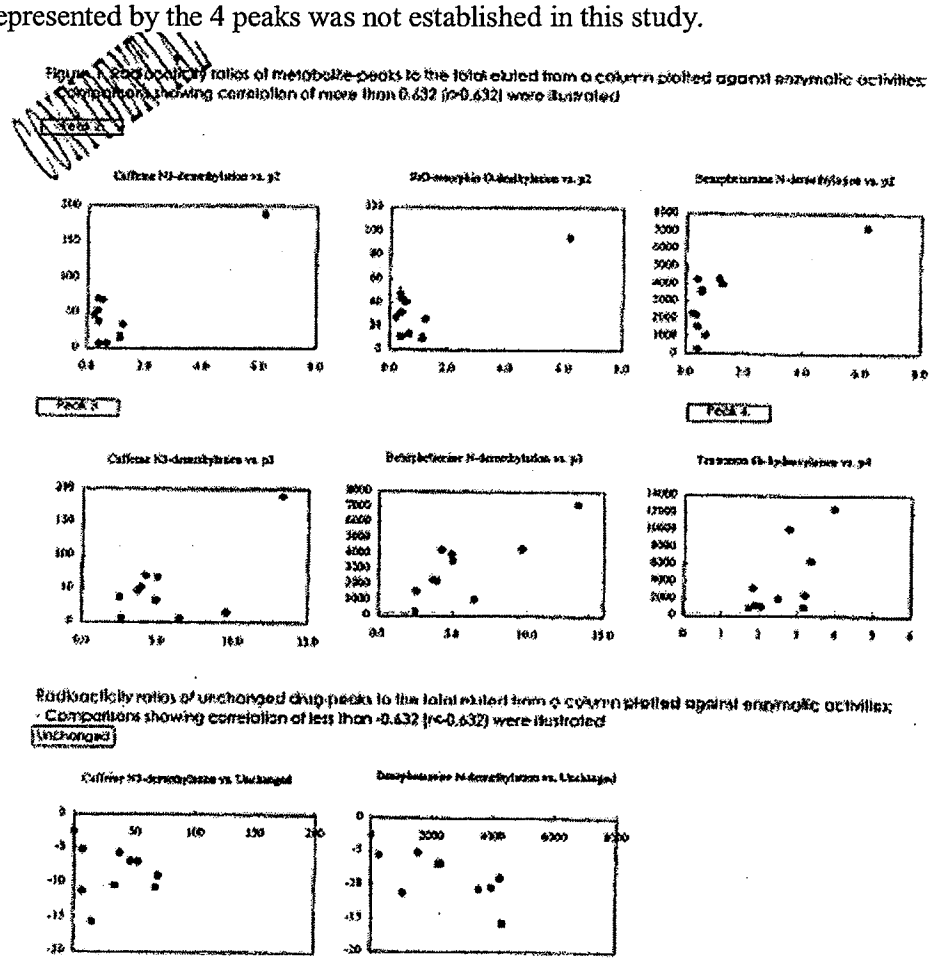


Figure 4. Correlation Plots (radioactivity ratios are displayed as x-axis and specific enzyme activities are displayed as y-axis).

Anti-human CYP isozyme antibodies Inhibition Method (Study 18-K-02001).

Study 18-K-02001: Study on the Inhibitory Effects of Anti-Human Cytochrome P450 Antibodies on the In Vitro Oxidative Metabolism of TEI-6720 Using Human Liver Microsomes

The study was conducted by Teijin Ltd., in Japan from April 2002 to January 2003.

Objective: The previous study (18-K-00002) using microsomes of cytochrome P-450 expression system suggested that several CYP isozymes contribute to the formation of TEI-6720 oxidative metabolites. In the present study, the formation of 67M-1 and 67M-2 and the inhibitory effects of anti-human CYP isozymes antibodies on their formation are examined.

Methods: Human liver microsomes (0.4 mg/mL) were incubated with TEI-6720 (100 μM) for 30 min in the presence of 5 or 10 μL of antibodies contained in sera derived from rabbits immunized by the respective CYP isozymes (CYP1A2, 2C8, 2C9, 2D6 and 3A4) that are commercially available. In addition, microsomes incubated in the presence and absence of rabbit sera containing no antibodies (serum control) served as control incubation.

Results and Discussion: In comparison with the control group, the serum control group showed an approximate 2.2-fold increase in the production of metabolite 67M-1, and an approximate 11% increase in the production of metabolite 67M-2. Although the amount of metabolite 67M-1 formed by human liver microsomes was not inhibited by addition of any of the antibodies tested, the increase in metabolite 67M-1 production may have cancelled out any possible inhibitory actions by the antibodies for the respective CYP isozymes. However, addition of antibodies for CYP1A2, CYP2C8, or CYP2C9 reduced the amounts of metabolite 67M-2 formed by 47.5%, 44.1%, and 33.6%, respectively, compared with those in the serum control group (Table 3). The total inhibition by these 3 isoforms was more than 100%. Because CYP2C9 antibody used also inhibited slightly CYP2C8 activity, it is estimated that 48% of 67M-2 was formed by CYP1A2 pathway and about 52% was formed by 2C8/9 pathway.

Table 3. Formation of Metabolites 67M-1 and 67M-2 in the Presence or Absence of CYP Antibodies

	Metabolite Formation (pmol/min/mg protein)[a]		% of Serum Control	
Test Group	**67M-1**	**67M-2**	**67M-1**	**67M-2**
CYP1A2 Inhibition	81.1 ±1.5	40.3 ±1.2	105.5%	52.5%
CYP2C8 Inhibition	74.7 ±1.8	42.9 ±3.4	97.1%	55.9%
CYP2C9 Inhibition	79.5 ±1.5	50.9 ±2.6	103.4%	66.4%
CYP2D6 Inhibition	81.3 ±1.7	73.9 ±9.5	105.7%	96.3%
CYP3A4 Inhibition	86.5 ±3.9	74.2 ±8.8	112.4%	96.7%
Serum Control	76.9 ±3.5	76.7 ±8.3	100%	100%
Control	35.2 ±0.9	69.2 ±2.1	45.8%	90.2%

a Mean ± standard deviation, N=3.

Reviewer's Comments:

This is the only experiment that could estimate the relative contribution of P450 isoforms in TMX-67 metabolism and metabolite formation. However, concentrations of TMX-67and its other metabolites (67M-3 and 67M-4) were not monitored in this experiment. In addition, the substrate concentration used (100 µM) was higher than the therapeutic C_{max} of 15 µM. A higher concentration may saturate the pathway with low Km and change the relative contribution of metabolic pathway.

Given these limitations, the data do suggest that both CYP1A2 (~48%) and CYP2C8/2C9 (52%) contribute to the formation of 67M-2, a finding consistent with that in Study 18-K-00002 for 67M-2.

Summary of Oxidative Metabolism of TMX-67 (Reviewer's Analysis)

Study 18-A-95018 and Study 18-A-95021

Potential Metabolites of TMX-67	**CYP 1 µM substrate**	**Correlation 1 µM substrate**
Peak 1	2C18 (formation is low)	None
Peak 2	1A1	1A, Other
Peak 3	1A1, 1A2, 2C8	1A, Other
Peak 4	1A2, 2C8, 2C9 (formation is low)	3A?

Study 18-K 00002 and Study 18-K-02001

Potential Metabolites of TMX-67	**CYP 30 µM substrate**	**Antibody 100 µM substrate**	***In vivo* abundance (Study C03-040)**
67M-1 (hydroxylation)	1A1, 1A2, 2C8, 2C9*1, 4A11 (formation is low)	None	10% of the dose
67M-2 (hydroxylation)	1A1, 1A2, 1B1, 2C8, 2C9*1, 3A4	1A2, 2C8, 2C9	11% of the dose
67M-3 (desbutylation)	1A1	Not studied	Negligible
67M-4 (carboxylation from 67M-1)	None	Not studied	14% of the dose

Because the Sponsor did not link Peaks 1-4 with metabolites 67M1-4, the results from Study 18-A-95018 and 18-A-95021 were viewed as preliminary. The Reviewer attempted to associate Peaks 1-4 with metabolites 67M1-4 (see below) based on the information available (including relative retention times).

Peak 1 = 67M-4
Peak 2 = 67M-3
Peak 3 = 67M-2
Peak 4 = 67M-1

- The relative contribution of each P450 isoform to the formation of oxidative metabolites is unclear. Based on the antibody study, both CYP1A2 (~48%) and CYP2C8/2C9 (~52%) contribute for the formation of 67M-2.
- It is likely that 67M-1 was mainly metabolized by non-CYP enzymes and same maybe true for its metabolite, 67M-4. It is not known which non-CYP enzyme may be responsible for the formation of 67M-1 and 67M-4. It is also likely that 67M-4 may be formed by extrahepatic enzymes because it is detected in a larger amount *in vivo* than *in vitro*.
- 67M-2 was mainly formed by CYP1A2, CYP2C8 and CYP2C9 in the liver. It was also metabolized by CYP1A1, whose level is low in healthy non-smoking subjects but it is inducible by smoking.
- 67M-3 was not detected in significant amount *in vivo*. It was mainly metabolized by CYP1A1, whose level is low in healthy non-smoking subjects.

Phase 2 Enzymes (UGTs):

Study 18-K-03003: Confirmation study of UGT isoforms participating in glucuronidation of TEI-6720

The study was conducted by Teijin Ltd., in Japan in September-December 2003.

Objective: To clarify the human UGT isoforms participating in glucuronidation of TEI-6720.

Methods: Control human (pooled from 50 donors) and recombinant human UGT microsomes (12 different expressed UGT isoforms that were commercially available) (1 mg/mL) were incubated at 37°C for 1 hour with febuxostat (100 μM) in the presence or absence of UDPGA (5 mM). Microsomes prepared from insect cells infected by baculovirus served as a negative control. Following incubation, the amounts of febuxostat glucuronide generated were measured by HPLC.

Results and Discussion: Among the 12 tested (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, and 2B17), febuxostat glucuronide was formed by 7 different kinds of human expressed microsomes in the presence of UDPGA (Table 7); in the absence of UDPGA no febuxostat glucuronide was formed.

The results indicate that the formation of the febuxostat glucuronide is UGT mediated, and that several UGT isoforms appear to be able to form febuxostat glucuronide. UGT isoforms express in both human liver and extrahepatic tissues (e.g., kidney, intestine, etc.) (Table 4), the data indicate that glucuronidation of febuxostat could be catalyzed by several UGT isforms not only in the liver but also in other organs. Because the abundance/expression amount of various UGT isoforms in human liver and extrahepatic tissues is not clear, the relative contribution of these UGT isoforms in the metabolism of febuxostat *in vivo* could not be estimated.

Table 4. Mean (± standard deviation) Amount of Febuxostat Glucuronide Formed After Incubation of Febuxostat with Human Hepatic Microsomes and Recombinant Human UGT Microsomes.

Microsome	Amount of Febuxostat Glucuronide Formed[a] (nmol/60 min/mg protein)	Tissue Distribution of UGT Isoforms
Human liver micosomes	35 ±2	NA
Control (UGT insect cell)	nd	NA
UGT1A1	19.2 ±0.8	Liver, Small Intestine, Large Intestine
UGT1A3	2.3 ±0.1	Liver, Small Intestine, Large Intestine
UGT1A4	nd	
UGT1A6	nd	
UGT1A7	3.0 ±0.1	Stomach
UGT1A8	10.2 ±0.1	Large Intestine
UGT1A9	9.7 ±0.3	Liver, Kidney, Large Intestine
UGT1A10	1.2 ±0.0	Small Intestine, Large Intestine, Stomach
UGT2B4	nd	
UGT2B7	2.1 ±0.1	Liver, Kidney, Small Intestine
UGT2B15	nd	
UGT2B17	nd	

nd: None detected (< 0.76 nmol/60 min/mg protein).
a Mean ± standard deviation. N=3.

Reviewer's Comments:
The Sponsor did not conduct in vivo study with UGT inhibitors/inducers because 1) several UGT isoforms are likely to be involved in glucuronidation, and 2) as febuxostat is also metabolized by oxidative metabolism, it is unlikely that significant increase/decrease in the concentration of febuxostat would be observed in vivo when co-administered with UGT inhibitors/inducers. However, most UGT inhibitors/inducers are not selective for UGT isoforms, i.e., they inhibit several isoforms.

b(4)

4.2.1.2.3 Inhibition of Cytochrome P450 Isoforms by Febuxostat (TMX-67)

Study 18-K-98005: Study on the Drug-Drug Interaction of TMX-67 Using Human Liver Microsomes: Inhibitory Activities of TMX-67 to the Metabolism of Human Cytochrome P-450 Isozyme-Specific Substrates

The study was conducted by Teijin Ltd., in Japan in July 1998.

Objective: To study the inhibitory action of TMX-67 on the metabolic activity of specific substrates for which the involvement of certain CYP isozymes is already known and thus investigate the potential effect of TMX-67 on the metabolism of other drugs.

Methods: The potential inhibitory effects of febuxostat on the metabolism of CYP isoform selective substrates were studied with pooled human hepatic microsomes (derived from livers of 5 American males and 5 American females).

The CYP450 isoform specific substrates used were phenacetin (CYP1A2), tolbutamide (CYP2C9), (S)-mephenytoin (CYP2C19), dextromethorphan (CYP2D6), and testosterone (CYP3A4). Each CYP substrate (at three different concentrations) was incubated with human liver microsomes in the presence of various concentrations of TMX-67 or positive control drugs (inhibitor). All incubations were carried out at 37°C and initiated by adding NADPH and terminated by adding acetonitrile. TMX-67 concentrations used were 0, 50 and 100 μM for all incubations. Lineweaver-Burk and Dixon plots were used to calculate K_m for substrates and K_i for inhibitors.

Results and Discussion: Febuxostat was found to be a competitive inhibitor of the CYP2D6 catalyzed *O*-demethylation of dextromethorphan, with a K_i of 40 μM (12.6 μg/mL) (Table 1). Febuxostat showed little inhibitory activity against other CYP isoform activities evaluated, with K_i values greater than 100 μM.

Table 1. Inhibition of CYP Isoform Activities by Febuxostat in Human Hepatic Microsomes.

CYP Isoform	Reaction	K_m (μM)	Febuxostat K_i			Positive Control (Ki)
			μM	ng/mL		
1A2	Phenacetin *O*-demethylation	45	>100 (>250)	>31610	Competitive (almost no inhibition)	
2C9	Tolbutamide hydroxylation	238	>100 (~180)	>31610	Mixed-type	Diclofenac (25 μM)
2C19	*S*-Mephenytoin 4'-hydroxylation	25	>100 (>250)	>31600	Appears no inhibition	
2D6	Dextromethorphan *O*-demethylation	8.3	40	12644	Competitive	Alprenolol (3 μM)
3A4	Testosterone 6β-hydroxylation	173	>100 (~160)	>31610	Competitive	Nifedipine (20 μM)

The C_{max} found in subjects given multiple 120 mg oral dose of febuxostat was approximately 5.3 μg/mL (15 μM), and $[C_{max}]/K_i$ is about 0.38 (>0.1) for CYP2D6, therefore a follow-up *in vivo* study with CYP2D6 substrate was recommended.

Reviewers Note:
A clinical drug interaction study with desipramine, a drug whose clearance is primarily mediated by CYP2D6, was conducted (See Drug Interaction Review for Study C02-005).

For CYP1A2, 2C9, 2C19 and 3A4, $[C_{max}]/K_i$ values are <0.1. It is unlikely that administration of febuxostat at the anticipated therapeutic doses (80 and 120 mg) would be associated with clinically significant drug interactions resulting from febuxostat inhibition of the CYP-mediated metabolism of other drugs that are substrates for CYP1A2, 2C9, 2C19 and 3A4.

4.2.1.2.4 In Vitro Absorption/Transport Study

— *Project No. 002596: Determination of the Apparent Permeability Coefficient ofTMX-67 Using the CACO-2 Absorption Assay*

The study was conducted by [redacted] in November 2000. b(4)

Objectives: To determine the apparent permeability coefficients (P_{app}) of TMX-67 in bi-directional transport when tested at 10 and 100 μM at pH 5.5 and 7.4, respectively. The possibility of P-glycoprotein (P-gp) involvement in TMX-67 transport will also be investigated. Finally its permeability will be ranked with three known reference compounds of high, moderate and low permeability. Reference standards selected were mannitol (low permeability, passive diffusion through the paracellular route), salicylic acid (moderate permeability, pH-dependent transport) and testosterone (highly permeability).

Methods: Caco-2 cells (obtained from [redacted] were grown as monolayers on [redacted] polycarbonate b(4) filters (0.4 μM pore size) and cultured for at least 21 days. Prior to transport assay, all monolayers were assayed for their transepithelial electrical resistance (TEER) (150-300 Ohm-cm^2). The permeability studies were initiated by adding cell culture medium (at pH 5.5 or 7.4) containing test compound TMX-67 at 10 or 100 μM or 50 μM of three reference compounds (radiolabeled) to either the apical (apical to basolateral transport) or basolateral (basolateral to apical transport) side of the monolayer. Samples were taken from the opposite side of the cell monolayers (receiver side) and replaced it with fresh medium at 1, and 2 hours. In addition, A-to-B transport was assessed in the presence of 100 μM verapamil (a competitive P-gp inhibitor) at pH 7.4 for TMX-67 (10 μM only) and all three reference compounds. All assays were conducted in triplicate. Recovery was determined in all the assays. At the end of the experiment, leakage of each monolayer is assessed with Lucifer Yellow. The concentrations for permeability calculations for reference compounds were analyzed by a liquid scintillation counter. Test articles in recovered samples were quantified using LC/MS at the [redacted]

All transport rates are calculated by comparison of the integrated MS areas of the 0 hour (donor) sample to the 1 and 2 hour (receiver) samples.

Results and Discussion: All controls appeared to work in the study (Table 1).

When tested at pH 7.4, TMX-67 appeared to have medium permeability as P_{app} of TMX-67 (10 and 100 μM) in both A-B and B-A directions were around 20 x 10^{-6} cm/sec, similar to those for salicylic acid (Table 9). At a concentration of 10 μM, the net flux (B-A/A-B) for TMX-67 was around 1.5, indicating an efflux activity. Verapamil (100 μM) at apical side did not appear to have an effect on the A-B transport rate of TMX-67. However, it is not clear whether verapamil would affect its B-A transport. Furthermore, because a positive control for P-gp activity (e.g., digoxin) was not included in the study, it was unclear about the functional expression of P-gp in the Caco-2 cells used. Therefore, the Sponsor's conclusion that P-gp is not involved in the transport of TMX-67 is not definitive. At a concentration of 100 μM, the net flux (B-A/A-B) for TMX-67 was around 0.9.

When tested at pH 5.5, the A-B permeability of febuxostat at both the 10 and 100 µM concentrations increased, ranking it among drugs of high permeability (such as testosterone). In addition, transport rates from apical to basolateral were higher than those from basolateral to apical (the net flux (A-B/B-A was about 2), indicating that absorption of TMX-67 was likely by a pH-dependent transport mechanism.

Table 1. Apparent Permeability Coefficient (P_{app}) of TMX-67 and Reference Compounds Across a Caco-2 Cell Momolayers.

Compound Name	TEER (Ohm-cm²)	Lucifer Yellow (%/hr)	Recovery (%)	1-hr *Papp* (cm/sec) $\times 10^{-6}$	2-hr *Papp* (cm/sec) $\times 10^{-6}$
Mannitol					
A-to-B (pH 7.4)	169.3 ± 16.2	0.36	99.3 ± 1.7	1.4 ± 0.2	1.3 ± 0.2
A-to-B (pH 5.5)	177.3 ± 5.8	0.27	96.2 ± 0.1	1.4 ± 0.1	1.3 ± 0.1
A-to-B (pH 7.4) Verapamil	160.7 ± 4.9	BLQ	97.9 ± 0.9	1.0 ± 0.2	1.0 ± 0.1
B-to-A (pH 7.4)	182.7 ± 15.0	1.36	101.9 ± 0.6	1.5 ± 0.1	1.3 ± 0.1
B-to-A (pH 5.5)	191.7 ± 15.5	0.64	99.6 ± 0.2	1.5 ± 0.3	1.4 ± 0.1
Salicylic Acid					
A-to-B (pH 7.4)	167.7 ± 11.0	0.27	93.9 ± 3.1	18.8 ± 5.9	18.7 ± 1.5
A-to-B (pH 5.5)	167.0 ± 14.7	1.09	93.9 ± 1.9	40.6 ± 4.5	31.1 ± 1.8
A-to-B (pH 7.4) Verapamil	175.7 ± 15.3	BLQ	91.8 ± 1.0	15.1 ± 2.6	17.3 ± 0.7
B-to-A (pH 7.4)	189.3 ± 17.1	BLQ	97.6 ± 1.0	17.4 ± 1.9	17.3 ± 1.6
B-to-A (pH 5.5)	192.0 ± 12.1	0.45	95.7 ± 4.0	43.9 ± 2.1	32.4 ± 4.0
Testosterone					
A-to-B (pH 7.4)	421.7 ± 24.3	BLQ	100.0 ± 4.5	34.2 ± 11.5	33.0 ± 2.2
A-to-B (pH 5.5)	437.0 ± 25.0	BLQ	92.6 ± 4.6	31.9 ± 10.8	26.9 ± 2.6
A-to-B (pH 7.4) Verapamil	445.3 ± 23.1	BLQ	92.6 ± 2.3	26.0 ± 6.0	25.3 ± 1.8
B-to-A (pH 7.4)	468.7 ± 25.0	BLQ	100.8 ± 1.3	38.1 ± 5.6	29.3 ± 3.0
B-to-A (pH 5.5)	475.0 ± 53.7	BLQ	96.3 ± 3.8	38.4 ± 1.5	30.8 ± 0.9

Compound Name	TEER (Ohm-cm²)	Lucifer Yellow (%/hr)	Recovery (%)	1-hr *Papp* (cm/sec) $\times 10^{-6}$	2-hr *Papp* (cm/sec) $\times 10^{-6}$
TMX-67, 10 µM					
A-to-B (pH 7.4)	187.3 ± 13.1	0.18	72.0 ± 2.4	18.2 ± 0.7	17.4 ± 1.9
A-to-B (pH 5.5)	204.0 ± 19.1	0.36	64.0 ± 2.5	32.5 ± 2.0	24.1 ± 1.5
A-to-B (pH 7.4) Verapamil	160.0 ± 1.7	0.09	73.8 ± 2.1	17.2 ± 3.2	15.6 ± 0.9
B-to-A (pH 7.4)	184.3 ± 12.7	0.64	73.8 ± 1.6	26.8 ± 1.4	25.4 ± 0.7
B-to-A (pH 5.5)	193.0 ± 9.5	0.18	75.9 ± 3.8	11.9 ± 0.4	13.6 ± 0.2
TMX-67, 100 µM					
A-to-B (pH 7.4)	204.3 ± 4.0	BLQ	63.0 ± 1.3	22.6 ± 2.2	19.2 ± 0.2
A-to-B (pH 5.5)	205.0 ± 13.0	0.52	62.8 ± 0.3	32.5 ± 8.7	24.1 ± 2.5
B-to-A (pH 7.4)	191.7 ± 18.2	BLQ	73.5 ± 1.5	18.8 ± 1.1	17.9 ± 0.8
B-to-A (pH 5.5)	205.0 ± 21.0	0.55	74.9 ± 2.1	12.0 ± 0.2	11.9 ± 0.1

Values are the means of triplicate determinations ± standard deviation.
BLQ: Below the Limit of Quantitation

Conclusions: The C_{max} of TMX-67 at the maximal proposed dose of 120 mg in healthy volunteers was around 5 µg/mL (15 µM). Data from Caco-2 cells indicated that TMX-67 had medium permeability at pH 7.4 and its permeability was enhanced by lowering pH. It is likely

that TMX-67 is a substrate of pH-dependent transporters. The basolateral to apical permeability (secretory direction) was 0.5 fold greater than the apical to basolateral permeability (absorptive direction) when tested at pH 7.4 with 10 μM of TMX-67 (close to its therapeutic concentration), suggesting that TMX-67 maybe a substrate of apically located efflux pumps. However, it was not clear whether P-gp was involved because of lack of positive control for P-gp activity in the assay.

Comments:

- The assay did not include a positive control to show functional P-gp efflux activity with a P-gp substrate such as digoxin. Therefore, the conclusion that TMX-67 is not subject to P-gp transport is not definitive because we could not rule out the possibility that Caco-2 cells used may not have high P-gp expression.
- Inhibition potential of TMX-67 on P-gp has not been studied.

Based on *in vitro* metabolism/transport review, the following information needs to be collected:

1. Induction potential of febuxostat for human CYPs

In addition, positive control for P-gp activity in the Caco-2 cells needs to be included to determine whether P-gp is involved in the efflux of febuxostat. Inhibition potential of febuxostat on P-gp may also be studied in the Caco-2 cells.

