

Table 2. Mean TMX-67 Plasma Pharmacokinetic Parameters on Day 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for Seven Days.

	t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	$C_{max,c}$ (ng/mL)	AUC_{24} ($\mu\text{g}\cdot\text{h/mL}$)	$AUC_{24,u}$ ($\text{ng}\cdot\text{h/mL}$)	$t_{1/2}$ ^a (h)	CL_r/F (L/h)	$CL_{r,c}/F$ (L/h)
Subjects 18-40 years old (N=24)								
Mean	0.94	4.0803	27.9306	8.1550	55.5561	6.2 (5.3)	10.72	1594.63
SD	0.37	1.6184	11.9258	2.6930	18.9019	2.6	3.17	509.55
Subjects ≥ 65 years old (N=24)								
Mean	0.99	4.0460	27.1805	9.1275	61.0854	7.2 (6.4)	9.46	1453.30
SD	0.34	1.2050	9.3723	2.6297	20.3494	2.3	2.64	492.41
Male Subjects (N=24)								
Mean	0.94	3.6209	23.6206	8.1662	53.8776	6.7 (5.8)	10.83	1687.53
SD	0.37	1.4739	9.7042	2.8939	22.5220	2.7	3.31	556.90
Female Subjects (N=24)								
Mean	0.99	4.5054	31.4905	9.1163	62.7638	6.7 (5.8)	9.35	1360.41
SD	0.34	1.2212	10.1918	2.4115	15.4562	2.3	2.41	382.82

^a Arithmetic Mean (Harmonic Mean)

SD – Standard Deviation

A summary of urinary pharmacokinetic parameter estimates for TMX-67 (unchanged, free) and total (unchanged + conjugated, total) TMX-67 is presented in Table 3.

Table 3. Mean TMX-67 Urinary Excretion and Renal Clearance on Day 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for Seven Days.

	Free			Total	
	Ae_{24} (μg)	f_e	CL_r (L/h)	Ae_{24} (μg)	f_e
Subjects 18-40 years old (N=24)					
Mean	1342	0.017	0.17	28422	0.355
SD	1815	0.023	0.20	7546	0.094
Subjects ≥ 65 years old (N=24)					
Mean	1280	0.016	0.15	28986	0.362
SD	1140	0.014	0.15	6337	0.079
Male Subjects (N=24)					
Mean	1241	0.016	0.17	28003	0.350
SD	779	0.010	0.11	6933	0.087
Female Subjects (N=24)					
Mean	1381	0.017	0.16	29406	0.368
SD	1995	0.025	0.23	6940	0.087

SD – Standard Deviation

Table 4. Comparison of Geometric Mean Ratios and Confidence Intervals for TMX-67 Total and Unbound C_{max} and AUC_{24} Following Administration of TMX-67 (80 mg) for 7 days. (Reviewer's Analysis)

Parameter	Group	Geometric Mean	Ratio	90%CI
C_{max} ($\mu\text{g/mL}$)	Gender			
	All Male	3.346	129.7	(109.3, 153.9)
	All Female	4.34		
	Age			
All Young	3.772	102.1	(85.03, 122.54)	
All Old	3.85			
AUC_{24} ($\mu\text{g}\cdot\text{h/mL}$)	Gender			
	All Male	7.749	113.9	(98.87, 131.26)
	All Female	8.828		
	Age			
All Young	7.788	112.8	(97.82, 130.01)	
All Old	8.783			
$C_{max,u}$ (ng/mL)	Gender			
	All Male	21.71	137.75	(114.35, 165.93)
	All Female	29.91		
	Age			
All Young	25.54	99.57	(81.33, 121.9)	
All Old	25.43			
$AUC_{24,u}$ ($\text{ng}\cdot\text{h/mL}$)	Gender			
	All Male	50.29	120.99	(103.7, 141.12)
	All Female	60.84		
	Age			
All Young	52.74	110	(93.81, 128.99)	
All Old	58.01			

Table 5a. P-values from ANOVA for TMX-67 Pharmacokinetic Parameters from Study TMX-01-016

Parameter	ANOVA P-Values		
	Age Category	Gender	Age \times Gender Interaction
t_{max}	0.636	0.636	0.468
$\ln(C_{max})$	0.845	0.016	0.898
$\ln(C_{max,u})$	0.969	0.006	0.248
$\ln(AUC_{24})$	0.161	0.129	0.898
$\ln(AUC_{24,u})$	0.298	0.041	0.163
λ_z	0.079	0.931	0.243

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

Table 5b. P-values from ANCOVA with Gender Effects for $\ln(C_{max})$, $\ln(C_{max,u})$ and $\ln(AUC_{24,u})$ from Study TMX-01-016

Parameter	P-values		
	ANOVA	ANCOVA with BW as Covariate	
	Gender ^a	BW	Gender
$\ln(C_{max})$	0.016	0.212	0.124
$\ln(C_{max,u})$	0.006	0.258	0.058
$\ln(AUC_{24,u})$	0.041	0.014	0.493