4.2.2 Single- and Multiple-Dose PK/PD Study in Healthy Subjects

4.2.2.1 Study TMX-99-001: A Multiple-Dose Safety, Pharmacokinetic, and Pharmacodynamic Study of Oral TMX-67 in Healthy Volunteers

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Study Period: November 7 1999 to April 15 2001

Sample Analysis Period: November 29, 1999 to October 4, 2001

Principle Investigators: [redacted] b(4)

Study Centers: [redacted]

Analytical Site: [redacted]

Objectives:

- Assess the safety of TMX-67;
- Determine the maximum tolerated dose (MTD) of TMX-67; and
- Determine the pharmacokinetic and pharmacodynamic profiles of TMX-67 following

oral administration of multiple daily doses over a range of doses and regimens (eg, once daily [QD] and/or twice daily [BID]).

Study Design: This was a Phase 1, randomized, double-blind, placebo-controlled, multi-center, multiple-dose, dose-escalation study. Each dose cohort includes 12 subjects (10 TMX-67, 2 placebo) who were administered either TMX-67 or placebo over 13 days (dosing was initiated on Day 1, interrupted on Day 2, and resumed on Days 3-14). The doses studied were 10, 20, 30, 40, 50, 70, 90, 120, 160, 180, 240 mg QD and 30 mg BID. The 50 mg dose panel was repeated due to possible traces of xanthine crystals observed in 3 subjects in the first 50 mg dose panel. Both serum and urine samples were collected for determination of TMX-67 and its metabolites, urate (uric acid), xanthine and hypoxanthine concentrations.

Safety assessments performed during the course of the study included physical examination, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory examinations, and monitoring adverse events and concomitant medication use.

154 adult subjects (87 males and 67 females) aged 19-45 years were enrolled and randomized in 13 dose groups including a repeat of the 50 mg dose group (Table 1). The majority of subjects were male (56%) and Caucasian (76%). Please refer to the summary table in the Appendix for demographic information.

Table 1. Disposition of Subjects.

	TMX-67 Group												
		QD										BID	
	Pbo	10	20	30	40	50	70	90	120	160	180	240	30
All Randomized Subjects	26	10	10	10	8	20	10	10	10	10	10	10	10
Completed Study	23	10	9	9	8	18	10	10	9	10	7	8	10
Prematurely Terminated	3	0	1	1	0	2	0	0	1	0	3	2	0
Adverse Event	1	0	0	1	0	1	0	0	1	0	3	2	0
Personal Reasons	2	0	1	0	0	0	0	0	0	0	0	0	0
Other [a]	0	0	0	0	0	1	0	0	0	0	0	0	0

a: Difficult venipuncture. Pbo = placebo

Three (3) subjects receiving 50 mg QD had very small possible traces of xanthine crystals through x-ray diffraction or FTIR. Due to these results, the 50 mg dose panel was repeated and the 40 mg dose was performed and evaluated and subsequently negative results for xanthine crystals were seen at these doses. In all analyses, the initial 50 mg QD and repeated 50 mg QD dose groups were summarized together, as were all placebo subjects.

Test Articles:

Study Drug	Strength Dosage Form	Teijin Bulk Lot Number	Abbott Bulk Lot Number	Finishing Lot Number
TMX-67	5 mg	TMXZ905A	57-010-AL	61-278-S2
	10 mg	TMXZ910A	56-989-AL	56-856-S2
	20 mg	TMXZ920A	57-011-AL	61-279-S2

		TMXT020A	63-141-AL	72-339-S2
		TMXT020A	63-141-AL	75-526-S2
Placebo for TMX-67		TMXZ900A	56-988-AL	56-855-S2
		TMXZ900A	56-988-AL	71-255-S2
		TMXZ900A	56-988-AL	75-525-S2
		TMXT000A	63-138-AL	72-338-S2

Reviewer' Note: The highest dose strength was 20 mg and for the highest studied dose, 240 mg, the subjects took 12 tablets.

The 20 mg tablet used in this study was designated as Formulation A3 by Abbott.

Sample Collection:

Pharmacokinetics (TMX-67 and its metabolites)

Blood (Plasma):

QD regimen:

Day	Blood Collection Time (hours)
1	0 (Predose), 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16
2 (no dose administered)	24, 30, 36 (after Day 1 dose)
3	48 (after Day 1 dose but prior to Day 3 dose)
5	0 (Predose)
8	0 (Predose)
11	0 (Predose)
13	0 (Predose)
14	0 (Predose), 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16
15 (no dose administered)	24, 30, 36 (after Day 14 dose)
16 (no dose administered)	48 (after Day 14 dose)

BID regimen:

Day	Blood Collection Time (hours) (post am dose)
1	0 (pre am dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (pre pm dose), 12.25, 12.5, 13, 13.5, 14, 15, 16
2 (no dose administered)	18, 24, 30, 36 (post day 1 am dose)
3	48 (after Day 1 dose but prior to Day 3 dose)
5	0 (Pre am dose)
8	0 (Pre am dose)
11	0 (Pre am dose)
13	0 (Pre am dose)
14	0 (pre am dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (pre pm dose), 12.25, 12.5, 13, 13.5, 14, 15, 16
15 (no dose administered)	18, 24, 30, 36 (post day 14 am dose)

Urine:

QD and BID:

Day	Urine Collection Time

1	pre-dose, 0-6, 6-12, 12-24 hours
2	24-48 hours post Day 1 dosing
14	first morning void, 0-6, 6-12, 12-24 hours

Pharmacodynamics (Uric acid, xanthine and hypoxanthine)
Blood (Serum):
QD:
Day -1: 0, 6, 12 hr
Days 1 and 8: 0, 6, 12, and 24 hr
Day 14: 0, 6, 12, 24, and 48 hr

BID:
Day -1: 0, 6, 12, and 18 hr
Days 1 and 8: 0, 6, 12, 18, and 24 hr
Day 14: 0, 6, 12, 18, 24, and 48 hr

Urine:
QD and BID:
Days -1 and 8: 0-6, 6-12, 12-24 hr
Days 1 and 14: 0-6, 6-12, 12-24, and 24-48 hr

Sample Analysis: All Sample analyses were conducted at [redacted] b(4)
[redacted] See Table 2 below for a summary of various methods used for analysis of TMX-67, its metabolites, uric acid, xanthine, and hypoxanthine in human plasma (serum) and urine.

Table 2. Summary of Analytical Methods for Study TMX-99-001.

Analyte	Matrix	Analytical Method	Limit of Quantitation (linear range)
TMX-67	Human EDTA Plasma	HPLC-Fluorescence Detection [redacted] PS 23150_1)	0.02µg/mL (0.01-20 µg/mL)
Total TMX-67 (Intact plus conjugates)	Human Urine (Urine samples were hydrolyzed with 2 N NaOH prior to extraction)	HPLC-Fluorescence Detection [redacted] PS 23150_3)	0.05 µg/mL (0.05-100 µg/mL) b(4)
Intact TMX-67	Human Urine	HPLC-Fluorescence Detection [redacted] PS 23150_2)	0.02 µg/mL (0.02-20 µg/mL)
67M-1, 67M-2, and 67M-4	Human EDTA Plasma	LC/MS/MS [redacted] PS 23150_4)	0.5 ng/mL (0.5-100 ng/mL)

Total 67M-1, 67M-2, and 67M-4 (Intact plus conjugates)	Human Urine (Urine samples were hydrolyzed with 2 N NaOH prior to extraction)	LC/MS/MS (PS 23150_6)	5 ng/mL (5-500 ng/mL)
Intact 67M-1, 67M-2, and 67M-4	Human Urine	LC/MS/MS (PS 23150_5)	0.5 ng/mL (0.5-100 ng/mL)
Urate	Human Serum	HPLC-UV Detection (PS 23151_1)	10 µM (10-1000 µM)
Uric Acid	Human Urine	HPLC-UV Detection (PS 23151_2)	10 µM (10-4500 µM)
Xanthine	Human Serum	HPLC-UV Detection (PS 23151_1)	0.2 µM (0.2-20 µM)
	Human Urine	HPLC-UV Detection (PS 23151_2)	10 µM (10-1000 µM)
Hypoxanthine	Human Serum	HPLC-UV Detection (PS 23151_1)	0.2 µM (0.2-20 µM)
	Human Urine	HPLC-UV Detection (PS 23151_2)	10 µM (10-1000 µM)

b(4

Pharmacokinetic and Statistical Analysis: Pharmacokinetic parameters of TMX-67 and metabolites were estimated from the plasma concentration values by standard noncompartmental methods using WinNonlin Professional™ V.3.1 (Pharsight Corporation, Mountain View, CA).

To investigate the effect of day and dose on the pharmacokinetics of the TMX-67 QD dosing regimens, an analysis of variance (ANOVA) was performed on T_{max}, λ_z, and the natural logarithms of the dose-normalized C_{max} and AUC on day 1 and day 14.

Pharmacodynamic and Statistical Analysis: Pharmacodynamic parameters were estimated using the serum and urine concentration values. The area under the serum concentration versus time curve for uric acid, xanthine, and hypoxanthine was estimated by using WinNonlin™ V.3.1.

To investigate the effect of day and dose on the pharmacodynamics of the TMX-67 QD dosing regimens, an ANOVA with factors for dose, subject nested within dose, day, and day by dose interaction was performed on the percent change from baseline (or change from baseline) to each time point (Day 1, 8, and 14) for each pharmacodynamic parameter.

Pharmacokinetics and Pharmacodynamics Analysis: To investigate the relationship of serum xanthine $C_{mean,24}$, and the percent change in serum urate $C_{mean,24}$ with TMX-67 AUC_{24} (QD regimens) for TMX-67 and placebo once a day dosing regimens, the data were fitted to an E_{max} model ($E = E_0 + [(E_{max} - E_0) \cdot AUC_{24}/(EAUC_{50} + AUC_{24})]$), using WinNonlin Professional™ V.3.1. The program software used Gauss-Newton (Levenberg and Hartly) minimization method for fitting the data. In this equation, E_0 represents the placebo effect; E_{max} represents the maximum

effect (therefore, E_{max}-E_0 represents the maximum TMX-67 effect); and $EAUC_{50}$ represents the AUC of TMX-67 at which an effect equal to $E_0 + (E_{max}-E_0)/2$ is attained.

Pharmacokinetic Results:

Plasma PK Profiles

The mean steady-state plasma concentration-time profiles of TMX-67 at 40 mg, 70 mg, 120 mg, and 240 mg QD and 30 mg BID (AM) are shown in Figures 1a (linear) and 1b (semi-log scale).

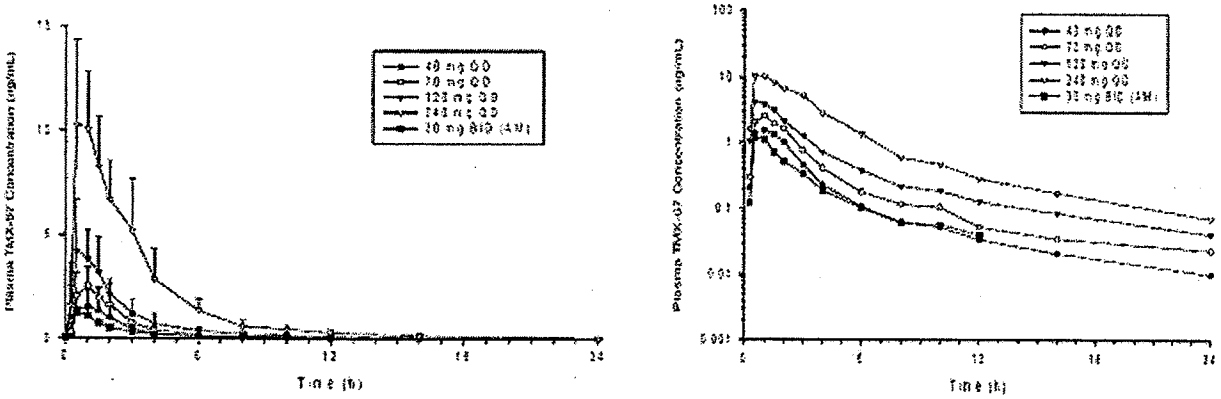


Figure 1. Mean (SD) plasma concentration-time profiles of TMX-67 at 40 mg, 70 mg, 120 mg, and 240 mg QD and 30 mg BID (AM) following oral administration of TMX-67 on Day 14. (Left, linear scale and Right, semi-log scale)

(Reviewer's Note: The sponsor did not have a plot that showed plasma concentration-time profiles for all the doses studied and only included a plot that showed 40, 70, 120 and 240 mg dose levels which covered the proposed doses of 80 and 120 mg.)

The plasma pharmacokinetic parameters for TMX-67, and its metabolites 67M-1, 67M-2, and 67M-4 (secondary metabolite generated from 67M-1) are summarized in Tables 3-6. TMX-67 reached peak concentrations at about 1 hr. Apparent terminal half-life was about 5-10 hrs at doses above 40 mg. Half-lives were shorter for doses lower than 40 mg, possibly due to assay limitation for capturing the "true" terminal phase. Due to enterohepatic circulation, some patients showed double peak in PK profiles.

Table 3. Summary of Pharmacokinetic Parameters of TMX-67 on Days 1 and 14 Following Oral Administration of TMX-67.

Dose QD	Day		t_{max} (h)	C_{max} (µg/mL)	AUC_t (µg·h/mL)	AUC^a (µg·h/mL)	$t_{1/2z}$[b] (h)	V_{ss}/F (L)	Cl/F (L/h)	C_{max}/D	AUC^a/D
10 mg	1	Mean	0.99	0.3362	0.6780	0.7269	1.5 (1.3)	38.2	15.12	0.0336	0.0727
		SD	0.41	0.1088	0.2116	0.2257	0.5	19.0	5.11	0.0109	0.0226
	14	Mean	0.70	0.3995	0.7394	0.9505	3.0 (2.0)	42.7	11.39	0.0399	0.0950
		SD	0.26	0.1866	0.2338	0.2712	1.9	30.4	3.45	0.0187	0.0271
20 mg	1	Mean	1.06	1.1123	2.0549	2.1816	3.2 (2.6)	29.2	10.00	0.0556	0.1091
		SD	0.81	0.4796	0.6358	0.6626	1.5	11.5	3.22	0.0240	0.0331

	14	Mean	0.89	0.9342	1.9096	2.1125	4.7 (3.8)	33.3	10.01	0.0467	0.1056
		SD	0.55	0.2870	0.5204	0.5044	1.8	19.4	2.68	0.0143	0.0252
30	1	Mean	0.72	1.1192	2.3596	2.5469	9.2 (4.6)	75.0	12.37	0.0373	0.0849
mg		SD	0.26	0.3386	0.5590	0.5724	13.7	98.2	3.03	0.0113	0.0191
	14	Mean	0.89	1.2835	2.4835	2.5681	6.7 (5.7)	62.7	12.19	0.0428	0.0856
		SD	0.42	0.4593	0.5486	0.5325	2.9	50.2	2.83	0.0153	0.0178
40	1	Mean	1.44	1.5282	3.8724	3.9770	4.2 (3.8)	48.7	12.60	0.0382	0.0994
mg		SD	0.78	0.7125	1.8266	1.8566	1.6	27.2	6.58	0.0178	0.0464
	14	Mean	1.19	1.8221	4.3124	4.2998	10.3 (6.3)	49.5	10.63	0.0456	0.1075
		SD	0.46	0.6823	1.5282	1.5366	7.4	27.5	4.51	0.0171	0.0384
50	1	Mean	0.78	1.9697	4.3016	4.4073	5.0 (4.5)	43.2	12.38	0.0394	0.0881
mg		SD	0.26	0.6275	1.3144	1.2981	2.1	19.3	3.86	0.0125	0.0260
	14	Mean	1.14	1.7917	4.4327	4.3785	10.1 (6.7)	59.1	12.30	0.0358	0.0876
		SD	0.68	0.6662	1.2543	1.1859	6.3	18.2	3.60	0.0133	0.0237
70	1	Mean	1.00	3.0819	6.8171	6.9335	5.0 (4.7)	41.6	11.21	0.0440	0.0990
mg		SD	0.75	1.5488	2.6791	2.6804	1.1	15.6	3.46	0.0221	0.0383
	14	Mean	1.10	2.6899	7.1283	6.9489	12.5 (8.5)	54.1	10.95	0.0384	0.0993
		SD	0.39	0.9145	2.4008	2.3294	7.7	23.2	3.11	0.0131	0.0333
90	1	Mean	0.95	3.4806	8.8792	9.0927	9.3 (6.8)	56.7	11.68	0.0387	0.1010
mg		SD	0.50	1.4588	3.7571	3.7577	6.2	33.7	5.31	0.0162	0.0418
	14	Mean	0.95	4.0589	9.9257	9.6467	14.6 (10.0)	63.7	11.17	0.0451	0.1072
		SD	0.44	1.7688	3.6722	3.6217	9.8	46.8	6.09	0.0197	0.0402
120	1	Mean	1.00	4.4720	11.1004	11.3131	11.4 (9.1)	57.8	11.09	0.0373	0.0943
mg		SD	0.56	1.3148	2.4228	2.4293	5.8	17.6	2.58	0.0110	0.0202
	14	Mean	1.11	5.3076	12.3618	11.9599	18.2 (11.9)	55.1	10.47	0.0442	0.0997
		SD	0.82	1.6824	2.6592	2.4244	13.9	15.8	2.48	0.0140	0.0202
160	1	Mean	0.75	7.2978	20.4793	20.7463	10.7	40.7	8.22	0.0456	0.1297
mg		SD	0.26	2.1619	4.8919	4.9089	(9.8) 3.4	15.7	2.44	0.0135	0.0307
	14	Mean	0.80	8.7711	22.9680	22.2821	11.8	36.1	7.82	0.0548	0.1393
		SD	0.35	2.7373	6.8952	6.5259	(9.5) 5.8	14.1	2.56	0.0171	0.0408
180	1	Mean	1.07	8.3986	24.9478	25.5887	23.6	54.6	7.75	0.0467	0.1422
mg		SD	0.53	3.2226	9.4311	9.5459	(11.0) 32.0	44.4	2.32	0.0179	0.0530
	14	Mean	1.00	8.0488	24.8368	23.9545	20.8	45.6	8.07	0.0447	0.1331
		SD	0.58	2.4018	7.6916	7.6651	(15.8) 13.7	17.4	2.08	0.0133	0.0426
240	1	Mean	1.06	8.3858	27.9550	28.2692	12.7	54.6	9.53	0.0349	0.1178
mg		SD	0.68	3.2197	9.0597	9.1213	(10.2) 5.3	29.4	4.09	0.0134	0.0380
	14	Mean	0.94	11.2630	35.6951	34.9763	9.9	31.3	7.28	0.0469	0.1457
		SD	0.42	4.0388	10.1521	9.9084	(8.1) 5.3	11.3	1.74	0.0168	0.0413

Dose	Day		t_{max} (h)	C_{max} (µg/mL)	AUC_t (µg·h/mL)	AUC^a (µg·h/mL)	$t_{1/2z}$[b] (h)	V_{ss}/F (L)	Cl/F (L/h)	C_{max}/D	AUC^a/D
30	1	Mean	0.90	1.3091	2.7025	2.8169	4.0	34.4	11.30	0.0436	0.0939
mg	AM						(3.8)				
BID		SD	0.46	0.4422	0.7757	0.7979	1.1	9.1	2.68	0.0147	0.0266
	14 AM	Mean	0.70	1.4882	2.9146	2.9146	4.9 (4.8)	41.1	10.81	0.0496	0.0972

		SD	0.35	0.3208	0.7564	0.7564	1.0	6.7	2.28	0.0107	0.0252
	14 PM	Mean	1.75	0.8986	3.7065	3.3083	11.1 (5.8)	61.0	9.88	0.0300	0.1103
		SD	0.68	0.2994	1.4081	1.1573	11.8	17.9	2.73	0.0100	0.0386

a AUC refers to AUC∞, AUC24, and AUC12 for Day 1 (QD & BID), Day 14 (QD), and Day 14 (BID), respectively.
b Arithmetic Mean (Harmonic Mean)
For all regimens, the number of subjects in each group ranged from 7 to 10, with the exception of the 50 mg group (17-18).

For the BID dosing regimen, even though there was a slight delay in T_{max} and a slight decrease in C_{max} when comparing the PM dosing to the AM dosing for 30 mg BID regimen, the AUC appeared to remain the same for the PM dosing as compared to the AM dosing (Table 3 and Figure 2).

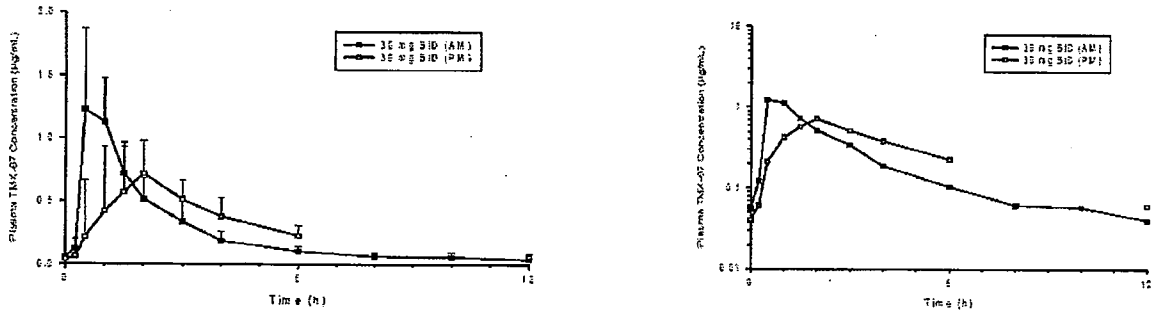


Figure 2. Mean (SD) Plasma TMX-67 Concentration versus Time Profiles Following AM and PM Oral Administration of TMX-67 (30 mg BID Regimen) on Day 14. (Left, linear scale and Right, semi-log scale)

Compared to TMX-67 levels in plasma, metabolites 67M-1, 67M-2 and 67M-4 all showed lower plasma exposure than TMX-67, with an AUC ratio of about 0.03 (Tables 4-6). Only the data for doses of 70, 90 and 120 mg were shown.

Table 4. Summary of Pharmacokinetic Parameters of 67M-1 on Days 1 and 14 Following Oral Administration of TMX-67.

Dose QD	Day		t_{max} (hr)	C_{max} (ng/mL)	AUCt (ng·h/mL)	AUC[a] (ng·h/mL)	$t_{1/2z}$[b] (h)	C_{max}/D (10^{-3}/L)	AUC[a]/D (10^{-3}h/L)	AUC[c] Ratio
70 mg	1	Mean	1.20	58.693	154.353	159.754	4.2	0.838	2.282	0.023
		SD	0.63	49.427	102.777	102.176	(3.6) 1.9	0.706	1.460	0.007
	14	Mean	1.15	46.924	159.037	156.321	14.7	0.670	2.233	0.023
		SD	0.24	18.118	84.886	80.563	(4.6) 18.2	0.259	1.151	0.008
90 mg	1	Mean	1.40	76.014	253.273	276.583	6.4	0.845	3.073	0.033
		SD	0.88	32.407	115.818	106.906	(4.0) 6.1	0.360	1.188	0.012
	14	Mean	1.10	94.776	275.643	280.175	10.2	1.053	3.028	0.032
		SD	0.39	43.266	104.298	108.174	(8.7) 4.7	0.481	1.165	0.013
120 mg	1	Mean	1.33	105.764	340.364	351.084	11.7	0.881	2.926	0.031
		SD	0.66	29.215	118.007	119.003	(9.4)	0.243	0.992	0.011

							4.0			
	14	Mean	1.22	125.751	373.215	356.580	15.3	1.048	2.972	0.030
		SD	0.75	51.460	136.990	125.263	(10.9) 9.1	0.429	1.044	0.009

a AUC refers to AUC∞, and AUC24 for Day 1, and Day 14, respectively.
b Arithmetic Mean (Harmonic Mean)
c 67M-1 to TMX-67 AUC Ratio
For all regimens, the number of subjects ranged from 7 to 10.

Table 5. Summary of Pharmacokinetic Parameters of 67M-2 on Days 1 and 14 Following Oral Administration of TMX-67.

Dose QD	Day		t_{max} (hr)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC^a (ng·h/mL)	$t_{1/2z}$ [b] (h)	C_{max}/D (10^{-3}/L)	AUC^a/D (10^{-3}h/L)	AUC^c Ratio
70 mg	1	Mean	1.45	43.686	153.003	157.539	3.8	0.624	2.251	0.024
		SD	0.83	28.137	68.625	68.353	(3.5) 1.2	0.402	0.976	0.008
	14	Mean	1.35	36.969	160.857	155.860	21.4	0.528	2.227	0.023
		SD	0.24	14.451	65.802	64.113	(7.8) 22.9	0.206	0.916	0.007
90 mg	1	Mean	2.00	79.800	299.727	312.580	13.2	0.887	3.473	0.039
		SD	0.94	26.685	64.682	60.352	(8.5) 11.3	0.296	0.671	0.016
	14	Mean	1.60	91.802	347.300	327.886	21.4	1.020	3.643	0.038
		SD	0.81	39.894	82.991	79.479	(14.9) 14.1	0.443	0.883	0.013
120 mg	1	Mean	1.50	81.141	362.411	377.000	15.9	0.676	3.142	0.035
		SD	0.66	18.180	104.475	104.134	(12.1) 8.7	0.151	0.868	0.015
	14	Mean	1.44	96.373	420.909	391.721	22.2	0.803	3.264	0.034
		SD	0.98	23.802	134.153	115.984	(15.0) 15.3	0.198	0.967	0.012

a AUC refers to AUC∞, and AUC24 for Day 1, and Day 14, respectively.
b Arithmetic Mean (Harmonic Mean)
c 67M-2 to TMX-67 AUC Ratio
For all regimens, the number of subjects ranged from 7 to 10.

Table 6. Summary of Pharmacokinetic Parameters of 67M-4 on Days 1 and 14 Following Oral Administration of TMX-67.

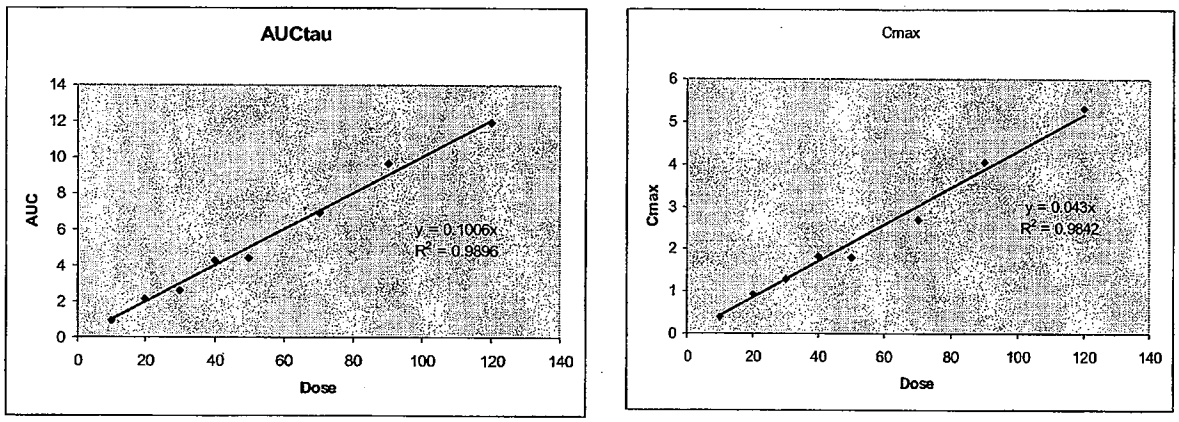
Dose QD	Day		t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC^a (ng·h/mL)	$t_{1/2z}$ [b] (h)	C_{max}/D (10^{-3}/L)	AUC^a/D (10^{-3}h/L)	AUC^c Ratio
70 mg	1	Mean	1.80	42.149	164.976	170.124	4.8 (4.4)	0.602	2.430	1.15
		SD	0.67	16.512	63.946	63.553	1.4	0.236	0.908	0.25
	14	Mean	1.80	42.247	195.059	185.168	14.9 (7.9)	0.604	2.645	1.27
		SD	0.54	9.908	74.080	61.924	8.3	0.142	0.885	0.30
90 mg	1	Mean	2.15	67.594	303.593	348.601	15.2 (7.3)	0.751	3.873	1.18
		SD	0.94	43.095	226.605	227.974	11.7	0.479	2.533	0.44
	14	Mean	1.65	79.752	361.975	370.152	23.9 (16.4)	0.886	3.782	1.27
		SD	0.58	44.810	202.280	180.201	19.2	0.498	2.159	0.34
120 mg	1	Mean	1.94	50.777	269.949	285.244	15.8 (9.4)	0.423	2.377	0.78
		SD	0.68	12.431	157.464	159.091	15.2	0.104	1.326	0.21
	14	Mean	1.83	60.638	313.439	285.759	23.3 (15.8)	0.505	2.381	0.79
		SD	1.17	19.855	167.735	140.587	18.1	0.165	1.172	0.20

a AUC refers to AUC∞, and AUC24 for Day 1, and Day 14, respectively.

b Arithmetic Mean (Harmonic Mean)
c 67M-4 to 67M-4 AUC Ratio
For all regimens, the number of subjects ranged from 7 to 10.

Dose Proportionality Analysis

Both AUC_τ and C_{max} of TMX-67 in plasma were dose-proportional to dose (10-120 mg) at steady state (Figure 3) as evidenced by the linear relationship between AUC_τ and dose, and C_{max} and dose. AUC_τ increased in a somewhat more than proportional manner at doses above 120 mg while C_{max} appeared to be dose proportional all the way to 240 mg (Figures not shown).



a. AUCτ **b. Cmax**

Figure 3. Relationship between TMX-67 AUCτ (a) and dose, and Cmax (b) and dose.

Mean AUC_τ and C_{max} of metabolites, 67M-1, 67M-2, and 67M-4 increased with doses at steady state. AUCτ of these metabolites appeared to increase more than dose proportionally at doses above 70 mg. AUC ratio to the parent drug (TMX-67) at steady state was rather constant over the dose of 10-240 mg.

Urinary Excretion of TMX-67and its Metabolites

At steady state (Day 14), approximately 0.9-6.1% and 24.6-47.4% of the orally administered daily dose was excreted in the urine as free drug (intact) and as total drug (intact plus conjugates), respectively, for each of the dosing regimens studied (Table 7). Therefore, renal clearance does not play an important role in the clearance of intact TMX-67. However, renal clearance of *conjugated* TMX-67 appears to be an important pathway in the elimination of TMX-67. With increasing doses, even though there were no consistent changes in the f_e and Cl_r of free TMX-67, the f_e of total TMX-67 appeared to decrease.

For metabolites of TMX-67, there were about 3.5-8% and 1.9%-6.7% of the orally administered daily dose was excreted in the urine as intact metabolites and total metabolites, respectively, indicating conjugation was not important for the elimination of these oxidative metabolites of TMX-67 (data not shown).

(Reviewer's Note: The results of TMX-67 and its metabolites in plasma and urine were consistent with what were observed in the ^{14}C-ADME study, C03-040.)

Table 7. Mean of Total Daily Urinary Excretion (Ae_t or Ae_{24}), Fraction of Dose Excreted (fe) in Urine and Renal Clearance (Clr) of Free and Total TMX-67 on Days 1 and 14 Following Oral Administration of TMX-67.

		Day 1					Day 14				
		Free			Total		Free			Total	
Dose		Ae_t (µg)	f_e	Cl_r (L/h)	Ae_t (µg)	f_e	Ae_{24} (µg)	f_e	Cl_r (L/h)	Ae_{24} (µg)	f_e
10 mg QD	Mean	234	0.023	0.35	3522	0.352	148	0.015	0.19	3443	0.344
	SD	174	0.017	0.32	1025	0.102	137	0.014	0.19	1149	0.115
20 mg QD[a]	Mean	225	0.011	0.10	7849	0.392	186	0.009	0.08	7376	0.369
	SD	187	0.009	0.06	1796	0.090	124	0.006	0.04	2070	0.104
30 mg QD[a]	Mean	305	0.010	0.11	6821	0.227	285	0.009	0.11	10842	0.361
	SD	365	0.012	0.12	4427	0.148	171	0.006	0.05	2196	0.073
40 mg QD	Mean	282	0.007	0.09	10749	0.269	435	0.011	0.15	13133	0.328
	SD	138	0.003	0.06	2980	0.074	360	0.009	0.18	5709	0.143
50 mg QD[a]	Mean	780	0.016	0.20	19475	0.390	594	0.012	0.15	17337	0.347
	SD	360	0.007	0.13	4075	0.081	360	0.007	0.11	4993	0.100
70 mg QD	Mean	617	0.009	0.10	22833	0.326	780	0.011	0.12	23705	0.339
	SD	220	0.003	0.05	6474	0.092	358	0.005	0.06	3691	0.053
90 mg QD	Mean	1958	0.022	0.24	29928	0.333	2060	0.023	0.22	34570	0.384
	SD	970	0.011	0.14	6033	0.067	1227	0.014	0.10	6613	0.073
120 mg QD[a]	Mean	1375	0.011	0.13	32101	0.268	7355	0.061	0.64	31768	0.265
	SD	492	0.004	0.06	5782	0.048	1928	0.016	0.20	10917	0.091
160 mg QD	Mean	8887	0.056	0.48	51394	0.321	8323	0.052	0.38	63775	0.399
	SD	4226	0.026	0.31	11061	0.069	7193	0.045	0.27	14412	0.090
180 mg QD[a]	Mean	3142	0.017	0.14	62998	0.350	5387	0.030	0.24	44298	0.246
	SD	1025	0.006	0.08	5436	0.030	4239	0.024	0.23	19067	0.106
240 mg QD[a]	Mean	1427	0.006	0.05	54343	0.226	1856	0.008	0.06	66749	0.278
	SD	811	0.003	0.03	27821	0.116	624	0.003	0.03	15417	0.064
30 mg BID (AM)	Mean	1639[a]	0.027[a]	0.28[a]	19042[a]	0.317[a]	947	0.032	0.34	14207	0.474
	SD	587	0.010	0.10	3832	0.064	236	0.008	0.09	3440	0.115
30 mg BID (PM)	Mean	-	-	-	-	-	1272	0.042	0.43	11394	0.380
	SD	-	-	-	-	-	707	0.024	0.32	3356	0.112

a For Day 1 (AM & PM doses combined)
For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18).

Pharmacodynamic Results:

Serum Uric Acid, Xanthine, and Hypoxanthine Concentrations and Pharmacodynamic Parameters

Hypoxanthine $\xrightarrow{XO}$ Xanthine $\xrightarrow{XO}$ Uric Acid

Serum Urate:

Following oral administration of TMX-67, the concentrations of uric acid in serum decreased with trough concentrations occurring between 6 and 12 h post-dose. The 24-hour mean uric acid serum concentrations and the percent decrease in the 24-hour mean estimates from the baseline (Day -1) on Days 1, 8, 14, and 15 for each of the dosing regimens are presented in Table 8.

Table 8. Summary of 24-hour Mean Serum Uric Acid Concentrations and Percent Change from Baseline in the 24-hour Mean Serum Uric Acid Concentrations on Days –1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Groups.

Dose mg		$C_{mean,24}$ (mg/dL)					% Change			
		Day-1	Day 1	Day 8	Day 14	Day 15	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	5.078	5.093	5.107	4.986	5.139	0.11	1.06	-0.98	1.59
	SD	1.201	1.259	1.228	1.133	1.231	6.51	8.57	7.97	6.99
10 QD	Mean	4.980	4.534	3.657	3.637	4.243	-9.12	-26.64	-27.35	-14.73
	SD	0.816	0.835	0.704	0.776	0.743	4.07	5.57	6.18	6.65
20 QD	Mean	4.831	4.137	3.322	3.205	3.930	-14.37	-31.41	-33.59	-17.74
	SD	1.135	0.987	0.949	0.867	0.841	4.30	9.38	8.38	9.11
30 QD	Mean	4.241	3.417	2.618	2.621	3.133	-19.53	-37.92	-37.74	-24.73
	SD	1.343	1.106	0.841	0.873	0.919	4.09	5.15	7.50	9.35
40 QD	Mean	5.290	4.339	3.311	3.224	3.868	-19.31	-38.85	-40.16	-26.75
	SD	1.772	1.592	1.397	1.313	1.370	7.78	14.44	13.56	12.76
50 QD	Mean	4.805	3.979	2.625	2.594	3.271	-18.07	-46.09	-46.85	-31.93
	SD	1.339	1.280	0.904	0.944	0.992	5.51	6.79	7.05	6.73
70 QD	Mean	4.426	3.617	2.383	2.228	2.962	-18.51	-47.30	-50.66	-33.59
	SD	0.977	0.891	0.966	0.864	1.046	9.35	15.28	11.26	14.37
90 QD	Mean	4.513	3.519	1.839	1.776	2.586	-22.92	-59.96	-60.86	-41.87
	SD	1.060	1.023	0.714	0.620	0.628	7.70	9.45	8.50	10.15
120 QD	Mean	4.663	3.773	1.665	1.556	2.288	-16.22	-63.28	-65.62	-48.85
	SD	1.042	0.631	0.486	0.356	0.404	18.76	10.33	8.07	13.47

Dose mg		$C_{mean,24}$ (mg/dL)					% Change			
		Day-1	Day 1	Day 8	Day 14	Day 15	Day 1	Day 8	Day 14	Day 15
160 QD	Mean	4.834	3.651	1.561	1.444	2.099	-25.39	-68.12	-70.39	-56.46
	SD	1.136	1.087	0.757	0.713	0.728	7.70	14.12	13.23	12.28
180 QD	Mean	5.257	3.872	1.442	1.487	2.014	-26.81	-72.80	-71.98	-61.82
	SD	1.061	0.959	0.458	0.512	0.531	3.63	5.63	6.81	5.78
240 QD	Mean	5.113	4.204	1.377	1.233	1.930	-18.56	-73.46	-76.12	-61.91
	SD	1.120	1.230	0.521	0.469	0.674	9.31	7.33	6.74	11.83
30 BID	Mean	5.659	4.632	2.274	2.076	2.869	-18.04	-59.54	-63.24	-49.09
	SD	0.789	0.634	0.464	0.503	0.542	3.44	8.22	8.17	8.40

For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18) and placebo (22-23).

For healthy subjects in this study, the baseline (Day-1) 24-hour mean serum concentrations for uric acid ranged from 4.241 to 5.659 mg/dL. Mean 24-hour serum urate concentrations decreased from baseline as doses increased on Day 1, 8, 14 and 15 (Day 14 data are shown in Figure 4). In addition, % changes increased from Day 1 to Day 8 (following multiple doses) but the maximum effect appeared to be achieved by Day 8. It appeared there were slight increases in the 24-hr serum urate concentrations on Day 15 (1 day after drug administration was stopped).

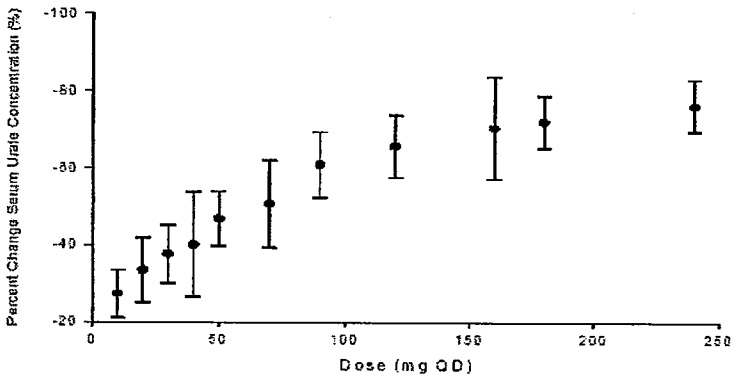


Figure 4. Mean (±SD) Percent Change in Serum Urate Concentration vs. Dose Following Multiple Oral Dosing with TMX-67 (10 mg QD, 20 mg QD, 30 mg QD, 40 mg QD, 50 mg QD, 70 mg QD, 90 mg QD, 120 mg QD, 160 mg QD, 180 mg QD, and 240 mg QD Regimens) on Day 14.

The relationship between the serum urate $C_{mean,24}$ on Day 14 and AUC_{24} on Day 14 could be described with a baseline E_{max} model, assuming Day 14 AUC_{24} equalled "0" for all placebo-treated subjects. The baseline E_{max} model fit the data well with an R^2 of 0.88 (Figure 5). Based on the results of the modeling, taking placebo would result in a percent decrease in serum urate $C_{mean,24}$ on Day 14 (E_0) of 2.64±1.78% (mean±SE). The maximum percent decrease in serum urate on Day 14 caused by taking multiple doses of TMX-67 (E_{max}-E_0) was predicted to be approximately 78.76% (E_{max} was estimated as 81.40±2.42%). The $EAUC_{50}$ value estimation was 3.3059±0.3886 µg.h/mL, achieved at the approximate 30-40 mg QD TMX-67 dosage range.

On Day 14, the observed percent change from the baseline for the 24-hour mean uric acid concentrations was 0.98% for the placebo, -40% for the 40 mg QD, -51% for the 70 mg QD, -66% for the 120 mg QD, -76% for the 240 mg QD, and -63% for the 30 mg BID regimens, respectively.

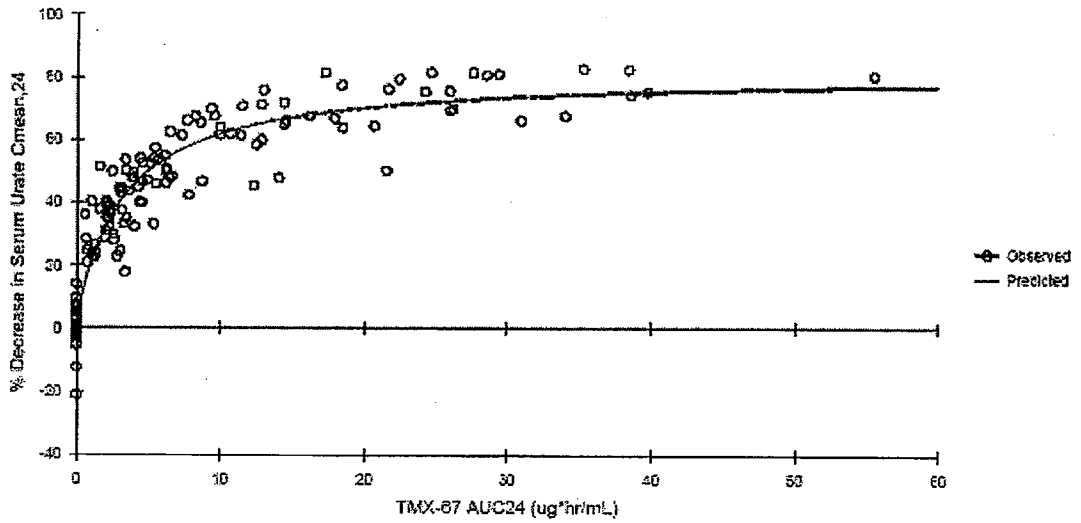


Figure 5. The Correlation Between the Percent Decrease in Serum Urate $C_{mean,24}$ from Baseline and TMX-67Area Under the Curve (AUC_{24}) Following Multiple Dosing with TMX-67.

As the inhibition of XO may increase xanthine and hypoxanthine's levels in the serum, levels of xanthine and hypoxanthine were also monitored.

Serum Xanthine:
Following administration of TMX-67, serum xanthine concentrations increased, with peak concentrations occurring at approximately 6 to 12 h post-dose. The 24-hour mean xanthine concentrations in serum on Days –1, 1, 8, 14 and 15 for each of the dosing regimens are presented in Table 9.

Table 9. Summary of 24-hour Mean Serum Xanthine Concentrations on Days –1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Groups.

Dose		$C_{mean,24}$(mg/dL)				
		Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	0.0301	0.0306	0.0288	0.0273	0.0322
	SD	0.0083	0.0093	0.0080	0.0065	0.0083
10 mg QD	Mean	0.0347	0.0637	0.0711	0.0577	0.0508
	SD	0.0080	0.0128	0.0094	0.0104	0.0093
20 mg QD	Mean	0.0259	0.0701	0.0836	0.0690	0.0467
	SD	0.0069	0.0163	0.0140	0.0145	0.0083
30 mg QD	Mean	0.0220	0.0605	0.0742	0.0718	0.0522
	SD	0.0066	0.0137	0.0175	0.0143	0.0150
40 mg QD	Mean	0.0264	0.0860	0.1086	0.1072	0.0693
	SD	0.0080	0.0189	0.0301	0.0384	0.0255
50 mg QD	Mean	0.0311	0.0961	0.1185	0.1208	0.0771
	SD	0.0087	0.0254	0.0284	0.0281	0.0155
70 mg QD	Mean	0.0236	0.1010	0.1253	0.1386	0.0956
	SD	0.0083	0.0298	0.0295	0.0299	0.0235
90 mg QD	Mean	0.0274	0.1114	0.1656	0.1696	0.1186
	SD	0.0057	0.0157	0.0280	0.0269	0.0223
120 mg QD	Mean	0.0267	0.1341	0.1912	0.1911	0.1402
	SD	0.0081	0.0180	0.0220	0.0273	0.0224
160 mg QD	Mean	0.0271	0.1342	0.2019	0.2114	0.1538
	SD	0.0067	0.0291	0.0566	0.0451	0.0461
180 mg QD	Mean	0.0236	0.1356	0.2009	0.1931	0.1526
	SD	0.0080	0.0245	0.0431	0.0386	0.0152
240 mg QD	Mean	0.0224	0.1559	0.2357	0.2250	0.1672
	SD	0.0077	0.0227	0.0409	0.0384	0.0560
30 mg BID	Mean	0.0221	0.1138	0.1921	0.1830	0.1424
	SD	0.0060	0.0118	0.0298	0.0265	0.0168

For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18) and placebo (22-23).

The baseline (Day -1) 24-hour mean serum concentrations for xanthine ranged from 0.0220-0.0347 mg/dL. Mean 24-hour serum xanthine concentrations increased from baseline as doses increased on Day 1, 8, 14 and 15. In addition, larger changes were observed on Days 8 and 14 compared to Day 1 but the maximum effect appeared to be achieved by Day 8 because no difference between Day 8 and Day 14. It appeared there were slightly decrease in 24-hr serum xanthine concentrations on Day 15 (1 day after drug administration was stopped). Following multiple dosing with TMX-67, on Day 14, the mean estimates for the 24-hour mean serum xanthine concentrations increased to approximately 1.5-10 times those of the baseline (Day -1) concentrations and these changes were statistically significant ($p \leq 0.05$). The mean estimates for the 24-hour mean serum xanthine concentrations increased to approximately 5 times those of the baseline at doses 70-120 mg (the proposed clinical dose).

There appeared to be a linear dose-response relationship between the 24-hour mean serum xanthine concentration and the dose for dosage range between 10 to 90 mg. Similar to the percent decrease in serum urate response, the 24-hour mean concentrations appeared to reach a plateau for doses above 90 mg. In addition, the plot of xanthine Cmean,24 versus AUC24 on Day 14 resembled a baseline Emax model, assuming AUC24 of 0 for all placebo-treated subjects. The baseline Emax model fit the data well with an R^2 of 0.81 (Figure 6). Based on the results of the modeling, the serum xanthine Cmean,24 on Day 14 in placebo (E0) was 0.0251±0.0061 mg/dL. The maximum increase in serum xanthine Cmean,24 caused by taking multiple doses of TMX-67 (Emax-E0) was predicted to be 0.2297 mg/dL (Emax was estimated as 0.2548±0.0122 mg/dL). The EAUC50 value estimation was 6.2009±01.0450 µg.h/mL, achievable at the approximate 60-70 mg QD dosage range.

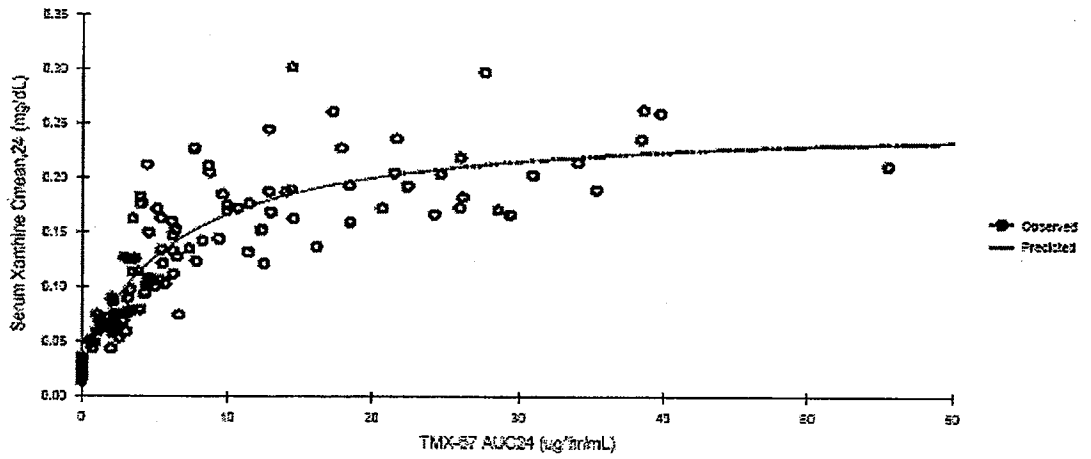


Figure 6. The Correlation Between the Serum Xanthine $C_{mean,24}$ and TMX-67 Area Under the Curve (AUC_{24}) Following Multiple Dosing with TMX-67.

Serum Hypoxanthine:
Following administration of TMX-67, the concentrations of hypoxanthine in serum did not change substantially (Table 10). The 24-hour mean serum hypoxanthine concentrations ranged from 0.1125 to 0.1400 mg/dL at baseline (Day -1). Following multiple dosing with TMX-67,

the 24-hour mean estimates on Day 14 were within 22% of those on Day -1. No clear trend of change with dose or by days was observed for hypoxanthine serum concentrations.

Table 10. 24-hour Mean Serum Hypoxanthine Concentrations on Days –1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Groups.