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

^a P-values from two-way ANOVA

Effect of Gender on TMX-67 Exposure

Maximal observed plasma concentrations of total and unbound TMX-67 on Day 7 following administration of daily 80 mg oral doses of TMX-67 for seven days were 30% and 38% higher in female subjects than in male subjects, respectively (Table 4). Likewise, the extent of plasma exposure of total and unbound TMX-67 was approximately 14% and 21% higher in female subjects (Table 4). The differences observed for the mean TMX-67 $\ln(C_{max})$, $\ln(C_{max,u})$, and $\ln(AUC_{24,u})$ values were statistically significant between male and female subjects ($p \leq 0.05$, Table 5a). However, for all three parameters, the p-values for testing the gender effect as well as the weight effect were not significant ($p > 0.05$) when body weight was included as a covariate in the model (Table 5b). These results indicated that the differences in mean TMX-67 $\ln(C_{max})$, $\ln(C_{max,u})$ and $\ln(AUC_{24,u})$ between males and females were likely related to differences in body weight and not to gender differences alone. Mean body weight for male subjects were 81 kg and for female subjects were 68 kg (18% higher for male subjects).

Elimination of free and total TMX-67 from plasma by renal excretion was similar in male and female subjects (Table 3). Urinary excretion of TMX-67 on Day 7 following administration of daily 80 mg oral doses of TMX-67 for seven days accounted for an average of 1.6% and 1.7% of the administered dose for male and female subjects, respectively. Urinary excretion of total TMX-67 accounted for an average of 35.0% and 36.8% of the administered dose in males and females, respectively. The renal clearance of TMX-67 was only 6% lower in female subjects, with mean Cl_r values of 0.17 L/h for males and 0.16 L/h for females.

Effect of Age on TMX-67 Exposure

Maximal observed plasma concentrations of total and unbound TMX-67 on Day 7 following administration of daily 80 mg oral doses of TMX-67 for seven days were similar between young (18-40 years) and old subjects (≥ 65 years) (Table 4). The extent of plasma exposure of total and unbound TMX-67 was approximately 13% and 10% higher in older subjects (age ≥ 65 yr) than younger subjects (18-40 yr) (Table 4). The differences observed for the mean TMX-67 $\ln(C_{max})$, $\ln(C_{max,u})$, $\ln(AUC_{24})$, and $\ln(AUC_{24,u})$ values were not statistically significant between old and young subjects ($p > 0.05$, Table 5a).

Elimination of free and total TMX-67 from plasma by renal excretion was generally similar in subjects aged 18-40 years and ≥ 65 years (Table 3). Urinary excretion of free TMX-67 on Day 7 following administration of daily 80 mg oral doses of TMX-67 for seven days accounted for an average of 1.7% and 1.6% of the administered dose for subjects aged 18-40 years and ≥ 65 years, respectively. In these same age groups, urinary excretion of total TMX-67 accounted for an average of 35.5% and 36.2% of the administered dose. The renal clearance of TMX-67 in older

subjects was about 12% lower than the renal clearance of younger subjects, with mean Cl_r values of 0.17 L/h for subjects 18-40 years and 0.15 L/h for subjects ≥65 years.

TMX-67 Metabolites PK

Data for metabolites were included in the Appendix (Tables A2 and A3). 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. Age and gender appeared to have minimal 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 4. It appears that steady-state was reached on Day 7 except for hypoxanthine which showed an increase in predose concentration on Day 7.

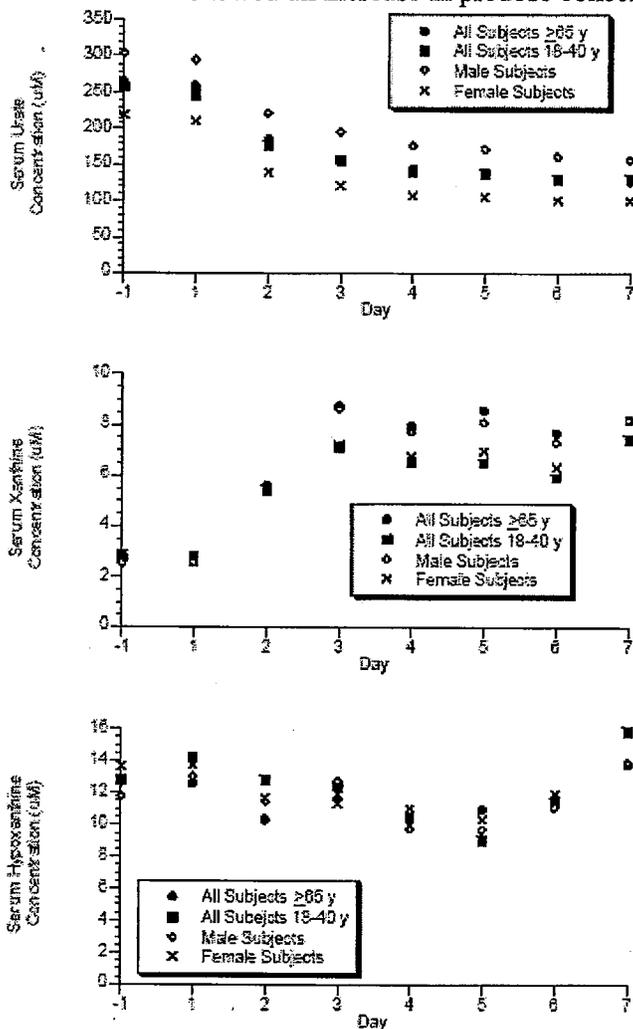


Figure 4. Mean Pre-dose Serum Urate, Xanthine, and Hypoxanthine Concentrations on Days -1 to 8 Following Administration of Daily 80 mg Oral Doses of TMX-67 on Days 1 to 7 to Subjects with Normal or Impaired Hepatic Function.