Dose		$C_{mean,24}$(mg/dL)				
		Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	0.1370	0.1368	0.1337	0.1277	0.1294
	SD	0.0366	0.0403	0.0353	0.0323	0.0309
10 mg QD	Mean	0.1390	0.1318	0.1537	0.1190	0.1396
	SD	0.0360	0.0343	0.0265	0.0263	0.0393
20 mg QD	Mean	0.1236	0.1093	0.1199	0.1066	0.1322
	SD	0.0350	0.0385	0.0305	0.0240	0.0231
30 mg QD	Mean	0.1125	0.0899	0.0818	0.1016	0.1089
	SD	0.0362	0.0309	0.0199	0.0318	0.0378
40 mg QD	Mean	0.1170	0.1253	0.1354	0.1263	0.1515
	SD	0.0263	0.0255	0.0294	0.0381	0.0392
50 mg QD	Mean	0.1400	0.1554	0.1519	0.1546	0.1373
	SD	0.0388	0.0484	0.0416	0.0480	0.0310
70 mg QD	Mean	0.1296	0.1266	0.1416	0.1465	0.1614
	SD	0.0484	0.0342	0.0495	0.0458	0.0483
90 mg QD	Mean	0.1361	0.1306	0.1639	0.1541	0.1476
	SD	0.0247	0.0208	0.0272	0.0322	0.0160
120 mg QD	Mean	0.1356	0.1675	0.1412	0.1518	0.1577
	SD	0.0356	0.0394	0.0263	0.0287	0.0269
160 mg QD	Mean	0.1348	0.1549	0.1656	0.1651	0.1699
	SD	0.0298	0.0320	0.0319	0.0425	0.0372
180 mg QD	Mean	0.1171	0.1370	0.1248	0.1137	0.1232
	SD	0.0210	0.0210	0.0224	0.0275	0.0227
240 mg QD	Mean	0.1236	0.1349	0.1469	0.1427	0.1549
	SD	0.0389	0.0309	0.0338	0.0427	0.0456
30 mg BID	Mean	0.1162	0.1378	0.1404	0.1307	0.1257
	SD	0.0245	0.0263	0.0486	0.0347	0.0233

For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18) and placebo (22-23).

Urine Uric Acid, Xanthine, and Hypoxanthine Concentrations and Pharmacodynamic Parameters

Urine Uric Acid:

Following multiple dosing with TMX-67, the mean urinary concentrations of uric acid in urine generally appeared to decline from baseline. The 24-hour mean concentrations of uric acid in urine on Day -1 ranged from 18.043 to 41.018 mg/dL. On Day 14, the mean 24-hour mean concentrations decreased from the baseline by approximately 37% to 80%, with greater percent changes with increasing doses (data not shown).

The 24-hour urinary excretion and renal clearance values for uric acid on Days –1, 1, 8, 14, and 15 are listed in Table 11.

Table 11. Summary of 24-hour Mean Renal Clearance (Clr) and Total Daily Urinary Excretion (Ae24) of Uric Acid in Urine on Days –1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Regimens to Subjects.

Dose mg		Cl_r(mL/min)					Ae_{24}(mg)				
		Day-1	Day 1	Day 8	Day 14	Day 15	Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	6.38	5.96	5.47	6.52	6.18	458.77	424.09	385.17	447.52	431.92
	SD	2.12	1.65	1.76	2.29	2.14	102.08	124.83	113.80	139.91	85.29
10 QD	Mean	6.41	6.34	4.03	5.31	5.75	453.88	399.60	206.99	271.40	344.05
	SD	2.02	2.78	1.47	2.22	2.93	144.32	146.77	66.48	112.94	148.84
20 QD	Mean	6.66	6.73	5.47	5.88	4.70	458.46	377.25	251.49	255.22	253.13
	SD	1.95	2.14	1.32	2.10	2.38	116.20	67.79	55.07	66.98	102.72
30 QD	Mean	8.11	6.46	5.66	5.55	5.97	471.48	305.80	201.00	202.51	261.71
	SD	1.94	1.59	2.43	2.65	2.42	107.73	93.12	86.60	103.21	128.87
40 QD	Mean	5.52	4.62	4.33	3.92	3.56	406.99	300.23	217.21	218.36	207.57
	SD	2.05	1.73	2.13	2.34	1.29	179.39	159.50	157.32	164.21	107.70
50 QD	Mean	6.38	6.01	5.93	5.74	5.61	434.51	338.28	218.41	214.95	262.02
	SD	1.45	2.17	1.60	1.47	1.62	144.39	159.09	80.19	94.23	108.46
70 QD	Mean	6.32	5.89	5.51	5.21	5.53	396.86	298.76	183.96	160.55	218.93
	SD	2.21	1.25	1.09	1.03	2.16	152.17	65.96	72.58	51.48	86.53
90 QD	Mean	7.13	7.19	5.42	5.69	6.63	445.72	345.27	137.72	136.41	239.25
	SD	2.21	2.79	1.35	1.98	1.72	107.01	115.29	48.09	52.07	53.93
120 QD	Mean	8.73	6.68	5.54	6.45	4.99	534.05	356.46	131.01	145.96	161.23
	SD	4.66	1.25	0.87	1.71	1.50	96.42	64.26	36.39	53.43	46.70
160 QD	Mean	7.66	7.89	4.94	9.00	6.52	520.11	404.17	106.80	183.78	191.54
	SD	2.54	2.57	1.98	3.19	2.58	156.30	138.44	68.07	117.57	86.72
180 QD	Mean	8.59	7.69	6.15	5.89	5.92	660.33	417.94	125.44	125.53	170.15
	SD	1.31	1.27	1.25	2.87	1.16	221.85	63.42	37.93	71.76	50.40
240 QD	Mean	6.67	5.25	4.45	4.89	4.16	466.18	308.28	90.77	88.33	114.50
	SD	3.01	2.15	1.28	1.08	0.88	152.29	110.63	48.99	43.03	47.41
30 BID	Mean	5.95	5.39	4.47	6.47	4.45	483.16	359.64	146.28	194.45	182.66
	SD	1.16	0.92	1.15	1.38	0.83	98.80	80.03	44.76	66.33	41.52

For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18) and placebo (22-23).

The baseline (Day -1) mean total daily urinary excretion of uric acid ranged from 396.86 to 660.33 mg. A statistically significant day by dose interaction was detected among the QD dosing

regimens on Days 1, 8, and 14 ($p \leq 0.05$), with smaller changes noted on Day 1 as compared to Days 8 and 14. Subsequent analyses on each day revealed a statistically significant dose effect ($p \leq 0.05$) and an apparent linear trend on Days 8 and 14, with greater changes with increasing doses. Following multiple dosing with TMX-67, on Day 14, the mean estimates for the total daily urinary excretion of uric acid decreased by as much as 81% and the decrease in the mean 24-hour urinary excretion of uric acid appeared to be greater with increasing doses ($p \leq 0.05$). Therefore, in conjunction with the decrease in uric acid urine concentrations, there was also a decrease in total daily uric acid excretion following multiple dosing with TMX-67. The extent of decrease appeared to increase with increasing doses (Figure 7).

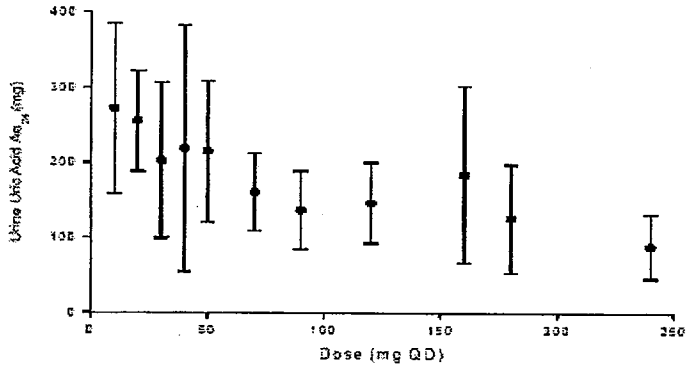


Figure 7. Mean (±SD) Urine Uric Acid Ae_{24} vs. Dose Following Multiple Oral Dosing with TMX-67 (10 mg QD, 20 mg QD, 30 mg QD, 40 mg QD, 50 mg QD, 70 mg QD, 90 mg QD, 120 mg QD, 160 mg QD, 180 mg QD, and 240 mg QD Regimens) on Day 14.

The mean baseline Clr values for uric acid ranged from 5.52 to 8.73 mL/min on Day -1 and 3.92 to 9.00 mL/min on Day 14. The renal clearance of uric acid did not change statistically significantly with increasing doses ($p > 0.05$). The data indicated that renal clearance of uric acid was not affected by TMX-67.

As expected, there was a good correlation between mean 24 hour serum urate concentration and mean daily urinary excretion (Ae24) of uric acid on Day 14 at each dose (Figure 8).

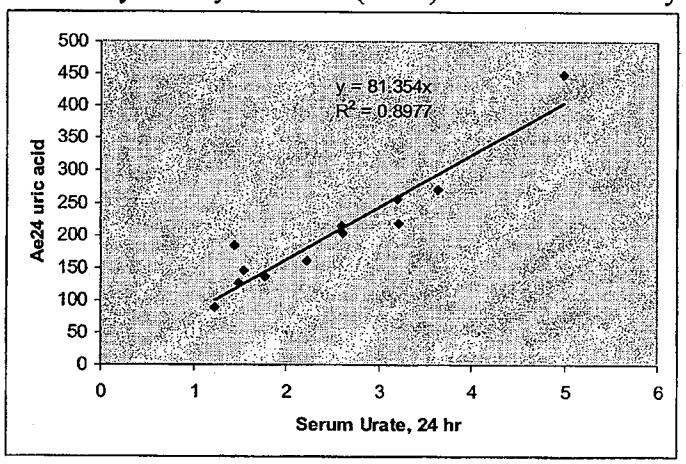


Figure 8. Correlation between mean 24 hour serum urate concentration and mean daily urinary excretion (Ae24) of Uric Acid on Day 14.

Urinary Xanthine:
Following administration of TMX-67, the urinary concentrations of xanthine increased substantially with the peak concentrations generally occurring in the 0 to 6 hour collection interval. The 24-hour mean concentrations of xanthine in urine on Days –1, 1, 8, 14, and 15 for each dosing regimen studied are shown in Table 12.

Table 12. Summary of 24-hour Mean Concentration (Cmean,24) of Xanthine in Urine on Days -1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Regimens.

Dose mg		$C_{mean,24}$(mg/dL)				
		Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	0.3243	0.3440	0.3999	0.3111	0.4876
	SD	0.2125	0.2588	0.2760	0.2040	0.3054
10 QD	Mean	0.6317	4.8359	4.3406	3.5021	1.0388
	SD	0.5441	3.9441	2.8733	2.3757	0.6310
20 QD	Mean	0.3753	5.2926	5.6658	4.6012	1.6818
	SD	0.2870	3.8092	4.5904	3.0313	1.0408
30 QD	Mean	0.3229	2.9201	4.5532	3.6949	2.1576
	SD	0.1805	1.4747	2.6719	2.2149	2.5093
40 QD	Mean	0.3778	3.5931	4.7966	4.8522	1.6843
	SD	0.3238	2.2007	2.8439	3.0289	0.8772
50 QD	Mean	0.2828	5.0145	5.4505	5.6008	2.8392
	SD	0.1355	2.2013	1.9519	2.2099	1.8975
70 QD	Mean	0.2903	4.1815	6.6706	7.6937	3.4102
	SD	0.2107	2.9579	3.2070	3.3047	2.5839
90 QD	Mean	0.3066	7.1526	8.7113	9.3792	5.3979
	SD	0.4086	5.4844	4.2365	7.7268	5.6504
120 QD	Mean	0.4463	6.9515	12.3860	11.5308	6.4463
	SD	0.4483	3.0863	4.6296	3.1272	2.1705
160 QD	Mean	0.2851	9.2643	13.0138	12.1348	9.4306
	SD	0.2888	4.1170	8.5877	9.0833	7.1162
180 QD	Mean	0.4588	9.9972	17.5554	18.6284	9.6318
	SD	0.3354	4.3099	9.8258	8.5571	5.9107
240 QD	Mean	0.4518	10.3317	18.4320	17.9918	10.1341
	SD	0.3238	10.6142	8.4865	7.9817	9.4855
30 BID	Mean	0.4820	4.8506	10.6108	10.7686	7.6973
	SD	0.4392	1.8210	3.0029	3.8810	5.7411

For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18) and placebo (22-23).

Mean baseline (Day -1) 24-hour mean urinary concentrations of xanthine for each of the regimens ranged from 0.2828 to 0.6317 mg/dL and the individual values were generally below 1 mg/dL. A statistically significant day by dose interaction was detected among the QD dosing

regimens on Days 1, 8, and 14 ($p \leq 0.05$), with smaller changes noted on Day 1 as compared to Days 8 and 14. Subsequent analyses on each day revealed a statistically significant dose effect ($p \leq 0.05$) and an apparent linear trend ($p \leq 0.05$) on each day, with greater changes with increasing doses. On Day 14, the 24-hour mean xanthine concentrations in urine ranged from 3.5021 to 18.6284 mg/dL. Therefore, there was a substantial increase in the urinary xanthine concentrations following administration of TMX-67 and the extent of increase in the 24-hour concentrations of xanthine appeared to be greater with increasing doses ($p \leq 0.05$) on Days 1, 8, and 14.

The 24-hour urinary excretion and renal clearance values for xanthine on Days –1, 1, 8, 14, and 15 are listed in Table 13. The mean total daily urinary excretion of xanthine on Day -1 ranged from 4.47 to 8.25 mg. A statistically significant day by dose interaction was detected among the QD dosing regimens on Days 1, 8, and 14 ($p \leq 0.05$), with smaller changes noted on Day 1 as compared to Days 8 and 14. Subsequent analyses on each day revealed a statistically significant dose effect and an apparent linear trend ($p \leq 0.05$) on each day, with greater changes with increasing doses. Following multiple dosing with TMX-67, on Day 14, the mean estimates for total daily excretion of xanthine reached 7 to 76 times those of the baseline (Day -1) daily excretions. Therefore, in conjunction with the increase in xanthine serum concentrations, there was also an increase in total daily xanthine excretion following multiple dosing with TMX-67 and the extent of increase in the 24-hour xanthine excretion values appeared to be greater with increasing doses ($p \leq 0.05$). There appeared to be a linear dose-response relationship between the daily urinary excretion of xanthine on Day 14 and the dose for doses between 10 to 90 mg (Figure 9). For doses above 90 mg, the amount of daily urinary excretion of xanthine appeared to reach a plateau (Figure 9). The magnitude of the increase in the excretion of xanthine appeared to be greater than proportional to the increase in the serum xanthine concentrations (7-76 times baseline vs.1.5-10 times baseline) due to substantial increases in renal clearance of xanthine following administration of TMX-67. A statistically significant day by dose interaction was detected among the QD dosing regimens on Days 1, 8, and 14 ($p \leq 0.05$), with no apparent pattern in the results. Subsequent analyses on each day revealed a statistically significant dose effect on Days 8 and 14 ($p \leq 0.05$), but not a significant trend with dose. On Day 14, the renal clearance of xanthine appeared to increase to 3 to 9 fold its baseline. In general, the renal clearance of xanthine did not appear to change with increasing dose.

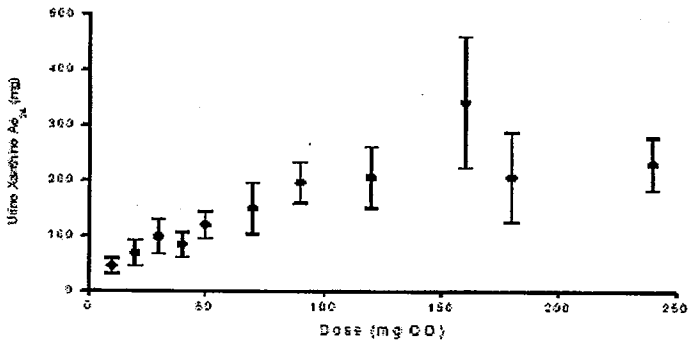


Figure 9. Mean (±SD) Urine Xanthine Ae24 vs. Dose and Ae24 vs. Percent Change in Serum Urate Concentration Following Multiple Oral Dosing with TMX-67 (10 mg QD, 20 mg QD, 30 mg QD, 40 mg QD, 50 mg QD, 70 mg QD, 90 mg QD, 120 mg QD, 160 mg QD, 180 mg QD, and 240 mg QD Regimens) on Day 14.

Table 13. Summary of 24-hour Mean Renal Clearance (Clr) and Total Daily Urinary Excretion (Ae24) of Xanthine in Urine on Days –1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Regimens to Subjects.

		Cl_r (mL/min)					Ae_{24} (mg)				
Dose mg		Day-1	Day 1	Day 8	Day 14	Day 15	Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	14.25	15.01	14.45	15.44	13.73	5.86	5.96	5.36	5.71	5.95
	SD	5.48	9.98	8.32	7.22	6.78	2.21	3.59	2.62	2.33	2.40
10 QD	Mean	14.71	60.21	45.70	56.85	11.17	6.96	53.59	47.03	45.69	7.93
	SD	8.93	20.91	16.80	21.64	5.12	3.63	16.97	20.50	14.03	2.98
20 QD	Mean	16.81	83.51	64.76	69.76	23.22	5.95	85.77	79.38	68.99	15.16
	SD	7.89	23.54	19.73	20.94	11.52	1.86	32.99	29.31	23.84	8.97
30 QD	Mean	23.56	91.90	94.75	96.25	56.03	7.07	81.49	100.48	98.56	42.67
	SD	9.40	19.57	28.69	30.37	59.87	2.70	29.50	33.62	31.29	42.59
40 QD	Mean	18.03	59.65	54.14	57.38	24.77	6.29	72.80	79.91	84.26	24.85
	SD	11.57	18.26	18.19	16.42	14.90	3.79	26.04	16.72	22.46	15.46
50 QD	Mean	15.56	74.73	76.77	73.18	37.93	6.55	101.91	126.11	120.05	41.61
	SD	5.81	22.22	20.18	18.96	12.33	2.59	29.49	24.70	23.70	13.70
70 QD	Mean	19.60	72.60	73.79	75.38	29.11	6.29	102.59	134.63	149.47	42.46
	SD	13.56	23.38	21.32	20.54	18.19	4.74	35.91	56.83	46.30	31.87
90 QD	Mean	15.38	79.73	72.92	82.89	37.46	5.53	123.71	168.65	196.03	63.35
	SD	12.72	36.46	23.98	23.11	11.31	3.92	46.67	41.40	36.90	20.01
120 QD	Mean	25.75	67.53	70.17	74.83	36.93	8.25	127.79	192.15	205.94	75.66
	SD	36.25	16.76	17.54	19.31	14.62	8.25	27.82	48.07	55.58	32.56
160 QD	Mean	12.61	77.76	66.55	113.31	49.04	4.47	147.07	189.11	341.46	108.86
	SD	13.57	27.48	22.07	36.04	25.66	4.01	51.40	66.28	118.61	57.55
180 QD	Mean	24.43	83.10	82.16	76.58	48.87	7.23	158.46	234.65	206.24	106.59
	SD	15.92	18.82	11.24	32.83	11.05	2.97	27.36	41.61	81.44	23.85
240 QD	Mean	18.09	70.91	63.22	72.64	32.90	5.94	154.52	207.90	230.05	86.55
	SD	5.87	20.45	16.02	18.38	21.19	3.39	29.78	33.43	48.02	72.65
30 BID	Mean	19.91	58.21	59.51	77.74	32.51	6.29	93.13	157.64	203.83	65.92
	SD	9.80	18.93	21.07	10.75	11.69	3.61	21.89	33.75	33.25	21.90

For all regimens, the number of subjects ranged from 7 to 10, with the exception of the 50 mg group (17-18) and placebo (22-23).

Urinary Hypoxanthine:

The 24-hour mean urine concentration, total daily urinary excretion, and renal clearance of hypoxanthine on Days –1, 1, 8, 14, and 15 for each dosing regimen studied are shown in Table 14. Similar to xanthine, the 24-hour mean urinary concentrations of hypoxanthine also increased substantially following administration of TMX-67, with the peak concentrations generally occurring in the 0 to 6 hour collection interval. The mean baseline (Day -1) 24-hour mean concentrations of hypoxanthine in urine for each of the regimens ranged from 0.2157 to 0.8613 mg/dL. A statistically significant day by dose interaction was detected among the QD dosing regimens on Days 1, 8, and 14 ($p \leq 0.05$), with smaller changes noted on Day 1 as compared to Days 8 and 14. Subsequent analyses on each day revealed a statistically significant dose effect and an apparent linear trend ($p \leq 0.05$) on Days 8 and 14, with greater changes with increasing doses. A statistically significant trend with dose ($p \leq 0.05$) was also noted on Day 1. On Day 14, the mean hypoxanthine Cmean, 24 values in urine ranged from 0.9342 to 3.6768 mg/dL. Therefore, there was also substantial increase in concentration of hypoxanthine in urine following administration of TMX-67 although the magnitude of the increase was less than that observed for xanthine. There appeared to be a greater increase in hypoxanthine 24-hour mean concentration with increasing dose ($p \leq 0.05$) on Days 1, 8, and 14.

Table 14. Summary of 24-hour Mean Concentration (Cmean,24) of Hypoxanthine in Urine on Days –1, 1, 8, 14,and 15 Following Oral Administration of TMX-67 or Placebo in all Dosing Regimens to Subjects.

Dose mg		$C_{mean,24}$(mg/dL)				
		Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	0.4111	0.4535	0.5468	0.4037	0.6242
	SD	0.2466	0.2564	0.2929	0.1704	0.2916
10 QD	Mean	0.8613	1.9355	1.7887	1.7011	0.9447
	SD	0.8767	1.7596	1.3588	1.3895	0.4438
20 QD	Mean	0.3995	1.4348	1.9454	1.5201	1.2588
	SD	0.1934	0.9374	1.4189	0.8134	0.6231
30 QD	Mean	0.2157	0.6812	1.1084	0.9342	0.9138
	SD	0.2367	0.4649	0.6720	0.5731	0.9092
40 QD	Mean	0.3711	0.9845	1.4307	1.6857	1.1801
	SD	0.4108	1.0454	1.1008	1.5333	0.6185
50 QD	Mean	0.4962	1.3201	1.6681	1.5639	1.5134
	SD	0.6872	0.8338	0.9608	0.8778	1.1001
70 QD	Mean	0.3596	1.0076	1.8982	2.7314	1.7061
	SD	0.1871	0.6908	1.1759	2.4797	1.4499
90 QD	Mean	0.2917	1.3943	2.2003	2.2493	2.4518
	SD	0.2114	0.8052	0.8786	1.4158	1.8021
120 QD	Mean	0.3681	1.2557	2.5484	2.5370	2.2305
	SD	0.1816	0.5319	1.0793	0.8935	0.6473
160 QD	Mean	0.3333	1.6736	2.6458	1.9479	2.7748
	SD	0.2033	0.7845	1.6606	1.2085	2.0121
180 QD	Mean	0.4080	1.7296	2.7692	3.6768	2.5790
	SD	0.1988	0.5867	1.1901	1.5622	0.9263
240 QD	Mean	0.4527	2.2161	3.7307	3.3176	2.7253
	SD	0.2879	2.2531	1.9687	1.5323	1.9807
30 BID	Mean	0.5221	1.4831	2.9788	3.1964	3.2577
	SD	0.2562	0.4057	0.8490	0.9286	1.2590

The 24-hour urinary excretion and renal clearance values for hypoxanthine on Days –1, 1, 8, 14, and 15 are listed in Table 15. The mean total daily urinary excretion of hypoxanthine on Day -1 ranged from 4.28 to 10.22 mg. A statistically significant day by dose interaction was detected among the QD dosing regimens on Days 1, 8, and 14 ($p \leq 0.05$), with smaller changes noted on Day 1 as compared to Days 8 and 14. Subsequent analyses on each day revealed a statistically significant dose effect and an apparent linear trend ($p \leq 0.05$) on each day, with greater changes with increasing doses. Following multiple dosing with TMX-67, on Day 14, the mean estimates for total daily excretion of hypoxanthine reached 2 to 10 times those of the baseline (Day -1) daily excretions. Even though there were no substantial changes in the hypoxanthine serum concentrations, the total daily hypoxanthine urinary excretion increased substantially, due to significant increases in the renal clearance of hypoxanthine following the administration of TMX-67. A statistically significant day by dose interaction was detected among the QD dosing regimens on Days 1, 8, and 14 ($p \leq 0.05$), with smaller changes noted on Day 1 as compared to

Days 8 and 14. Subsequent analyses on each day revealed a statistically significant dose effect ($p \leq 0.05$) on each day and an apparent linear trend ($p \leq 0.05$) on Days 8 and 14, with greater changes with increasing doses. On Day 14, the mean renal clearance value for hypoxanthine increased to as much as 8 fold its baseline value. In general, the renal clearance of hypoxanthine did not appear to change with increasing dose.

Table 15. Summary of 24-hour Mean Renal Clearance (Clr) and Total Daily Urinary Excretion (Ae24) of Hypoxanthine in Urine on Days –1, 1, 8, 14, and 15 Following Oral Administration of TMX-67 or lacebo in all Dosing Regimens to Subjects.

Dose mg		Cl_r(mL/min)					Ae_{24}(mg)				
		Day-1	Day 1	Day 8	Day 14	Day 15	Day-1	Day 1	Day 8	Day 14	Day 15
Placebo	Mean	4.02	4.39	4.20	4.41	4.41	7.61	8.16	7.61	7.83	7.61
	SD	1.85	2.27	1.66	1.47	2.59	3.18	3.65	2.53	2.72	3.01
10 QD	Mean	5.41	12.45	8.57	13.56	4.26	10.22	22.17	19.06	22.59	8.01
	SD	2.75	5.88	3.07	4.99	2.11	4.88	9.04	7.61	7.10	3.67
20 QD	Mean	4.00	16.03	17.17	16.48	6.24	7.21	23.74	28.22	24.24	11.64
	SD	1.46	6.34	4.84	5.72	2.93	3.00	7.83	5.51	5.81	5.28
30 QD	Mean	3.00	15.62	22.61	19.83	14.22	4.28	18.13	25.12	26.01	18.36
	SD	2.69	10.91	9.74	9.08	15.32	2.83	9.14	9.73	7.12	14.02
40 QD	Mean	3.57	9.64	12.40	15.41	6.99	5.93	17.97	23.76	28.12	14.39
	SD	2.36	4.91	4.73	7.24	2.73	4.46	10.15	9.38	12.35	4.30
50 QD	Mean	3.74	11.02	13.70	15.32	11.08	7.60	24.61	29.58	32.45	21.21
	SD	2.91	4.30	4.61	5.86	3.88	6.42	11.63	10.79	11.31	7.41
70 QD	Mean	4.72	14.22	21.63	25.56	8.28	8.32	24.18	40.11	53.23	19.51
	SD	2.50	6.03	19.01	17.32	4.00	4.19	6.88	27.93	39.56	11.62
90 QD	Mean	3.03	13.85	19.29	22.75	15.17	6.16	26.29	45.01	49.56	32.13
	SD	1.08	4.48	7.74	4.87	4.78	2.82	9.95	18.08	11.24	9.82
120 QD	Mean	3.95	10.36	20.40	21.76	12.02	6.90	23.47	39.29	45.98	26.50
	SD	2.80	3.93	9.22	9.15	6.43	3.12	5.96	12.76	18.91	11.55
160 QD	Mean	3.17	12.92	16.85	26.55	13.72	6.03	27.54	39.79	60.77	32.91
	SD	1.95	6.08	7.17	13.35	6.65	4.05	12.61	18.90	33.31	17.81

Dose mg		Cl_r(mL/min)					Ae_{24}(mg)				
		Day-1	Day 1	Day 8	Day 14	Day 15	Day -1	Day 1	Day 8	Day 14	Day 15
180 QD	Mean	3.91	14.43	22.86	23.35	18.49	6.76	28.08	39.98	38.15	31.45
	SD	1.64	3.33	6.94	7.11	6.24	3.54	5.29	9.60	13.17	7.78
240 QD	Mean	3.33	17.44	22.57	21.39	10.17	5.78	31.79	45.52	41.14	20.91
	SD	1.39	6.73	12.28	5.76	5.34	2.60	9.65	25.64	4.52	8.79
30 BID	Mean	4.66	15.46	23.70	36.20	18.48	7.49	29.44	44.29	62.91	31.35
	SD	1.74	5.45	8.47	15.04	9.60	2.29	6.98	9.98	16.07	11.71

Discussion and Conclusions:

PK:

- Following oral administration, TMX-67 was rapidly absorbed with a T_{max} of ~ 1hr. The apparent terminal half-life was about 5-10 hr. There was little accumulation at steady-state compared to single dose following QD dose regimen.
- Exposure (AUC_{0-24} and C_{max}) of TMX-67 was dose-proportional from 10-120 mg. The proposed clinical doses are 80 and 120 mg. For doses above 120 mg, a greater than dose-proportional increase in AUC of TMX-67 was observed, possibly due to a decrease in renal elimination leading to an increase in the extent of enterohepatic recycling of TMX-67.
- Three oxidative metabolites, 67M-1, 67M-2, and 67M-4 (a secondary metabolite from 67M-1), were also monitored for systemic exposure. AUC ratio of metabolite to TMX-67 at steady state was about 0.03. Pharmacologically, these metabolites are equal or less potent than TMX-67. However, because these metabolites all showed a much lower plasma exposure than TMX-67, TMX-67 would be the prominent active molecule for the effect.
- A greater portion of the TMX-67 dose was excreted in urine as the conjugate of TMX-67 (25-47%) than as its oxidative metabolites and their conjugates (<10%) indicating that conjugation is the major metabolic pathway in metabolism of TMX-67.
- Despite the decreased C_{max} and delayed T_{max}, diurnal variability appeared to have no effect on the total exposure (AUC) to TMX-67 and its metabolites.

PD:

- Compared to the placebo arm, each regimen of TMX-67 resulted in decreased uric acid and increased xanthine concentrations in serum (see summary Table 16). The maximum changes were reached by Day 8. The effect also appeared to be reversible after stopping the dose of TMX-67. In contrast, serum hypoxanthine concentrations were not affected by TMX-67.
- There appeared to be a dose-response relationship for the percent change in 24-hour mean serum urate concentrations and the 24-hour mean serum xanthine concentrations. The effects appeared to be linear for the initial doses and reach a plateau at higher doses. In addition, the percent change in the 24-hour mean serum urate and the 24-hour mean serum xanthine concentrations versus plasma TMX-67 AUC24 data appeared to follow a baseline Emax model.
- Consistent with changes seen in serum, a decrease in the total daily urinary excretion and urinary uric acid concentration and an increase in total daily urinary excretion, urinary concentration, and renal clearance of xanthine from the baseline were observed.
- Although serum concentrations of hypoxanthine remained unchanged, there was an increase in the urinary concentration and total daily urinary excretion and renal clearance of hypoxanthine from the baseline.

Table 16. Summary of Change from Baseline (Day -1) in PD Parameters with 14 days of TMX-67 Administration (10-240 mg QD) on Day 14.

	Hypoxanthine $\xrightarrow{XO}$ Xanthine	Xanthine $\xrightarrow{XO}$ Uric Acid
$C_{mean,24}$ in Serum	↔	↑ (1.5-10 x)	↓ (27-76%)
$C_{mean,24}$ in Urine	↑ (2-9 x)	↑ (5-40 x)	↓ (37-80%)
CLr	↑ (2-8 x)	↑ (3-9 x)	↔
Total Daily Urinary Excretion	↑ (2-10 x)	↑ (7-76 x)	↓ (40-81%)

Appendix for Study TMX-99-001. Summary of Demographic Characteristics.

		TMX-67 Group											
		QD										BID	
Demographic Characteristic	Pbo (N=26)	10 mg (N=10)	20 mg (N=10)	30 mg (N=10)	40 mg (N=8)	50 mg (N=20)	70 mg (N=10)	90 mg (N=10)	120 mg (N=10)	160 mg (N=10)	180 mg (N=10)	240 mg (N=10)	30 mg (N=10)	TOTAL (N=154)
Gender														
Male	16 (62%)	8 (80%)	5 (50%)	6 (60%)	5 (63%)	9 (45%)	5 (50%)	5 (50%)	5 (50%)	4 (40%)	6 (60%)	5 (50%)	8 (80%)	87 (56%)
Female	10 (38%)	2 (20%)	5 (50%)	4 (40%)	3 (38%)	11 (55%)	5 (50%)	5 (50%)	5 (50%)	6 (60%)	4 (40%)	5 (50%)	2 (20%)	67 (44%)
Race														
	4 (15%)	1 (10%)	3 (30%)	0	0	0	0	2 (20%)	0	0	0	0	0	10 (6%)
	1 (4%)	2 (20%)	1 (10%)	2 (20%)	0	3 (15%)	0	2 (20%)	1 (10%)	0	1 (10%)	1 (10%)	0	14 (9%)
Caucasian	19 (73%)	5 (50%)	6 (60%)	7 (70%)	8 (100%)	12 (60%)	10 (100%)	6 (60%)	9 (90%)	8 (80%)	8 (80%)	9 (90%)	10 (100%)	117 (76%)
Hispanic	1 (4%)	2 (20%)	0	1 (10%)	0	4 (20%)	0	0	0	2 (20%)	1 (10%)	0	0	11 (7%)
Other	1 (4%)	0	0	0	0	1 (5%)	0	0	0	0	0	0	0	2 (1%)
Age (years#)														
19-30	12 (46%)	6 (60%)	5 (50%)	3 (30%)	2 (25%)	7 (35%)	5 (50%)	4 (40%)	5 (50%)	5 (50%)	4 (40%)	7 (70%)	7 (70%)	72 (47%)
31-45	9 (35%)	4 (40%)	5 (50%)	7 (70%)	3 (38%)	9 (45%)	3 (30%)	6 (60%)	2 (20%)	4 (40%)	5 (50%)	2 (20%)	3 (30%)	62 (40%)
46-65	5 (19%)	0	0	0	3 (38%)	4 (20%)	2 (20%)	0	3 (30%)	1 (10%)	1 (10%)	1 (10%)	0	20 (13%)
Mean (SD)	33.3 (9.85)	27.5 (6.22)	30.2 (6.86)	35.1 (8.94)	39.4 (10.21)	34.9 (11.49)	32.3 (11.52)	31.4 (8.77)	33.8 (12.09)	32.6 (11.07)	31.5 (9.62)	29.8 (10.54)	28.1 (8.75)	32.5 (9.96
Range	20-51	19-36	19-39	19-44	25-53	20-54	19-52	19-45	20-49	19-53	21-49	20-50	21-44	19-54
Weight (pounds)#														
Mean	175.9	167.1	165.7	171.6	181.5	178.0	171.7	157.7	174.2	166.5	181.3	173.0	179.8	173.2
(SD)	(34.61)	(31.93)	(21.16)	(31.62)	(57.11)	(31.29)	(38.14)	(26.27)	(23.32)	(43.56)	(31.59)	(36.97)	(19.70)	32.92
Range	122.0-252.0	133.0-234.0	140.0-208.0	134.0-215.0	111.5-275.0	127.0-241.0	88.0-219.0	119.0-200.0	138.0-220.0	113.5-238.0	144.5-231.0	119.0-245.0	154.0-226.0	88.0-275.0
Height (inches)#														
Mean (SD)	67.5 (3.50)	68.4 (2.58)	67.0 (3.41)	66.8 (3.58)	67.3 (4.48)	68.0 (4.63)	66.7 (4.02)	68.2 (4.36)	68.4 (3.30)	67.5 (4.45)	68.7 (3.30)	68.9 (2.99)	70.1 (3.17)	67.9 (3.71
Range	61.0-77.0	65.0-72.0	63.0-73.5	60.5-72.0	61.5-74.0	61.5-76.0	60.0-72.0	60.0-74.0	64.0-75.0	62.0-76.0	62.0-74.0	65.0-73.0	65.0-74.0	60.0 -77.0

At baseline

4.2.3 Special Population Studies

4.2.3.1 Study TMX-01-008: A Multiple-Dose Safety, Pharmacokinetic, and Pharmacodynamic Study of Oral TMX-67 in Healthy Volunteers

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Study Period:	May 16, 2001 to December 18, 2001
Sample Analysis Period:	July 20, 2001 to October 9, 2002
Principle Investigators:	Multiple
Study Centers:	3 U.S. sites
Analytical Sites:	b(4)

Objective: To evaluate the safety, pharmacokinetic and pharmacodynamic profile of TMX-67 after 7 consecutive days of 80 mg once daily (QD) dosing in otherwise healthy subjects with varying degrees of renal impairment and subjects with normal renal function.

Study Design: This was a Phase 1, open-label, parallel group, multiple-dose study in 32 subjects (18 males and 14 females) between ages 26 and 76 (Table 1). The study population was predominantly Caucasian (63%) and male (56%). One female subject (#1104) in the severe renal impairment group was prematurely terminated from the study after receiving 5 doses of TMX-67 due to personal reasons. She was later reenrolled as Subject #1110 and completed the study. She had a positive drug screen due to Ativan use, but was approved for enrollment. Please refer to Tables A.1 and A.2 in the Appendix for detailed demographic information. Eight (8) subjects were to be assigned to each of 4 groups based on creatinine clearance results (Cockcroft-Gault method) at the screening visit, as outlined below:

Group I	Normal Renal Function (Cl_{cr} > 80 mL/min)
Group II:	Mild Renal Impairment (Cl_{cr} 50-80 mL/min)
Group III:	Moderate Renal Impairment (Cl_{cr} 30-49 mL/min)
Group IV:	Severe Renal Impairment (Cl_{cr} 10-29 mL/min)

(Reviewer's Note: Although the Cockcroft-Gault equation was used to estimate creatinine clearance for enrollment, the 24-hour measured creatinine clearance on Day –1, rounded to the nearest whole number, was used by the Sponsor to classify the subjects into four renal function groups for PK and PD descriptive summary. Subject 1111 who had an estimated Clcr of 29.7 mL/min and without a Day -1 measured creatinine clearance was placed in Group III because the sponsor used regression analysis to calculate its Day-1 creatinine clearance to be 32.8 mL/min. This subject was placed in Group III for all the PK analysis and was excluded from the PD analysis (due to lack of Day-1 uric acid measurement) and analysis of renal impairment on PK and PD.)

Each subject received TMX-67 80 mg (4 x 20-mg tablets) once daily for 7 consecutive days after an overnight fast of at least 8 hours.

Safety of TMX-67 was assessed throughout the study by monitoring adverse events, laboratory tests, physical examination with fundoscopic eye exam, concomitant medication use, vital signs, and 12-lead electrocardiogram (ECG).

Table 1. Summary of Demographic Data (Mean □SD) by Renal Function Groups.

Group	Renal Function	N	Gender	Age (years)	Height (in)	Weight (lb)	Cl_{cr} (mL/min)
I	Normal	11	8 M/3 F	52.6 ± 12.4	67.5 ± 5.7	180.6 ± 30.3	111.8 ± 17.1
II	Mild Impairment	6	2 M/4 F	51.2 ± 14.0	65.9 ± 5.1	154.8 ± 28.1	64.2 ± 11.7
III	Moderate Impairment	7	3 M/4 F	54.3 ± 12.5	65.3 ± 2.4	164.9 ± 19.6	41.7 ± 6.5
IV	Severe Impairment	7[a]	5 M/2 F	57.3 ± 11.2	65.9 ± 4.5	192.7 ± 49.2	18.8 ± 4.9

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.

a Subject 1104 prematurely terminated from the study and was therefore excluded from the descriptive statistics.

Test Articles:

Study Drug	Strength Dosage Form	Manufacturer's Lot Number	Bulk Lot Number	Finishing Lot Number
TMX-67	20 mg	TMXT020B	63-142-AL	76-631-S2

Formulation A3

Sample Collection:

Pharmacokinetics (TMX-67 and its metabolites)

Blood (Plasma):

Day	Blood Sample Collection Time
1-6	Pre-dose[a]
7	0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose

a All pre-dose samples were collected within 5 minutes prior to dosing.

An additional 15-mL fasted blood sample was obtained from each subject on Day 1 prior to dosing for protein binding analysis.

Urine:

Day	Urine Sample Collection Intervals
1	Pre-dose
7	0-6, 6-12, 12-24 hours post-dose (samples were pooled within those intervals, volume measured and a 20-mL aliquot collected).

Pharmacodynamics (Uric acid, xanthine and hypoxanthine)

Blood (Serum):

Day	Blood Sample Collection Time
-1	24, 18 and 12 hours prior to Day 1 dose
1-6	Pre-dose[a]
7	Pre-dose[a], 6, 12 and 24 hours post-dose

a All pre-dose samples on Days 1-7 were collected within 5 minutes prior to dosing.

Urine:

Day	Urine Sample Collection Intervals
-1	24-18, 18-12, 12-0 hours prior to Day 1 dose (samples were pooled within those intervals, volume measured, and a 20-mL aliquot collected)
7	0-6, 6-12, 12-24 hours post-dose (samples were pooled within those intervals, volume measured, and a 20-mL aliquot collected)

Sample Analysis: Samples for PK and PD analyses were conducted at [redacted] b(4)
The same validated analytical methods used for sample analyses in Study TMX-99-001 were used for analysis of TMX-67 and its metabolites in human plasma and urine, and uric acid, xanthine, and hypoxanthine in human serum. Please refer to Review for Study TMX-99-001 (Section 4.2.2.1) for details. A different validated analytical method which utilized LC/MS/MS was used to analyze uric acid, xanthine and hypoxanthine in human urine (Table 2).

Table 2. Summary of Analytical Method for Uric Acid, Xanthine, and Hypoxanthine Analyses in Human Urine in Study TMX-01-008.

Analyte	Matrix	Analytical Method	Internal Standard	Limit of Quantitation (linear range)
Uric Acid	Human Urine	LC/MS/S [redacted] PS 23151_5)	[redacted] b(4)	100 µM (100-4500 µM)
Xanthine	Human Urine	LC/MS/S [redacted] PS 23151_5)		10 µM (10-1000 µM)
Hypoxanthine	Human Urine	LC/MS/S [redacted] PS 23151_5)		10 µM (10-1000 µM)

Samples for *in vitro* protein binding of [^{14}C]TMX-67 at a nominal concentration of 1 µg/mL were analyzed using an equilibrium dialysis technique by [redacted] b(4)

Pharmacokinetic and Statistical Analysis: Pharmacokinetic parameters of TMX-67 and metabolites were estimated from the plasma concentration values by standard noncompartmental methods using WinNonlin Professional™ V.3.1 (Pharsight Corporation, Mountain View, CA). The SAS System Version 8.2 was used to perform the statistical analyses.

Pharmacodynamic and Statistical Analysis: Pharmacodynamic parameters were estimated using the serum and urine concentration values. The area under the serum concentration versus time curve for uric acid, xanthine, and hypoxanthine was estimated by standard noncompartmental methods using WinNonlin Professional™ V.3.1.

Subjects 1110 and 1111 (both with severe renal impairment) were excluded from the pharmacodynamic analyses since their Day -1 (baseline) pharmacodynamic samples were collected after the first dose of study drug on Day 1 and their change from baseline values would be affected. Since the creatinine measurements for these subjects were also collected after the first dose of study drug, the Day -1 Clcr values were not obtained. A request was sent to the Sponsor to also exclude these two subjects from the regression analysis to determine the effect of

renal impairment on the pharmacokinetics and pharmacodynamics of TMX-67 and its metabolites. Day –1 serum Clcr measurements for the rest of subjects were used in the analysis.

Subject 1114 (severe renal impairment) tested positive at screening for hepatitis C but was allowed to enroll in the study because of normal liver chemistry levels (ALT and AST). After calculation of the pharmacokinetic parameters for this subject, it was noted that the metabolic ratios for metabolites 67M-1 and 67M-2 to parent drug were far less than those observed for the other subjects with severe renal impairment, indicating that this subject may have had some degree of hepatic impairment in addition to renal impairment. Given that it has been reported that, even with normal liver chemistries (ALT and AST), hepatitis C patients could have advanced liver histopathology, the pharmacokinetics of TMX-67 and its metabolites in this subject could have been affected by decreased hepatic function as well as renal impairment. Therefore, the effect of renal impairment on the pharmacokinetics and pharmacodynamics of TMX-67 and its metabolites was evaluated using regression analyses excluding Subject 1114.

Subject 1104 (severe renal impairment) prematurely discontinued from the study due to personal reasons and was excluded from the pharmacokinetic and pharmacodynamic analyses.

Pharmacokinetic Results:

Protein Binding

[^{14}C]TMX-67 was highly bound to plasma proteins in all renal function groups, but on average the binding was slightly lower in subjects with severe renal impairment (98.8%) compared to that from subjects in the other renal function groups (99.1-99.2%) (Table 3).

Table 3. Mean (± SD) *In Vitro* Protein Binding Data for [14C]TMX-67 (1 µg/mL) in Human Plasma from Study TMX-01-008

Renal Function	N	Protein Binding (fraction unbound)
Normal	11	0.009 ± 0.002
Mild Impairment	6	0.009 ± 0.001
Moderate Impairment	7	0.008 ± 0.001
Severe Impairment	7	0.012 ± 0.003

Subject 1104 (severe renal impairment) prematurely discontinued from the study and was therefore excluded from the descriptive statistics.

Plasma PK Profiles

TMX-67:

Predose TMX-67 plasma concentrations on Days 1-7 were shown in Figure 1. Steady-state was reached on Day 7.

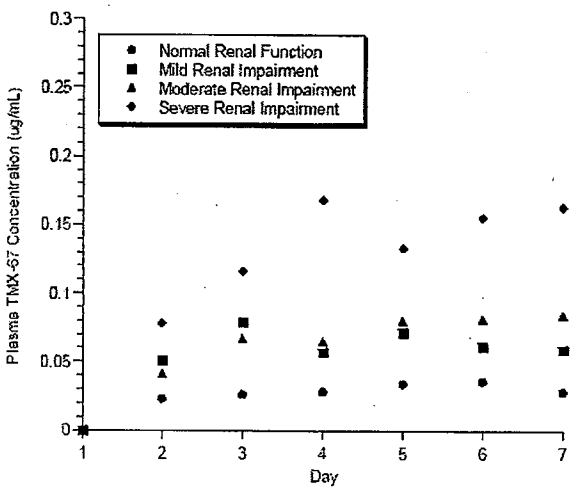

Figure 1. Mean TMX-67 Pre-dose Plasma Concentrations Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days to Subjects in Study TMX-01-008.

Plasma concentration-time profiles for TMX-67 in subjects with different degree of remal function are shown in Figure 2.

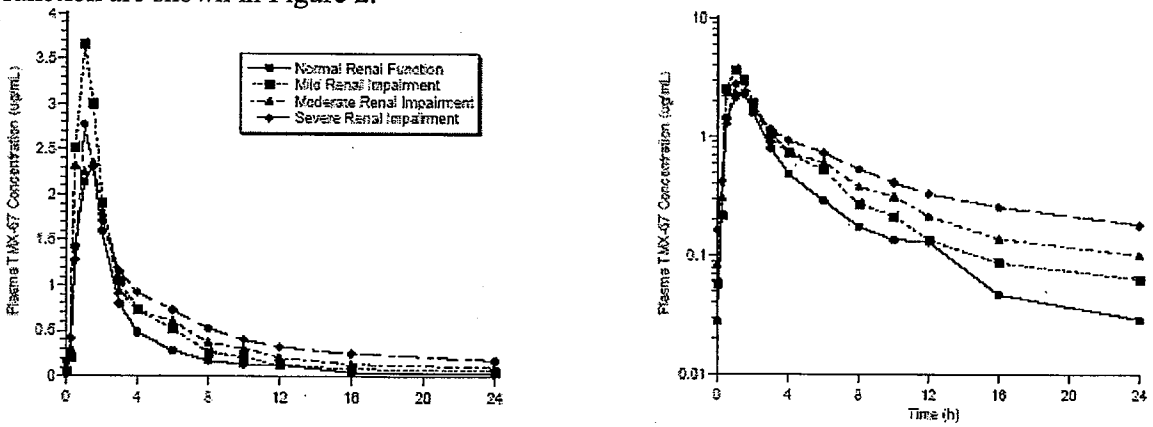

Figure 2. Mean TMX-67 Plasma Concentration-Time Profiles on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days to Subjects in Study TMX-01-008 (Left: Linear scale; Right: Semi-log scale).

A summary of TMX-67 and unbound TMX-67 plasma pharmacokinetic parameter estimates for subjects in each renal function group on Day 7 following administration of a daily 80 mg oral dose of TMX-67 for 7 days is presented in Table 4.

Table 4. Mean (SD) TMX-67 Plasma Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

Group	t_{max} (h)	C_{max} (µg/mL)	$C_{max,u}$ (ng/mL)	AUC_{24} (µg□h/mL)	$AUC_{24,u}$ (ng□h/mL)	$t_{1/2z}$ [a] (h)	Cl_{ss}/F (L/h)	$Cl_{ss,u}/F$ (L/h)
I	1.14	2.8656	24.9587	7.5024	65.4888	4.7 [4.5]	12.18	1513.50
N=11	(0.45)	(1.2487)	(12.8153)	(2.6801)	(28.0596)	(1.1)	(5.08)	(908.08)
II	1.33	4.0348	35.8864	11.1359	100.3031	7.6 [6.7]	7.28	817.66
N=6	(0.88)	(1.6859)	(14.2262)	(1.3563)	(18.7275)	(3.5)	(0.94)	(130.64)
III	0.93	2.9168	24.2733	11.1306	91.5613	9.1 [7.7]	7.76	905.26
N=7	(0.45)	(1.0601)	(9.1650)	(2.9240)	(16.5998)	(4.0)	(2.68)	(206.61)
IV[b]	0.92	2.3147	26.3183	9.3501	106.9054	6.6 [5.8]	12.88	1093.68
N=6	(0.38)	(1.4055)	(14.9890)	(5.8319)	(67.8804)	(2.3)	(9.29)	(780.69)

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.
a $t_{1/2z}$ arithmetic mean [harmonic mean in brackets]
b Subjects 1104 (prematurely discontinued) and 1114 (hepatitis C positive) were excluded from the PK analysis.

The AUC and $T_{1/2}$ of TMX-67 increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. $AUC_{24,u}$ of TMX-67 increased about 60% from normal to mild, moderate and severe renal impairment (Table 4).

A summary of urinary pharmacokinetic parameter estimates for TMX-67 (unchanged) and total (unchanged + conjugated) TMX-67 is presented in Table 5.

Table 5. Mean (SD) TMX-67 Urinary Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

	Unchanged			Total	
Group	Ae_{24} (µg)	fe	Clr (L/h)	Ae_{24} (µg)	fe
I	1360	0.017	0.24	28093	0.351
N=11	(1436)	(0.018)	(0.34)	(5334)	(0.067)
II	1381	0.017	0.12	24814	0.310
N=6	(679)	(0.008)	(0.06)	(7134)	(0.089)
III	1004	0.013	0.13	14185	0.177
N=7	(1114)	(0.014)	(0.20)	(7054)	(0.088)
IV[a]	505	0.006	0.06	4698	0.059
N=6	(595)	(0.007)	(0.05)	(2677)	(0.033)

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.
a Subjects 1104 (prematurely discontinued) and 1114 (hepatitis C positive) were excluded from the PK analysis.

As expected, amount of both unchanged TMX-67 and total TMX-67 (unchanged plus conjugated) excreted in urine decreased with decreased renal function (Table 5). Consistent with results from the ADME study (Study C03-40), renal clearance of intact TMX-67 is small compared to total clearance. It was likely that increase of TMX-67 AUC and half-life with increasing renal impairment was due to a decrease in the renal clearance of conjugated TMX-67 and hence an increase in the extent of enterohepatic cycling.

Linear regression analysis was performed to determine the correlation between measured creatinine clearance and $AUC_{24,u}$ of TMX-67. As shown in Figure 3, $AUC_{24,u}$ is somewhat

negatively correlated with Clcr. With every 20 mL/min increase in Clcr, $AUC_{24,u}$ would decrease 10 ng*h/mL).

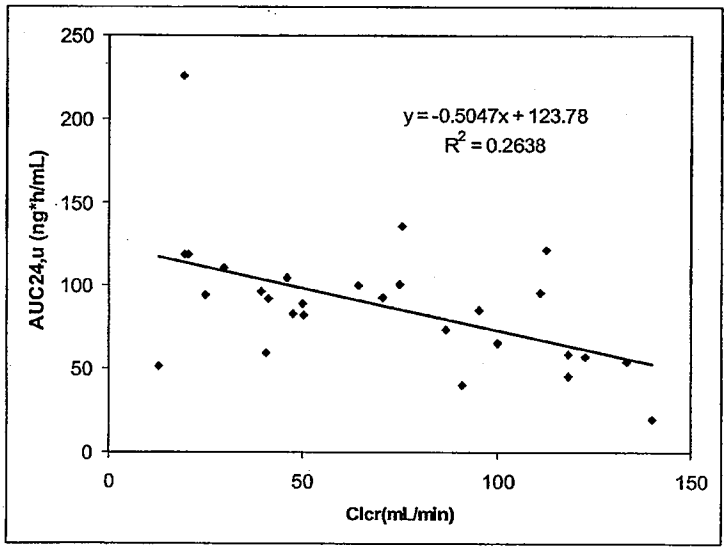

Figure 3. Simple Linear Regression Plot of $AUC_{24,u}$ of TMX-67 versus Creatinine Clearance.

Based on results from the regression models for $AUC_{24,u}$, $AUC_{24,u}$ predictions and the 95% prediction intervals for a hypothetical subject with Cl_{cr} at about the midpoint of each renal function category were calculated, and are presented in Table 6. The 95% prediction intervals for $AUC_{24,u}$ were wide and had substantial overlap between groups which is consistent with the overall flat distribution of the data.

Table 6. Individual Predictions (Ind. Pred.) and 95% Prediction Intervals (95% P.I.) for TMX-67 $AUC_{24,u}$ in Study TMX-01-008.

	Predictions for Hypothetical Subjects with Indicated Clcrin each Renal Function Group							
	Normal (Clcr=100 mL/min)		Mild Impairment (Clcr=65 mL/min)		Moderate Impairment (Clcr=40 mL/min)		Severe Impairment (Clcr=20 mL/min)	
Parameter	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.
$AUC_{24,u}$	73.3	(2.2, 144.4)	91.0	(20.6, 161.3)	103.6	(32.5, 174.6)	113.7	(41.3, 186.0)

Units for $AUC_{24,u}$ are ng·h/mL.

67M-1, 67M-2, and 67M-4:

A summary of pharmacokinetic parameters of major metabolites, 67M-1, 67M-2, and 67M-4, for subjects in each renal function group on Day 7 following administration of a daily 80 mg oral dose of TMX-67 for 7 days is presented in Table 7.

Table 7. Mean (SD) 67M-1, 67M-2, and 67M-4 Plasma Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

Group	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng□h/mL)	AUC_{24} (ng□h/mL)	$t_{1/2z}$ [a] (h)	λ_z (1/h)	AUC Ratio[b]
67M-1							
I	1.41	64.202	207.540	209.524	5.6 [5.2]	0.134	0.028
	(0.38)	(36.510)	(98.689)	(97.404)	(1.8)	(0.039)	(0.006)
II	1.50	97.317	335.220	335.882	7.9 [5.9]	0.117	0.030
	(0.77)	(48.344)	(108.168)	(107.723)	(4.7)	(0.069)	(0.008)
III	1.57	87.580	454.930	454.930	9.8 [8.6]	0.081	0.042
	(0.45)	(41.750)	(156.084)	(156.084)	(4.0)	(0.030)	(0.012)
IV[c]	1.33	73.375	466.852	467.923	7.8 [6.5]	0.107	0.049
	(0.41)	(36.039)	(299.534)	(298.081)	(3.7)	(0.054)	(0.005)
67M-2							
I	1.86	49.100	209.091	210.142	6.2 [5.2]	0.134	0.029
	(0.64)	(13.373)	(78.291)	(77.360)	(2.6)	(0.061)	(0.008)
II	2.00	70.336	358.936	358.936	9.5 [8.3]	0.083	0.033
	(1.05)	(24.479)	(125.001)	(125.001)	(4.3)	(0.027)	(0.012)
III	1.68	84.822	546.657	546.657	12.0 [10.3]	0.067	0.050
	(0.66)	(40.111)	(200.663)	(200.663)	(5.5)	(0.025)	(0.014)
IV[c]	1.83	90.168	764.962	764.962	9.6 [8.1]	0.085	0.085
	(0.61)	(48.650)	(511.599)	(511.599)	(4.3)	(0.036)	(0.022)
67M-4							
I	2.09	47.876	210.725	211.557	7.1 [6.1]	0.113	1.06
	(0.63)	(15.650)	(80.861)	(79.967)	(2.5)	(0.050)	(0.28)
II	2.08	71.625	366.388	366.388	9.5 [8.9]	0.078	1.13
	(1.02)	(38.984)	(132.167)	(132.167)	(2.3)	(0.022)	(0.42)
III	2.57	88.385	637.048	637.048	9.7 [8.8]	0.079	1.37
	(1.59)	(35.490)	(338.309)	(338.309)	(3.4)	(0.023)	(0.36)
IV[c]	2.17	62.641	491.962	493.139	10.3 [7.2]	0.096	1.032
	(0.68)	(33.363)	(310.892)	(309.342)	(6.2)	(0.071)	(0.42)

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.
a $t_{1/2z}$ arithmetic mean [harmonic mean in brackets].
b AUC_{24} ratios: For 67M-1, 67M-1/TMX-67 ratio; for 67M-2, 67M-2/TMX-67 ratio; for 67M-4, 67M-4/67M-1 ratio.
c Subjects 1104 (prematurely discontinued) and 1114 (hepatitis C positive) were excluded from the PK analysis.

Mean C_{max}, AUC_{24} and $T_{1/2}$ values for metabolites 67M-1, 67M-2, and 67M-4 generally increased with the increasing renal impairment (Table 7).

A summary of urinary pharmacokinetic parameter estimates for unchanged and total 67M-1, 67M-2, and 67M-4 is presented in Table 8.

Table 8. Mean (SD) 67M-1, 67M-2, and 67M-4 Urinary Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

	Unchanged			Total	
Group	Ae_{24} (μg)	f_e	Cl_r (L/h)	Ae_{24} (μg)	f_e
67M-1					
I	2793 (1325)	0.033 (0.016)	13.84 (4.66)	4319 (1868)	0.051 (0.022)
II	2937 (1663)	0.035 (0.020)	8.27 (3.08)	4598 (2321)	0.055 (0.028)
III	1454 (626)	0.017 (0.007)	3.28 (1.04)	2303 (1013)	0.027 (0.012)
IV[a]	529 (417)	0.006 (0.005)	1.08 (0.41)	905 (645)	0.011 (0.008)
67M-2					
I	2495 (963)	0.030 (0.011)	12.33 (3.62)	3260 (1103)	0.039 (0.013)
II	2402 (879)	0.029 (0.010)	7.03 (2.30)	3296 (877)	0.039 (0.010)
III	1715 (472)	0.020 (0.006)	3.39 (1.01)	2132 (525)	0.025 (0.006)
IV[a]	892 (681)	0.011 (0.008)	1.16 (0.43)	1175 (829)	0.014 (0.010)
67M-4					
I	1955 (752)	0.022 (0.009)	9.40 (2.21)	2057 (750)	0.023 (0.009)
II	2224 (1166)	0.025 (0.013)	5.87 (1.62)	2381 (1211)	0.027 (0.014)
III	1549 (835)	0.018 (0.009)	2.59 (0.88)	1599 (933)	0.018 (0.011)
IV[a]	486 (323)	0.006 (0.004)	0.91 (0.23)	496 (331)	0.006 (0.004)

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.
a Subjects 1104 (prematurely discontinued) and 1114 (hepatitis C positive) were excluded from the PK analysis.

Similar to TMX-67, amount of both unchanged 67M-1, 67M-2, and 67M-4 and total 67M-1, 67M-2, and 67M-4 (unchanged plus conjugated) excreted in urine decreased with decreased renal function (Table 8), especially for moderate and severe renal impairment patients. Consistent with results from the ADME study (Study C03-40), a greater portion of the total metabolites was excreted in urine as unchanged metabolites. In contrast to TMX-67, it appears that the kidney plays a greater role in elimination of metabolites. As a result, decreased renal clearance of the metabolites with increased renal impairment would lead to a decrease in the elimination of the metabolite from the body and hence an increase in the metabolites AUC. Therefore, the increase in the metabolites AUC with increasing renal impairment was likely the result of the increase in TMX-67 AUC and a decrease in renal clearance of the metabolites with increasing renal impairment.

Because the exposure levels for metabolites 67M-1, 67M-2, and 67M-4 were <10% in plasma relative to that for TMX-67 in all the renal function groups, analysis of the effect of renal impairment on these metabolites were not shown.

Pharmacodynamic Results:
A summary of serum $C_{mean,24}$ estimates for urate, xanthine, and hypoxanthine, and the Day 7 percent change from Day -1 for urate following administration of a daily 80 mg oral dose of TMX-67 for 7 days are presented in Table 9.

Table 9. Mean (SD) Serum Urate, Xanthine, and Hypoxanthine $C_{mean,24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

	Urate			Xanthine		Hypoxanthine	
	$C_{mean,24}$ (mg/dL)		% Change	$C_{mean,24}$(mg/dL)		$C_{mean,24}$(mg/dL)	
Group	Day -1	Day 7	Day 7	Day -1	Day 7	Day -1	Day 7
I	5.288	2.195	-58.16	0.0291	0.1496	0.1260	0.1384
N=11	(1.291)	(0.708)	(11.17)	(0.0092)	(0.0213)	(0.0525)	(0.0373)
II	5.053	1.892	-63.55	0.0291	0.2118	0.1265	0.1544
N=6	(1.473)	(0.881)	(6.93)	(0.0081)	(0.0867)	(0.0173)	(0.0223)
III[a]	6.801	2.907	-56.71	0.0243	0.3817	0.1326	0.1544
N=6	(0.862)	(0.290)	(6.96)	(0.0020)	(0.0857)	(0.0218)	(0.0231)
IV[b]	7.509	3.399	-54.38	0.0232	0.5526	0.1050	0.1054
N=5	(1.390)	(0.787)	(8.67)	(0.0097)	(0.2353)	(0.0389)	(0.0354)

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.
a Subjects 1111 (no baseline level) was excluded from the PD analysis.
b Subjects 1110 (no baseline level), 1104 (prematurely discontinued) and 1114 (hepatitis C positive) were excluded from the PD analysis.

A summary of urinary $C_{mean,24}$, Ae_{24}, and Cl_r values for uric acid, xanthine, and hypoxanthine following administration of a daily 80 mg oral dose of TMX-67 for 7 days is presented in Table 10.

Table 10. Mean (SD) Urinary Uric Acid, Xanthine, and Hypoxanthine $C_{mean,24}$, Ae_{24}, and Cl_r Values on Days -1 and 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days to Subjects.

	C_{mean24}(mg/dL)		Ae_{24}(mg)		Cl_r(mL/min)	
Group	Day -1	Day 7	Day -1	Day 7	Day -1	Day 7
Uric Acid						
I	21.915	7.550	603.74	213.16	8.33	7.09
N=11	(9.900)	(4.183)	(105.70)	(86.51)	(2.20)	(3.03)
II	23.368	5.110	433.58	115.02	6.03	4.78
N=6	(16.217)	(0.776)	(117.26)	(31.24)	(0.91)	(2.02)
III[a]	14.128	2.810	358.60	67.37	3.71	1.59
N=6	(3.700)	(2.486)	(59.93)	(51.82)	(0.81)	(1.12)
IV[b]	15.276	5.160	344.70	108.79	3.15	2.26
N=5	(5.646)	(1.130)	(157.91)	(31.53)	(1.17)	(0.67)

Xanthine						
I N=11	0.2058 (0.1489)	5.6938 (2.9368)	5.10 (3.08)	159.50 (43.40)	12.34 (7.03)	74.63 (19.21)
II N=6	0.1854 (0.1903)	6.8982 (2.7559)	2.96 (1.26)	144.47 (18.27)	7.82 (4.50)	51.84 (14.52)
III[a] N=6	0.0190 (0.0300)	4.9905 (1.0051)	0.48 (0.74)	126.89 (32.54)	1.36 (2.12)	24.54 (8.63)
IV[b] N=5	0.0000 (0.0000)	3.9906 (2.0596)	0.00 (0.00)	79.56 (35.89)	0.00 (0.00)	9.77 (1.62)
Hypoxanthine						
I N=11	0.1835 (0.1525)	0.9163 (0.4527)	4.69 (3.71)	25.97 (7.02)	3.11 (3.28)	13.84 (5.29)
II N=6	0.1575 (0.1683)	0.9481 (0.2930)	2.48 (1.47)	20.71 (5.74)	1.35 (0.73)	9.25 (1.83)
III[a] N=6	0.0067 (0.0165)	0.4175 (0.2413)	0.14 (0.33)	11.07 (5.88)	0.07 (0.18)	5.02 (2.58)
IV[b] N=5	0.0000 (0.0000)	0.1613 (0.0848)	0.00 (0.00)	3.12 (0.98)	0.00 (0.00)	2.37 (1.26)

Group I: Normal renal function; Group II: Mild renal impairment; Group III: Moderate renal impairment; Group IV: Severe renal impairment.
a Subjects 1111 (no baseline level) was excluded from the PD analysis.
b Subjects 1110 (no baseline level), 1104 (prematurely discontinued) and 1114 (hepatitis C positive) were excluded from the PD analysis.

Uric Acid:

Baseline uric acid serum level increased slightly with decreased renal function, but overall % change from baseline after 7 days of TMX-67 administration did not differ among different renal function groups (Table 9). As expected, renal clearance of uric acid decreased with decreased renal function (Table 10). Both $C_{mean,24}$ and Ae_{24} of urinary uric acid decreased on Day 7 from baseline for all the renal function groups. However, TMX-67 appeared to have little effect on renal clearance of uric acid (as observed in other studies).

Regression analysis for the percent decrease in serum urate concentration indicated a statistically significant quadratic relationship with Cl_{cr} (Figure 4). The predicted percent decrease in serum urate concentration from the regression model for a subject at about the midpoint Cl_{cr} for each renal impairment group differed from that of the normal renal function group by no more than 13%, and the 95% prediction intervals for percent change in serum urate had substantial overlap between groups (Table 11), suggesting that the estimated percent change in serum urate is expected to be similar regardless of renal function.

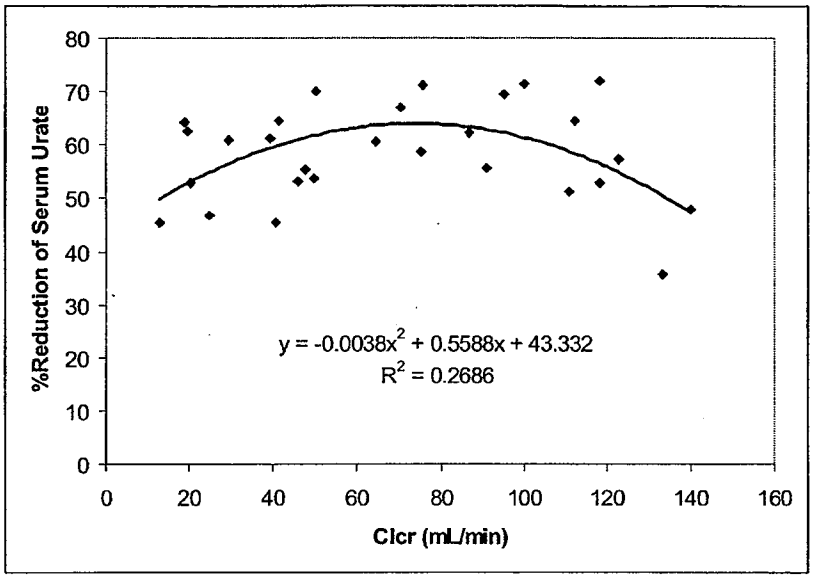

Figure 4. Quadratic Regression Plot of Parameter Percent Decrease in Serum Urate Concentration vs. Creatinine Clearance – Pharmacodynamic Parameter.

Table 11. Individual Predictions (Ind. Pred.) and 95% Prediction Intervals (95% P.I.) for Serum Urate Percent Change in $C_{mean,24}$.

Predictions for Hypothetical Subjects with Indicated Cl_{cr} in each Renal Function Group							
Normal (Cl_{cr}=100 mL/min)		Mild Impairment (Cl_{cr}=65 mL/min)		Moderate Impairment (Cl_{cr}=40 mL/min)		Severe Impairment (Cl_{cr}=20 mL/min)	
Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.
61.4	43.9– 78.8	63.7	46.1 – 81.2	59.6	42.3-77.0	53.0	35.0-71.0

Xanthine:

Baseline xanthine serum level did not differ among different renal function groups. However, serum xanthine levels on Day 7 increased with decreased renal function (Table 9). Although serum xanthine concentrations on Day 7 for subjects with severe renal impairment were higher than those for subjects with normal renal function, the 24-hour mean serum xanthine concentrations (0.55 ± 0.24 mg/dL) were substantially lower than the solubility limit of xanthine in pH 7.4 serum (10 mg/dL), indicating the less likelihood of xanthine stone formation.

As expected, renal clearance of xanthine decreased with decreased renal function (Table 10). The changes were more dramatic than what was observed for uric acid (about 100-fold difference between normal and severe renal impairment patients). *(It should be noted that the lower limit of quantitation in the assay method for xanthine was approximately 0.152 mg/dL (10 µmol/L). Urinary xanthine concentrations less than 0.152 mg/dL were considered as 0 mg/dL in the calculation of $C_{mean,24}$ values. Therefore, mean baseline urinary xanthine $C_{mean,24}$ values for subjects in the moderate and severe renal impairment groups may be artificially lower than those for subjects in the mild renal impairment or normal renal function groups due to the detection limits of the assay.)* Both $C_{mean,24}$ and Ae_{24} of urinary xanthine increased on Day 7

from baseline for all the renal function groups. TMX-67 appeared to significantly increase renal clearance of xanthine (as observed in other studies).

Hypoxanthine:
Baseline hypoxanthine serum level did not differ among different renal function groups. Similar to what observed in healthy subjects, serum level of hypoxanthine on Day 7 did not change from baseline in all the renal function groups (Table 9).

As expected, renal clearance of hypoxanthine decreased with decreased renal function (Table 10). The changes were more dramatic than what was observed for uric acid and similar to what was observed for xanthine (>100-fold different between normal and severe renal impairment patients). *(Similar to xanthine, it should also be noted for hypoxanthine that the lower limit of quantitation in the assay method for hypoxanthine was approximately 0.136 mg/dL (10 μmol/L). Urinary hypoxanthine concentrations less than 0.136 mg/dL were considered 0 in the calculation of $C_{mean,24}$ values. Therefore, mean baseline urinary hypoxanthine $C_{mean,24}$ values for subjects in the moderate and severe renal impairment groups may be artificially lower than those for subjects in the mild renal impairment or normal renal function groups due to the detection limits of the assay.)* Both $C_{mean, 24}$ and Ae_{24} of urinary hypoxanthine increased on Day 7 from baseline for all the renal function groups. TMX-67 appeared to significantly increase renal clearance of hypoxanthine (as observed in other studies).

Discussion and Conclusion:

- AUC and $T_{1/2}$ of TMX-67 increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. $AUC_{24, u}$ of TMX-67 increased about 60% from normal to mild, moderate and severe renal impairment (Table 4). Based on ADME data (Study C03-40), renal clearance of intact TMX-67 is not significant. It was likely that increase of TMX-67 AUC and half-life with increasing renal impairment was due to a decrease in the renal clearance of conjugated TMX-67 and hence an increase in the extent of enterohepatic cycling.
- AUC and $T_{1/2}$ of TMX-67 metabolites also increased in subjects with renal impairment in comparison to subjects with normal renal function. Exposure levels of metabolites in plasma relative to that of TMX-67 were <10% in all the renal function groups. Similar to TMX-67, amount of both unchanged 67M-1, 67M-2, and 67M-4 and total 67M-1, 67M-2, and 67M-4 (unchanged plus conjugated) excreted in urine decreased with decreased renal function (Table 8), especially for moderate and severe renal impairment patients. Consistent with results from the ADME study (Study C03-40), a greater portion of the total metabolites was excreted in urine as unchanged metabolites. The increase in the metabolites AUC with increasing renal impairment was likely the result of the increase in TMX-67 AUC, due to increased enterohepatic cycling, and a decrease in renal clearance of the metabolites with increasing renal impairment.
- Although exposure of TMX-67 and its metabolites increased in patients with renal impairment, the maximum C_{max} and AUC values of TMX-67 and its metabolites obtained for subjects with renal impairment did not exceed the exposure levels observed in healthy subjects who were safely administered doses of TMX-67 in previously conducted studies.

- Because the exposure at 80 mg is towards the plateau of the exposure/PD response curve observed in healthy subjects, a change in AUC (< 2-fold) did not result in big change in serum uric acid reduction. The percent decrease in serum urate appeared to be similar regardless of the renal function.

b(4)

- PK or PD of febuxostat in end-stage renal impairment patients who are on dialysis has not been studied. However, febuxostat is not expected to be routinely used in end-stage renal impairment patients who are on dialysis because dialysis alone effectively removes uric acid.
- Although serum xanthine concentrations on Day 7 for subjects with severe renal impairment were about 3-fold higher than those for subjects with normal renal function, the 24-hour mean serum xanthine concentrations (0.55 ± 0.24 mg/dL) were substantially lower than the solubility limit of xanthine in pH 7.4 serum (10 mg/dL), indicating the low likelihood of xanthine stone formation.

Appendix (Study TMX-01-008).

Table A.1. Demographic Data for Subjects in Study TMX-01-008

Subject	Group	Gender	Race	Age (years)	Height (cm)	Height (in)	Weight (kg)	Weight (lb)	Cl_{cr} (mL/min)	Estimated Cl_{cr} (mL/min)
1102	I	Male	Caucasian	66	186.7	73.5	112.7	248.3	140.1	94.8
1103	I	Male	Caucasian	41	171.5	67.5	74.2	163.5	133.5	115.1
1108	I	Male	Caucasian	54	175.9	69.3	91.6	201.8	122.8	99.6
1115	I	Male	Native American	37	167	65.8	71.7	158	118.3	114.3
2102	I	Male	Caucasian	35	172.7	68	74.5	164	91.1	68
2103	I	Male	Caucasian	50	177.8	70	87.2	192	111.0	73.3
2105	I	Male	Caucasian	68	185.4	73	84.4	186	87.0	63.1
2111	I	Female	Black	43	160	63	83.1	183	118.3	96.2
2112	I	Male	Caucasian	64	190.5	75	90.8	200	112.5	95
3101	I	Female	Hispanic	67	144.8	57	65.4	144	100.1	82.9
3102	I	Female	Hispanic	53	152.4	60	66.3	146	95.3	87.6
1101	II	Female	Caucasian	56	156.2	61.5	62.7	138	64.3	78.6
1107	II	Female	Caucasian	26	174	68.5	66.7	147	50.2	49.4
1109	II	Female	Caucasian	65	163.2	64.3	64.5	142	70.5	56.8
2101	II	Male	Caucasian	62	177.8	70	72.6	160	75.1	60
2104	II	Male	Caucasian	51	182.9	72	94.9	209	49.8	55.6
3105	II	Female	Hispanic	47	149.9	59	60.4	133	75.5	76.4
1111[b]	III	Male	Caucasian	40	161.9	63.8	75.1	165.5	N/A	29.7
1112	III	Male	Caucasian	40	172.7	68	66.6	146.8	40.5	30.2
2106	III	Female	Black	66	172.7	68	62.7	138	29.5	20.7
2108	III	Female	Caucasian	60	157.5	62	74.9	165	47.5	44.8
2109	III	Female	Black	70	165.1	65	88.5	195	39.2	40.6
2110	III	Female	Caucasian	59	161.3	63.5	83.1	183	41.2	38
3103	III	Male	Black	45	170.2	67	73.1	161	45.9	35.8

1104[a]	IV	Female	Caucasian	45	157.5	62	104.7	230.5	13.9	26.71
1105	IV	Male	Caucasian	66	175.3	69	98	215.8	24.9	34.51
1106	IV	Male	Black	52	173.5	68.3	64.8	142.8	12.9	12.04
1110[b]	IV	Female	Caucasian	46	157.5	62	107.3	236.3	N/A	24.6
1113	IV	Male	Caucasian	76	158.8	62.5	62.7	138	19.0	15.3
1114[c]	IV	Female	Black	53	152.4	60	76.6	168.8	23.2	24.9
2107	IV	Male	Black	62	184.2	72.5	122.1	269	20.4	19.7
3104	IV	Male	Hispanic	46	170.2	67	80.8	178	19.5	19.2

Note: Subjects were placed into renal function groups based on the 24-hour Day -1 Cl_{cr} values rounded to the nearest whole number.
a Subject 1104 prematurely terminated from the study and was therefore excluded from both PK and PD analysis
b Subjects 1110 and 1111 were excluded from PD analysis due to lack of baseline creatinine clearance data.
c Subject 1114 was excluded from both PK and PD analysis due to hepatitis C positive that may have an impact on liver function.

Table A.2. Demographic Data at Baseline.

Demographic Characteristic	Normal Renal Function (N=11)	Mild Renal Impairment (N=6)	Moderate Renal Impairment (N=7)	Severe Renal Impairment (N=8)	Total (N=32)
Gender					
Male	8 (73%)	2 (33%)	3 (43%)	5 (63%)	18 (56%)
Female	3 (27%)	4 (67%)	4 (57%)	3 (38%)	14 (44%)
Race					
Black	1 (9%)	0 (0%)	3 (43%)	3 (38%)	7 (22%)
Caucasian	7 (64%)	5 (83%)	4 (57%)	4 (50%)	20 (63%)
Hispanic	2 (18%)	1 (17%)	0 (0%)	1 (13%)	4 (13%)
Other	1 (9%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Age (years)#					
25-45	4 (36%)	1 (17%)	3 (43%)	1 (13%)	9 (28%)
46-65	4 (36%)	5 (83%)	2 (29%)	5 (63%)	16 (50%)
66-80	3 (27%)	0 (0%)	2 (29%)	2 (25%)	7 (22%)
Mean (SD)	52.5 (12.42)	51.2 (14.02)	54.3 (12.47)	55.8 (11.22)	53.5 (11.95)
Range	35-68	26-65	40-70	45-76	26-76
Weight (pounds)#					
Mean (SD)	180.6 (30.31)	154.8 (28.10)	164.9 (19.59)	197.4 (47.47)	176.5 (35.31)
Range	144-248	133-209	138-195	138-269	133-269
Height (inches)#					
Mean (SD)	67.5 (5.67)	65.9 (5.11)	65.3 (2.38)	65.4 (4.39)	66.2 (4.58)
Range	57-75	59-72	62-68	60-73	57-75

Renal function was based on measured 24 hr creatinine clearance on Day -1.

4.2.3.2 Study TMX-01-012: Safety, Pharmacokinetics, and Pharmacodynamic Study of TMX-67 in Subjects with Normal or Impaired Hepatic Function

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Study Period: September 12, 2001 to May 1, 2002
Sample Analysis Period: February 26, 2002 to October 9, 2002
Principle Investigators:
Study Centers:

b(4)

Analytical Sites:

(for protein binding)

Objective: To compare the safety, pharmacokinetic and pharmacodynamic profile of TMX-67 in subjects with hepatic impairment to subjects with normal hepatic function.

Study Design: This was a Phase 1, parallel group, open-label, multiple-dose study in 28 male (15) and female (13) subjects between ages 39 and 62 (Table 1). All 28 subjects completed the study, but one subject (Subject 1123, Group I) was suspected of missing doses during the study. Therefore this subject was excluded from all the analysis. Of the rest 27 subjects enrolled, 15 were Caucasian, 9 were Hispanic, and 3 were Black. Please refer to the Tables A1 and A2 in the Appendix for detailed demographic information.

Subjects were placed into study groups based on the Child-Pugh Classification of their hepatic function: normal, mildly impaired (Child-Pugh A), or moderately impaired (Child-Pugh B). An attempt was made to enroll subjects in the normal hepatic function group who matched subjects in each of the impaired hepatic function groups with respect to gender, weight (± 10 kg) and age (± 4 years).

Table 1. Demographic Data (Mean ± SD) at Baseline.

Group	Hepatic Function	N	Gender	Age (years)	Height (cm)	Weight (kg)
I	Normal	11[a]	6M/5F	50.2 ± 5.7	169.95 ± 9.47	78.62 ± 14.02
II	Mild Impairment (Class A)	8	4M/4F	52.9 ± 5.2	168.28 ± 9.67	71.34 ± 11.47
III	Moderate Impairment (Class B)	8	5M/3F	50.4 ± 5.4	173.04 ± 11.31	84.84 ± 19.98

a Subject 1123 (Hispanic female) was suspected of missing doses during the study, therefore she was excluded from the descriptive statistics.

Each subject received TMX-67 80 mg (4 x 20-mg tablets) once daily for 7 consecutive days after an overnight fast of at least 8 hours. Blood and urine samples were to be collected for determination of pharmacokinetic and pharmacodynamic parameters.

Test Articles:

Study Drug	Strength Dosage Form	Manufacturer's Lot Number	Bulk Lot Number	Finishing Lot Number
TMX-67	20 mg	TMXX020B	67-205-AL	78-847-S2

Formulation A3

Sample Collection:
Plasma, serum, and urine samples were collected for the determination of TMX-67, metabolites 67M-1, 67M-2, and 67M-4, uric acid, xanthine, and hypoxanthine concentrations, as outlined in the following table:

Procedure	Study Day(s)		
	–1	1-6	7
TMX–67 & Metabolites (Plasma)	-	Predose[a]	X[b]
Protein Binding (Plasma)	-	Predose[a] (Day 1 only)	-
UXH (Serum)	24, 18, and 12 hours prior to Day 1 dose	Predose[a]	X[c]
TMX–67 & Metabolites (Urine)	-	Predose (Day 1 only)	0-6, 6-12, and 12-24 hours post-dose
UXH (Urine)	24-18, 18-12, and 12-0 hours prior to Day 1 dose	-	0-6, 6-12, and 12-24 hours post-dose

UXH: Uric acid, xanthine, and hypoxanthine.
a: All predose samples were to be collected within 5 minutes prior to dosing.
b: Predose, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, and 24 hours post-dose.
c: Predose, 6, 12, and 24 hours post-dose.

Sample Analysis: Samples for PK and PD analyses were conducted at [redacted] b(4) Same validated analytical methods used for sample analyses in Study TMX-01-008 were used in this study. Please refer to Review for Study TMX-01-008 (Section 4.2.3.1) for details.

The *in vitro* protein binding of [^{14}C]TMX-67 at a nominal concentration of 1 µg/mL was determined in pre-dose plasma samples, obtained from each of the subjects who participated in the study. Samples were analyzed using an equilibrium dialysis technique by [redacted] b(4)

Pharmacokinetic and Statistical Analysis: Pharmacokinetic parameters of TMX-67 and metabolites were estimated from the plasma concentration values by standard noncompartmental methods using WinNonlin Professional™ V.3.1 (Pharsight Corporation, Mountain View, CA).

Pharmacodynamic and Statistical Analysis: Pharmacodynamic parameters were estimated using the serum and urine concentration values. The area under the serum concentration versus time curve for uric acid, xanthine, and hypoxanthine was estimated by standard noncompartmental methods using WinNonlin Professional™ V.3.1.

The relationship of hepatic function and the pharmacokinetic plasma and urine parameter estimates and the percent change from baseline in serum urate Cmean,24 were assessed via an analysis of variance (ANOVA) that included hepatic function group as the factor.

Pharmacokinetic Results:

Protein Binding

The *in vitro* protein binding of [^{14}C]TMX-67 at a nominal concentration of 1 µg/mL was determined in plasma samples obtained from each of the subjects who participated in the study using an equilibrium dialysis technique, the results of which are summarized in Table 2.

Table 2. Mean (± SD) *In Vitro* Protein Binding Data for [14C]TMX-67 (1 µg/mL) in Human Plasma from Study TMX-01-012

Hepatic Function	N	Protein Binding (fraction unbound)
Normal	11	0.007 ± 0.001
Mild Impairment	8	0.007 ±0.001
Moderate Impairment	8	0.006 ±0.001

Subject 1123 (Group I) was suspected of missing doses during the study, therefore she was excluded from the descriptive statistics

[^{14}C]TMX-67 was highly bound to plasma proteins, and on average was nearly the same for all hepatic function groups (99.3-99.4%).

Plasma PK Profiles

Predose TMX-67 plasma concentrations on Days 1-7 were shown in Figure 1. Steady-state appeared to be reached on Day 7. Interestingly, the predose TMX-67 levels for patients with moderate hepatic impairment decreased from Day 3 to Day 7.

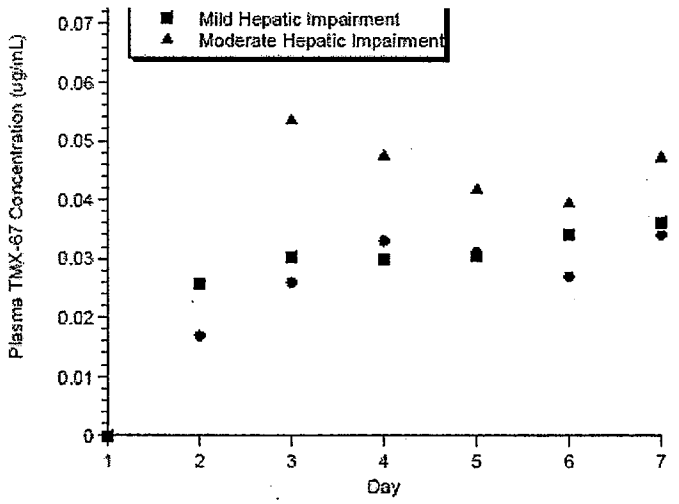

Figure 1. Mean TMX-67 Pre-dose Plasma Concentrations Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days to Subjects in Study TMX-01-012 (● Normal Hepatic Function).

Plasma concentration-time profiles for TMX-67 in subjects with different degree of hepatic function are shown in Figure 2.

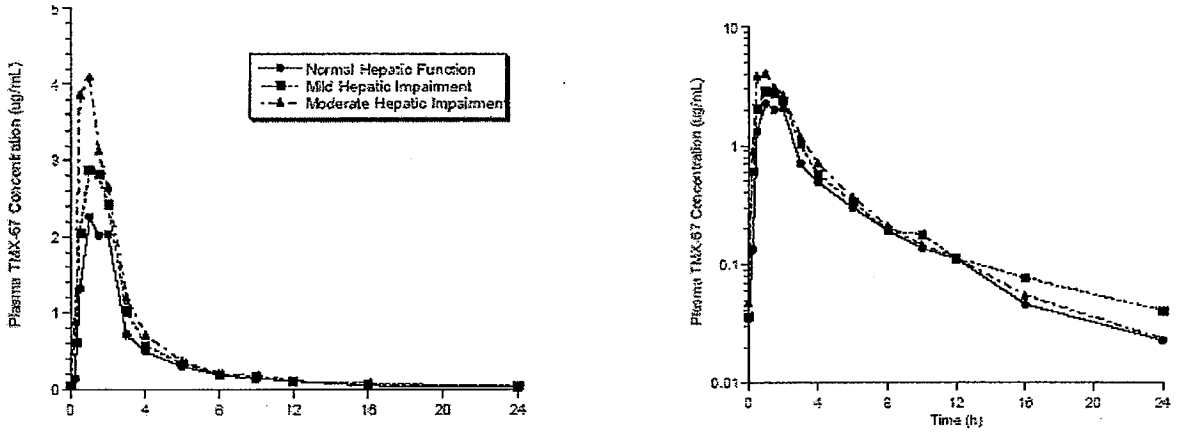

Figure 2. Mean TMX-67 Plasma Concentration-Time Profiles on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days to Subjects in Study TMX-01-012 (Left: Linear scale; Right: Semi-log scale).

A summary of TMX-67 and unbound TMX-67 plasma pharmacokinetic parameter estimates for subjects in each hepatic function group on Day 7 following administration of a daily 80 mg oral dose of TMX-67 for 7 days is presented in Table 3. Subjects with moderate hepatic impairment showed big variability in PK parameters.

Table 3. Mean (SD) TMX-67 Plasma Pharmacokinetic Parameters for Hepatic Function Groups I-III on Day 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for 7 Days.

Group	t_{max} (h)	C_{max} (µg/mL)	$C_{max,u}$ (ng/mL)	AUC_{24} (µg·h/mL)	$AUC_{24,u}$ (ng·h/mL)	$t_{1/2z}$[a] (h)	CL_{ss}/F (L/h)	$CL_{ss,u}/F$ (L/h)
I	1.23 (0.61)	2.8416 (0.9415)	19.1204 (7.1544)	7.6107 (2.6454)	51.2183 (18.9836)	5.5 [5.4] (0.9)	11.81 (4.24)	1789.81 (715.02)
II	1.25 (0.53)	3.5098 (0.7809)	23.7034 (6.4302)	9.8696 (2.5537)	65.6789 (15.2293)	6.9 [5.5] (4.3)	8.51 (1.81)	1281.98 (318.34)
III	0.75 (0.27)	4.3593 (2.3641)	23.7438 (12.5733)	11.7724 (7.0652)	63.5004 (36.0660)	5.6 [4.9] (1.8)	10.31 (7.51)	1828.61 (1265.60)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.
a $t_{1/2z}$ arithmetic mean [harmonic mean in brackets].

A summary of urinary pharmacokinetic parameter estimates for TMX-67 (unchanged) and total (unchanged + conjugated) TMX-67 is presented in Table 4.

Table 4. Mean (SD) TMX-67 Urinary Pharmacokinetic Parameters for Hepatic Function Groups I-III on Day 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for 7 Days.

Group	Unchanged			Total (unchanged + conjugated)	
	Ae_{24} (µg)	f_e	Cl_r (L/h)	Ae_{24} (µg)	f_e
I	1921 (1507)	0.024 (0.019)	0.31 (0.33)	31984 (6290)	0.400 (0.079)
II	2525 (2901)	0.032 (0.036)	0.27 (0.30)	37528 (9338)	0.469 (0.117)
III	2625 (1390)	0.033 (0.017)	0.32 (0.22)	41284 (8885)	0.516 (0.111)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.

An analysis of variance (ANOVA) with a factor of hepatic function group was performed on t_{max}, λ_z, Ae_{24}, Cl_r, and the natural logarithms of C_{max}, $C_{max,u}$, AUC_{24}, and $AUC_{24,u}$. The p-values from the ANOVA model are presented in Table 5.

Table 5. P-values from ANOVA for TMX-67 Pharmacokinetic Parameters from Study TMX-01-012

Parameter	ANOVA P-Values		
	Effect	Comparisons	
	Hepatic Function	Mild vs. Normal	Moderate vs. Normal
t_{max}	0.095	0.924	0.054
$\ln(C_{max})$	0.376	0.285	0.209
$\ln(C_{max,u})$	0.574	0.297	0.682
$\ln(AUC_{24})$	0.286	0.189	0.178
$\ln(AUC_{24,u})$	0.408	0.186	0.620
λ_z	0.784	0.853	0.593
Unchanged Ae_{24}	0.704	0.520	0.454
Unchanged Cl_r	0.929	0.756	0.945
Total Ae_{24}	0.059	0.152	**0.020**

Statistical significance was defined at the $\alpha = 0.05$ level for all effects.

ANOVA analysis conducted by the Sponsor showed that only total TMX-67 excreted in urine was significantly different between moderate hepatic impairment patients and healthy patients.

The urinary excretion of TMX-67 following the administration of daily 80 mg oral doses of TMX-67 for 7 days accounted for an average of 2.4% of the administered dose for subjects with normal hepatic function, and 3.2% and 3.3% of the dose for subjects with mildly and moderately impaired hepatic function, respectively (Table 4). The difference between the normal and mildly and moderately impaired hepatic function groups was not statistically significant ($p > 0.05$, Table 5).

The urinary excretion of total (unchanged + conjugated) TMX-67 following the administration of daily 80 mg oral doses of TMX-67 for 7 days accounted for an average of 40.0% of the administered dose for subjects with normal hepatic function, and 46.9% and 51.6% of the dose for subjects with mildly and moderately impaired hepatic function, respectively (Table 4). Total TMX-67 Ae24 values for subjects with mild and moderate hepatic impairment were approximately 17% and 29% higher, respectively, than the Ae24 for subjects with normal

hepatic function. The difference between the normal and mildly and moderately impaired hepatic function groups was not statistically significant for total TMX-67 Ae24 ($p > 0.05$, Table 5). However, the difference between the normal and moderately impaired hepatic function groups was statistically significant for total TMX-67 Ae_{24} ($p \leq 0.05$, Table 5).

Based on one-sided t-test analysis conducted by the reviewer, the 90% confidence interval of total and unbound C_{max} and AUC_{24} values for hepatically impaired groups (mild and moderate) relative to those of normal subjects were not within 80% and 125% boundary (Table 6). Both total and unbound C_{max} and AUC_{24} values were higher in hepatic impaired patients compared to healthy group. If combined both hepatically impaired groups, $C_{max,u}$ and $AUC_{24,u}$ were about 20% higher than the healthy group.

Table 6. Comparison of Geometric Mean Ratios and Confidence Intervals for TMX-67 Total and Unbound Cmax and AUC24, and Unbound CLss/F Following Administration of TMX-67 (80 mg) for 7 days in Healthy Subjects and Subjects with Hepatic Impairment. (Reviewer's Analysis)

Parameter	Group	Geometric Mean	Ratio	90%CI
$C_{max,u}$ (ng/mL)	I	18		
	II	22.89	127.2	(86.43, 187.19)
	III	19.76	109.8	(74.61, 161.58)
	II + III	21.27	118.18	(85.73, 162.91)
$AUC_{24,u}$ (ng·h/mL)	I	47.92		
	II	64.06	133.65	(92.85, 192.38)
	III	53.34	111.3	(77.32, 160.21)
	II + III	58.46	121.97	(89.97, 165.35)
$CL_{ss,u}/F$ (L/h)	I	1669.18		
	II	1248.87	74.82	(51.98, 107.7)
	III	1499.69	89.85	(62.42, 129.32)
	II + III	1368.55	81.99	(60.48, 111.15)
C_{max} (μg/mL)	I	2.70		
	II	3.44	127.38	(87.23, 186.01)
	III	3.59	133.10	(91.14, 194.36)
AUC_{24} (μg·h/mL)	I	7.19		
	II	9.62	133.85	(92.52, 193.63)
	III	9.70	134.92	(93.26, 195.18)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.

Data for metabolites were included in the Appendix (Tables A3-A4). The exposure levels for metabolites 67M-1, 67M-2, and 67M-4 were only about 3% in plasma relative to that for TMX-67, They are comparable to data obtained in healthy subjects from other studies. Hepatic impairment appeared to have little effects on the plasma pharmacokinetics of metabolites 67M-1, 67M-2, and 67M-4.

Pharmacodynamic Results:

Mean pre-dose serum concentrations of urate, xanthine, and hypoxanthine in mg/dL on Days -1 to 8 are illustrated in Figure 3. It appears that steady-state was reached on Day 7.

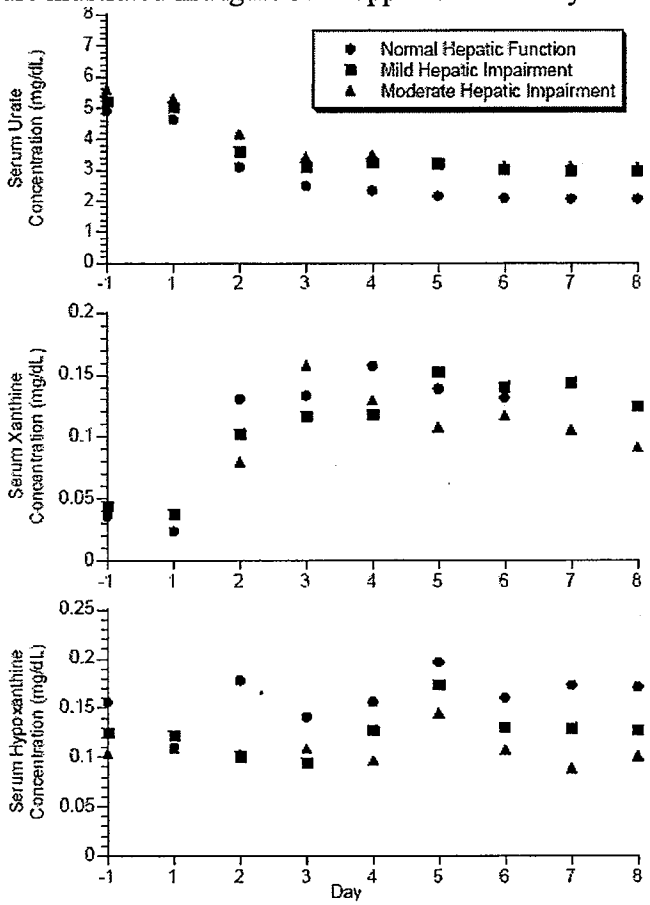

Figure 3. Mean Pre-dose Serum Urate, Xanthine, and Hypoxanthine Concentrations on Days –1 to 8 Following Administration of Daily 80 mg Oral Doses of TMX-67 on Days 1 to 7 to Subjects with Normal or Impaired Hepatic Function.

A summary of serum $C_{mean,24}$ estimates for urate, xanthine, and hypoxanthine, and the Day 7 percent change from Day -1 for urate following administration of a daily 80 mg oral dose of TMX-67 for 7 days are presented in Table 7.

Table 7. Mean (SD) Serum Urate, Xanthine, and Hypoxanthine $C_{mean,24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days

	Urate			Xanthine		Hypoxanthine	
	$C_{mean,24}$ (mg/dL)		% Change	$C_{mean,24}$ (mg/dL)		$C_{mean,24}$ (mg/dL)	
Group	Day -1	Day 7	Day 7	Day -1	Day 7	Day -1	Day 7
I	4.767	1.830	-62.48	0.0256	0.1593	0.1224	0.1379
	(1.284)	(0.688)	(7.48)	(0.0068)	(0.0349)	(0.0373)	(0.0359)
II	4.950	2.664	-48.88	0.0342	0.1770	0.1104	0.1182
	(1.851)	(1.451)	(13.48)	(0.0073)	(0.1013)	(0.0494)	(0.0349)
III	5.448	2.845	-47.83	0.0318	0.1525	0.0905	0.0789
	(0.951)	(0.631)	(6.82)	(0.0117)	(0.0336)	(0.0299)	(0.0298)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.

A summary of urinary $C_{mean,24}$, Ae_{24}, and Cl_r values for uric acid, xanthine, and hypoxanthine following administration of a daily 80 mg oral dose of TMX-67 for 7 days is presented in Table 8.

Table 8. Mean (SD) Urinary Uric Acid, Xanthine, and Hypoxanthine $C_{mean,24}$, Ae_{24}, and Cl_r Values on Days -1 and 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

	$C_{mean,24}$(mg/dL)		Ae_{24}(mg)		Cl_r(mL/min)	
Group	Day -1	Day 7	Day -1	Day 7	Day -1	Day 7
Uric Acid						
I	31.998	9.106	585.78	169.11	8.78	6.46
	(18.864)	(4.524)	(272.89)	(67.83)	(3.62)	(1.27)
II	25.392	8.958	434.45	171.73	7.05	5.69
	(19.882)	(5.537)	(111.63)	(93.93)	(3.27)	(3.66)
III	31.013	14.614	489.31	216.49	6.57	5.17
	(24.804)	(12.048)	(312.64)	(114.06)	(4.49)	(2.15)
Xanthine						
I	0.4069	10.8584	7.63	205.12	22.30	91.04
	(0.2235)	(5.0377)	(3.69)	(52.25)	(13.48)	(20.24)
II	0.4551	6.8973	7.72	146.01	16.41	70.67
	(0.3094)	(1.8752)	(1.21)	(49.43)	(4.57)	(33.10)
III	0.5973	8.4006	9.07	134.97	23.67	64.22
	(0.4171)	(2.5999)	(4.60)	(12.21)	(16.23)	(15.51)
Hypoxanthine						
I	0.3113	2.1414	5.41	37.96	3.51	20.21
	(0.2507)	(1.4711)	(3.81)	(16.90)	(3.62)	(10.68)
II	0.4186	1.5669	6.08	33.53	5.12	22.62
	(0.4247)	(0.4809)	(3.47)	(12.69)	(4.35)	(12.87)
III	0.4435	1.8055	5.41	27.39	5.06	24.53
	(0.4698)	(1.0384)	(5.58)	(15.25)	(6.33)	(14.84)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.

Table 9. P-values from ANOVA for Percent Change in Serum Urate Cmean,24 from Day –1 to Day 7 in Study TMX-01-012.

	ANOVA P-Values		
	Effect	Pairwise Comparisons	
Parameter	Hepatic Function	Mild vs. Normal	Moderate vs. Normal
% Decrease in serum urate $C_{mean,24}$	0.003	0.005	0.003

Statistical significance was defined at the $\alpha = 0.05$ level for all effects.

Both baseline (Day –1) and Day 7 mean serum urate $C_{mean,24}$ values in subjects with normal hepatic function were lower than those in subjects with mild or moderate hepatic impairment. Following the administration of daily 80 mg oral doses of TMX-67 for 7 days, Day 7 serum urate $C_{mean,24}$ values decreased by an average of 62% (from 4.767 mg/dL to 1.830 mg/dL) from Day –1 values in subjects with normal hepatic function, and by 49% (from 4.950 mg/dL to 2.664 mg/dL) and 48% (from 5.448 mg/dL to 2.845 mg/dL) in subjects with mild and moderate hepatic impairment, respectively (Table 7). The effect of hepatic function on the percent change in serum urate $C_{mean,24}$ was statistically significant between subjects with normal hepatic function and those with hepatic impairment ($p \leq 0.05$, Table 9).

Serum xanthine baseline (Day –1) $C_{mean,24}$ concentrations were slightly lower in subjects with normal hepatic function compared to those in subjects with hepatic impairment. Following the administration of daily 80 mg oral doses of TMX-67 for 7 days, serum xanthine $C_{mean,24}$ concentrations, urinary xanthine $C_{mean,24}$, total daily xanthine excretion and the renal clearance of xanthine all increased substantially from the baseline levels for each hepatic function group (Tables 7 and 8). The increases in each parameter were lower in subjects with hepatic impairment compared to the increases in those with normal hepatic function.

Baseline serum hypoxanthine $C_{mean,24}$ concentrations were higher in subjects with normal hepatic function compared to subjects with mild or moderate hepatic impairment. Following the administration of daily 80 mg oral doses of TMX-67 for 7 days, serum hypoxanthine concentrations did not change substantially for any of the hepatic function groups (Table 7). Baseline urinary concentrations of hypoxanthine were generally lower in subjects with normal hepatic function compared to those with hepatic impairment. Following the administration of daily 80 mg TMX-67 doses for 7 days, urinary hypoxanthine $C_{mean,24}$ concentrations increased substantially for each hepatic function group (Table 8). However, the magnitude of the increase was less than that observed for xanthine. Likewise, the mean total daily excretion and renal clearance of hypoxanthine increased from baseline following administration of TMX-67 for 7 days. All changes from baseline for Day 7 urinary hypoxanthine $C_{mean,24}$, Ae_{24}, and Cl_r, were statistically significant ($p \leq 0.05$) and similar for each hepatic function group.

Safety Results:

The overall incidence of adverse events during dosing was higher for subjects in the moderate hepatic impairment (75% [6/8]) and mild hepatic impairment (63% [5/8]) groups as compared to subjects in the normal hepatic function group (25% [3/12]). The most commonly occurring adverse events in any group were abdominal pain (25% [2/8]) and headache (25% [2/8]) among

subjects in the mild hepatic impairment group and diarrhea (25% [2/8]) and urinary frequency (25% [2/8]) among subjects in the moderate hepatic impairment group. All other adverse events in the mild and moderate hepatic impairment groups were reported by one subject only. No adverse events were reported by more than one subject in the normal hepatic function group. All adverse events were of mild intensity and most were considered either possibly, probably, or definitely related to study drug.

Discussion and Conclusion:
The plasma exposure to TMX-67 was greater in subjects with mild or moderate hepatic impairment compared to subject with normal hepatic function following the administration of daily 80 mg oral doses of TMX-67 for 7 days. An average of 20-30% increase was observed for both Cmax and AUC24 (total and unbound) in hepatically impaired groups.

Greater exposure of TMX-67 in hepatically impaired groups did not translate to greater reduction in serum uric acid levels on Day 7. %Reduction in both mild (49%) and moderate (48%) hepatic impairment groups were 13 and 14% less than the reduction observed in healthy group (62%). The mean percent decrease in serum urate for healthy subjects in other special population studies ranged from 52% to 58% (Study TMX-01-008 and Study 01-016). Therefore, 48-49% reduction of uric acid level observed in this study appeared to be comparable to healthy groups. The data are also consistent with the previous finding that 80 mg is approaching the plateau of the dose-response curve for uric acid reduction.

Hepatic impairment appeared to have minimal effects on the plasma pharmacokinetics of metabolites 67M-1, 67M-2, and 67M-4.

Based on the urinary pharmacokinetic parameters of TMX-67 and its metabolites, it appears that phase-I metabolism of TMX-67 may have been minimally affected in subjects with hepatic impairment. It was also shown that the urinary excretion of total TMX-67 was greater in subjects with increasing hepatic impairment. This increase in the fraction of the dose excreted as total TMX-67 with increasing hepatic impairment was likely the result of a decrease in the biliary excretion of total TMX-67.

Based on exposure results and serum uric acid reduction activity results from this study, dose adjustments for TMX-67 in subjects with mild or moderate hepatic impairment are not necessary. PK or PD of TMX-67 in subjects with severe hepatic impairment has not been studied. A dose recommendation could not be made for severe hepatic impairment patients.

Appendix (Study TMX-01-012).

Table A1. Demographic Data for Subjects in Study TMX-01-012

Subject	Initial Dose	Gender	Group	Match (Subject #)	Race	Nicotine Use	Age (years)	Height (in)	Height (cm)	Weight (lb)	Weight (kg)
1110	26 SEP 01	Male	I	1105	Black	Ex-Tobacco User	46.00	68.00	172.72	172.00	78.09
1112	03 OCT 01	Male	I	1104, 1111	Caucasian	Non-Tobacco User	55.00	71.00	180.34	186.00	84.44
1113	03 OCT 01	Male	I	1103, 1108	Hispanic	Ex-Tobacco User	52.00	67.00	170.18	162.00	73.55
1114	03 OCT 01	Female	I	1101	Hispanic	Ex-Tobacco User	56.00	63.00	160.02	162.00	73.55
1115	03 OCT 01	Female	I	1102	Hispanic	Non-Tobacco User	39.00	64.00	162.56	210.00	95.34
1117	02 NOV 01	Male	I	1109	Black	Non-Tobacco User	46.00	69.00	175.26	202.00	91.71
1118	02 NOV 01	Male	I	1106	Hispanic	Tobacco User	60.00	72.00	182.88	172.00	78.09
1122	14 DEC 01	Male	I	1119, 1125	Caucasian	Ex-Tobacco User	50.00	72.00	182.88	226.00	102.60
1123[a]	11 DEC 01	Female	I	1107	Hispanic	Non-Tobacco User	51.00	62.00	157.48	160.00	72.64
1124	14 DEC 01	Female	I	1120	Hispanic	Non-Tobacco User	50.00	64.00	162.56	134.00	60.84
2102	13 DEC 01	Female	I	1121, 2101	Caucasian	Non-Tobacco User	48.00	64.00	162.56	153.00	69.46
2103	12 FEB 02	Female	I	1116	Caucasian	Non-Tobacco User	50.00	62.00	157.48	126.00	57.20
1101	12 SEP 01	Female	II	1114	Black	Tobacco User	59.00	62.00	157.48	152.00	69.01
1105	12 SEP 01	Male	II	1110	Hispanic	Non-Tobacco User	48.00	66.00	167.64	162.00	73.55
1106	12 SEP 01	Male	II	1118	Caucasian	Ex-Tobacco User	62.00	70.00	177.80	198.00	89.89
1107	26 SEP 01	Female	II	1123	Caucasian	Tobacco User	51.00	62.00	157.48	142.00	64.47
1108	26 SEP 01	Male	II	1113	Caucasian	Tobacco User	54.00	69.00	175.26	174.00	79.00
1111	03 OCT 01	Male	II	1112	Hispanic	Tobacco User	51.00	71.00	180.34	170.00	77.18
1116	17 OCT 01	Female	II	2103	Caucasian	Tobacco User	51.00	68.00	172.72	113.00	51.30
2101	12 DEC 01	Female	II	2102	Caucasian	Ex-Tobacco User	47.00	62.00	157.48	146.00	66.28
1102	12 SEP 01	Female	III	1115	Caucasian	Ex-Tobacco User	42.00	67.00	170.18	205.00	93.07
1103	12 SEP 01	Male	III	1113	Caucasian	Tobacco User	51.00	64.00	162.56	156.00	70.82
1104	12 SEP 01	Male	III	1112	Caucasian	Tobacco User	59.00	72.00	182.88	202.00	91.71
1109	17 OCT 01	Male	III	1117	Hispanic	Non-Tobacco User	50.00	72.00	182.88	194.00	88.08
1119	11 DEC 01	Male	III	1122	Caucasian	Non-Tobacco User	48.00	72.00	182.88	251.00	113.95
1120	11 DEC 01	Female	III	1124	Caucasian	Tobacco User	54.00	65.00	165.10	130.00	59.02
1121	11 DEC 01	Female	III	2102	Hispanic	Tobacco User	45.00	61.00	154.94	131.00	59.47
1125	25 APR 02	Male	III	1122	Caucasian	Tobacco User	54.00	72.00	182.88	226.00	102.60

a Subject is suspected of missing doses during the study, therefore she is excluded from the descriptive statistics and analysis.

Table A2. Summary of Race/Ethnicity Distribution for Subjects.

	Number of Subjects					
	Male			Female		
Group	Caucasian	Hispanic	Black	Caucasian	Hispanic	Black
I	2	2	2	2	3	0
II	2	2	0	3	0	1
III	4	1	0	2	1	0
All Subjects	8	5	2	7	4	1

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.
Subject 1123 (Group I) was suspected of missing doses during the study, therefore she was excluded.

Table A3. Mean (SD) 67M-1, 67M-2, and 67M-4 Plasma Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days

Group	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{24} (ng·h/mL)	$t_{1/2z}$[a] (h)	λ_z (1/h)	AUC Ratio[b]
			67M-1				
I	1.68 (0.60)	54.160 (17.027)	180.623 (68.041)	181.023 (67.600)	6.4 [5.7] (2.2)	0.123 (0.052)	0.025 (0.007)
II	1.56 (0.42)	60.838 (28.309)	226.830 (106.415)	227.815 (105.548)	8.3 [4.7] (9.7)	0.146 (0.081)	0.023 (0.009)
III	1.56 (0.73)	53.731 (30.333)	203.937 (106.951)	204.571 (106.471)	6.1 [5.2] (2.1)	0.132 (0.070)	0.022 (0.015)
			67M-2				
I	1.77 (0.56)	46.001 (13.912)	195.740 (63.657)	195.740 (63.657)	8.2 [7.7] (2.2)	0.090 (0.022)	0.027 (0.010)
II	1.81 (0.26)	56.077 (25.823)	233.744 (107.484)	234.302 (106.750)	8.5 [5.9] (5.9)	0.117 (0.076)	0.024 (0.012)
III	1.88 (0.23)	48.119 (33.256)	211.665 (139.339)	212.564 (138.455)	5.8 [5.0] (1.9)	0.139 (0.070)	0.026 (0.025)
			67M-4				
I	2.09 (0.49)	43.734 (18.910)	200.513 (108.116)	200.678 (107.910)	7.1 [6.7] (1.6)	0.103 (0.025)	1.075 (0.248)
II	1.75 (0.27)	41.387 (23.766)	190.030 (118.188)	190.634 (117.574)	7.1 [5.1] (3.4)	0.136 (0.097)	0.798 (0.337)
III	1.81 (0.26)	35.993 (21.487)	156.746 (92.059)	157.523 (91.632)	6.3 [5.0] (2.9)	0.140 (0.089)	0.757 (0.264)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.
a $t_{1/2z}$ arithmetic mean [harmonic mean in brackets].
b AUC_{24} ratios: For 67M-1, 67M-1/TMX-67 ratio; for 67M-2, 67M-2/TMX-67 ratio; for 67M-4, 67M-4/67M-1 ratio.

Table A4. Mean (SD) 67M-1, 67M-2, and 67M-4 Urinary Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days

	Unchanged			Total (unchanged + conjugated)	
Group	Ae_{24} (µg)	f_e	Cl_r (L/h)	Ae_{24} (µg)	f_e
		67M-1			
I	3083 (776)	0.037 (0.009)	18.69 (7.64)	4667 (1404)	0.056 (0.017)
II	3067 (1244)	0.036 (0.015)	14.14 (4.23)	4403 (1832)	0.052 (0.022)
III	2270 (723)	0.027 (0.009)	13.18 (5.32)	3771 (1269)	0.045 (0.015)
		67M-2			
I	2687 (671)	0.032 (0.008)	14.91 (5.93)	3541 (943)	0.042 (0.011)
II	2596 (935)	0.031 (0.011)	12.11 (3.38)	3446 (1282)	0.041 (0.015)
III	2034 (1092)	0.024 (0.013)	11.49 (4.87)	2864 (1743)	0.034 (0.021)
		67M-4			
I	1870 (630)	0.021 (0.007)	10.52 (3.55)	2218 (934)	0.025 (0.011)
II	1437 (685)	0.016 (0.008)	9.24 (4.02)	1917 (887)	0.022 (0.010)
III	1349 (682)	0.015 (0.008)	10.16 (4.42)	1578 (759)	0.018 (0.009)

Group I: Normal hepatic function; Group II: Mild hepatic impairment; Group III: Moderate hepatic impairment.

4.2.2.3 Study TMX-01-016: The Effect of Gender and Age on the Safety, Pharmacodynamics and Pharmacokinetics of TMX-67 in Healthy Subjects

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Study Period: December 6, 2001 to December 22, 2001.
Sample Analysis Period: January 15, 2002 to September 5, 2002
Principle Investigator:
Study Center:
Analytical Sites: / / (b(4)

(for protein binding)

Objective: To evaluate the effect of gender and age on the safety, pharmacodynamics and pharmacokinetics of TMX-67 when administered for 7 consecutive days.

Study Design: This was a Phase 1, parallel-group, open-label, multiple-dose study in male and female subjects between the ages of 18 and 40, inclusive and 65 years of age and older. Subjects were categorized into different study groups based on age and gender.

Group I: Males, 18 to 40 years of age, inclusive
Group II: Females, 18 to 40 years of age, inclusive
Group III: Males, 65 years of age and older
Group IV: Females, 65 years of age and older

Twenty-four adult male and twenty-four adult female subjects were enrolled and completed the Study TMX-01-016 (Table 1). Of the 48 subjects, 35 (73%) were Hispanic, 10 (21%) were Caucasian, and three (6%) were Black. Please refer to the Tables A1 in the Appendix for additional demographic information.

Table 1. Summary of Demographic Characteristics.

Category	N	Age (years)	Height (in)	Height (cm)	Weight (lb)	Weight (kg)
Subjects 18-40 y	24	31.8 ±6.9	64.9 ±3.5	164.8 ±8.9	161.1 ±30.1	73.2 ±13.7
Subjects ≥65 y	24	69.9 ±3.6	64.6 ±4.0	164.1 ±10.2	166.8 ±26.0	75.7 ±11.8
Male Subjects	24	51.3 ±21.5	67.7 ±2.5	172.0 ±6.2	177.5 ±24.2	80.6 ±11.0
Female Subjects	24	50.5 ±18.8	61.8 ±2.0	156.9 ±5.0	150.4 ±25.2	68.3 ±11.4

Each subject received TMX-67 80 mg (4 x 20-mg tablets) once daily for 7 consecutive days after an overnight fast of at least 8 hours. Blood and urine samples were to be collected for determination of pharmacokinetic and pharmacodynamic parameters.

Test Articles:

Study Drug	Strength Dosage Form	Manufacturer's Lot Number	Bulk Lot Number	Finishing Lot Number
TMX-67	20 mg	TMXT020B	63-142-AL	82-044-S2

Formulation A3

Sample Collection:
Plasma, serum, and urine samples were collected for the determination of TMX-67, metabolites 67M-1, 67M-2, and 67M-4, uric acid, xanthine, and hypoxanthine concentrations, as outlined in the following table:

Procedure	Study Day(s)		
	–1	1-6	7
TMX–67 & Metabolites (Plasma)	-	Predose[a]	X[b]
Protein Binding (Plasma)	-	Predose[a] (Day 1 only)	-
UXH (Serum)	24, 18, and 12 hours prior to Day 1 dose	Predose[a]	X[c]
TMX–67 & Metabolites (Urine)	-	Predose (Day 1 only)	0-6, 6-12, and 12-24 hours post-dose
UXH (Urine)	24-18, 18-12, and 12-0 hours prior to Day 1 dose	-	0-6, 6-12, and 12-24 hours post-dose

UXH: Uric acid, xanthine, and hypoxanthine.
a: All predose samples were to be collected within 5 minutes prior to dosing.
b: Predose, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, and 24 hours post-dose.
c: Predose, 6, 12, and 24 hours post-dose.

Sample Analysis: Samples for PK and PD analyses were conducted at [redacted]. Same validated analytical methods used for sample analyses in Study TMX-01-008 were used in this study. Please refer to Review for Study TMX-01-008 (Section 4.2.3.1) for details. b(4)

The *in vitro* protein binding of [^{14}C]TMX-67 at a nominal concentration of 1 µg/mL was determined in pre-dose plasma samples, obtained from each of the subjects who participated in the study. Samples were analyzed using an equilibrium dialysis technique by [redacted] b(4)

Pharmacokinetic and Statistical Analysis: Pharmacokinetic parameters of TMX-67 and metabolites were estimated from the plasma concentration values by standard noncompartmental methods using WinNonlin Professional™ V.3.1 (Pharsight Corporation, Mountain View, CA).

A two-way analysis of variance (ANOVA) was used to investigate the effects of gender and age on TMX-67 pharmacokinetic parameters. This ANOVA model included factors for age category, gender and the interaction of age category and gender. Age was treated as a categorical variable with subjects either in the younger (18-40 years) or the older (≥65 years) age categories. The plasma parameters analyzed included t_{max}, λ_z, and the natural logarithms of C_{max}, $C_{max,u}$, AUC_{24} and $AUC_{24,u}$. The urine parameters analyzed included Ae and Clr.

When the main effect for gender was statistically significant for a parameter, analyses of covariance (ANCOVAs) were performed to explore the explanatory value of body weight by including it as a continuous variable in the statistical model.

Pharmacodynamic and Statistical Analysis: Pharmacodynamic parameters were estimated using the serum and urine concentration values. The area under the serum concentration versus time curve for uric acid, xanthine, and hypoxanthine was estimated by standard noncompartmental methods using WinNonlin Professional™ V.3.1.

A two-way ANOVA was used to investigate the effects of gender and age on the Day 7 percent change from baseline in serum urate $C_{mean,24}$. Age was treated as a categorical variable with subjects either in the younger (18-40 years) or the older (≥65 years) age categories.

When the main effect for gender was statistically significant for a parameter, analyses of covariance (ANCOVAs) were performed to explore the explanatory value of body weight and $AUC_{24,u}$ by including them as continuous variables in the statistical model.

Pharmacokinetic Results:

Protein Binding

[^{14}C]TMX-67 was highly bound to plasma proteins in all subjects, with the mean fraction unbound (f_u) in plasma determined to be 0.007, corresponding to a mean protein binding value of 99.3%. The observed differences of the mean fraction unbound between older and younger subjects or between male and female subjects were minimal.

Plasma PK Profiles

Predose TMX-67 plasma concentrations on Days 1-7 were shown in Figure 1. Steady-state appeared to be reached on Day 7.

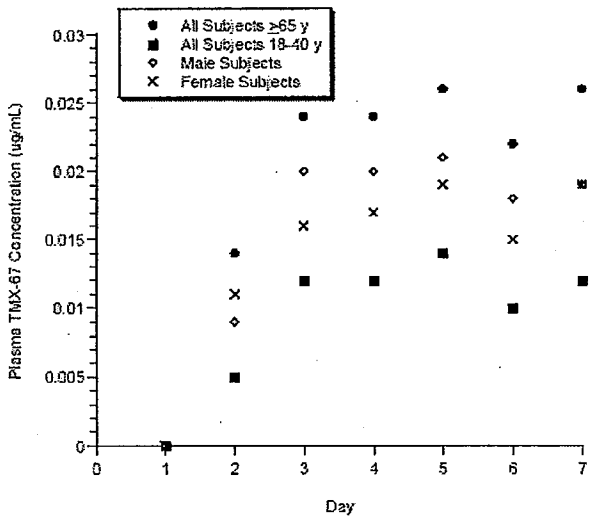

Figure 1. Mean TMX-67 Pre-dose Plasma Concentrations Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days to Subjects in Study TMX-01-016.

Plasma concentration-time profiles for TMX-67 in subjects based on age are shown in Figure 2. Plasma concentration-time profiles for TMX-67 in subjects based on gender are shown in Figure 3.

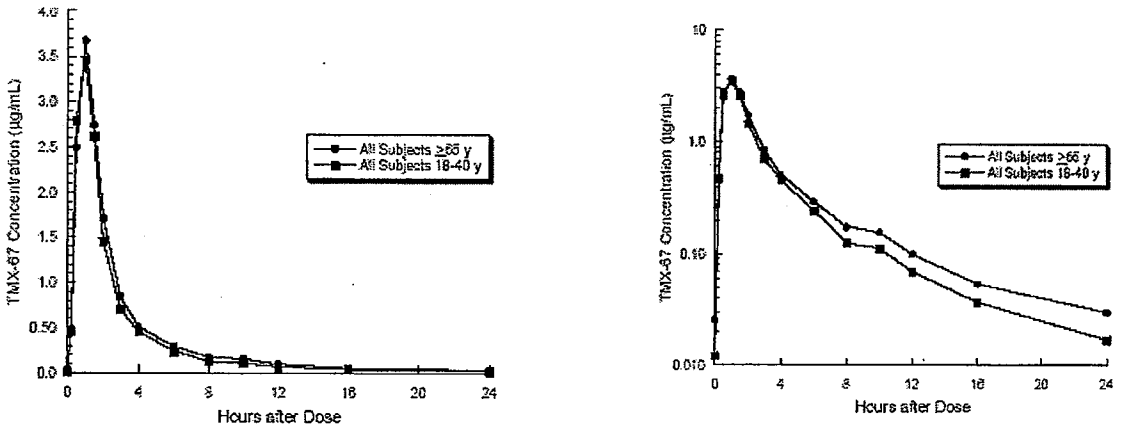

Figure 2. Mean TMX-67 Plasma Concentration-Time Profiles on Day 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for Seven Days to Subjects Aged 18-40 and ≥65 Years in Study TMX-01-016 (Left: Linear scale; Right: Semi-log scale).

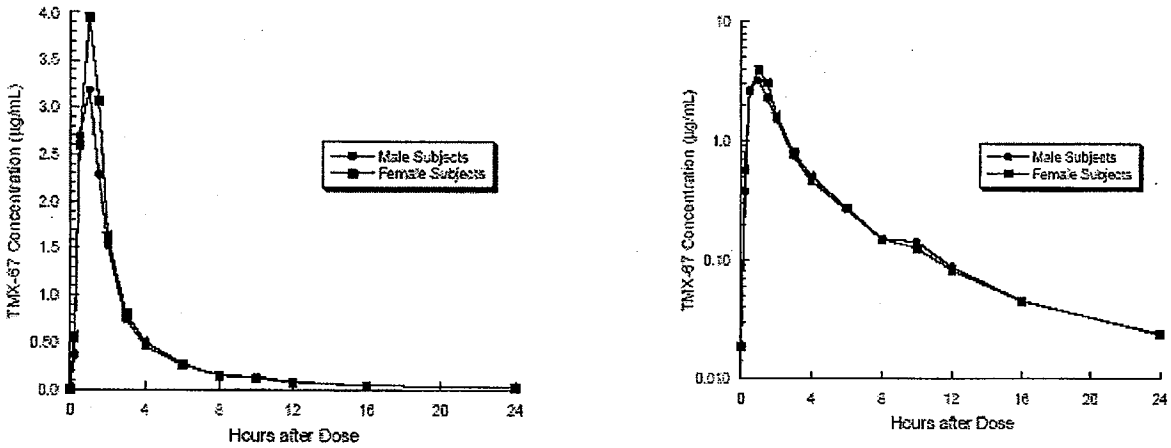

Figure 3. Mean TMX-67 Plasma Concentration-Time Profiles on Day 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for Seven Days to Subjects in Study TMX-01-016 (Left: Linear scale; Right: Semi-log scale).

A summary of TMX-67 and unbound TMX-67 plasma pharmacokinetic parameter estimates for subjects based on age or gender on Day 7 following administration of a daily 80 mg oral dose of TMX-67 for 7 days is presented in Table 2.