A summary of serum $C_{\text{mean},24}$ 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 6.

Table 6. Mean Serum Urate, Xanthine, and Hypoxanthine $C_{\text{mean},24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of Daily 80 mg Oral Doses of TMX-67 for Seven Days to Subjects in Study TMX-01-016.

	Urate			Xanthine		Hypoxanthine	
	$C_{\text{mean},24}$ (mg/dL)		% Change	$C_{\text{mean},24}$ (mg/dL)		$C_{\text{mean},24}$ (mg/dL)	
	Day -1	Day 7	Day 7	Day -1	Day 7	Day -1	Day 7
Subjects 18-40 years old (N=24)							
Mean	4.107	1.887	-54.89	0.0393	0.1327	0.1919	0.1871
SD	1.112	0.680	7.51	0.0116	0.0197	0.0467	0.0266
Subjects ≥65 years old (N=24)							
Mean	4.277	1.895	-56.15	0.0371	0.1548	0.1619	0.1618
SD	1.052	0.694	9.28	0.0077	0.0393	0.0384	0.0376
Male Subjects (N=24)							
Mean	4.879	2.362	-51.75	0.0379	0.1564	0.1797	0.1640
SD	0.952	0.595	7.02	0.0064	0.0362	0.0507	0.0296
Female Subjects (N=24)							
Mean	3.505	1.420	-59.29	0.0385	0.1311	0.1742	0.1849
SD	0.683	0.356	8.03	0.0125	0.0233	0.0392	0.0368

SD – Standard Deviation

A summary of urinary $C_{\text{mean},24}$, A_{e24} , 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 7.

Table 7. Summary of 24-Hour Mean Concentration ($C_{\text{mean},24}$), Mean Renal Clearance (Cl_r) and Total Daily Urinary Excretion (A_{e24}) of Uric Acid in Urine on Days -1 and 7 Following Administration of Daily 80 mg Oral Doses of TMX-67 for Seven Days to Subjects in Study TMX-01-016

Uric Acid:

	$C_{\text{mean},24}$ (mg/dL)			A_{e24} (mg)		Cl_r (mL/min)	
	Day -1	Day 7	%Change	Day -1	Day 7	Day -1	Day 7
All Subjects 18-40 years old (N=24)							
Mean	9.492	5.099	-28.23	262.05	101.77	4.63	3.99
SD	6.739	3.558	71.40	118.04	51.27	2.22	2.19
All Subjects ≥65 years old (N=24)							
Mean	10.787	3.595	-63.46	273.10	84.76	4.76	3.23
SD	7.241	2.434	27.01	134.36	48.21	3.62	1.97
Male Subjects (N=24)							
Mean	12.786	5.672	-45.75	321.06	119.23	4.94	3.70
SD	7.796	3.022	43.13	136.20	45.68	3.66	1.78
Female Subjects (N=24)							
Mean	7.494	3.022	-46.67	214.09	67.30	4.45	3.52
SD	4.830	3.640	66.77	86.78	40.13	2.13	2.40

SD – Standard Deviation

Reviewer's Note: The mean percent decrease in the younger subjects may have been underestimated due to a single subject (Subject 123, female) whose value (a 240% increase from baseline Day -1 values) appeared to be an outlier as compared to the median value for the category (-51.83%).

Xanthine:

	C _{mean,24} (mg/dL)		Ae ₂₄ (mg)		Cl _r (mL/min)	
	Day -1	Day 7	Day -1	Day 7	Day -1	Day 7
Subjects 18-40 years old (N=24)						
Mean	0.1890	6.0125	5.29	123.25	9.98	65.60
SD	0.1404	3.5006	2.93	37.48	5.61	22.36
Subjects ≥65 years old (N=24)						
Mean	0.1918	5.2659	4.97	130.10	9.46	61.52
SD	0.1293	1.7294	2.84	25.09	5.43	20.91
Male Subjects (N=24)						
Mean	0.2114	5.7115	5.35	124.51	10.18	56.64
SD	0.1399	2.3395	2.81	32.12	5.28	16.30
Female Subjects (N=24)						
Mean	0.1694	5.3669	4.91	128.84	9.27	70.49
SD	0.1262	3.1704	2.95	31.90	5.74	24.08

SD – Standard Deviation

Hypoxanthine:

	C _{mean,24} (mg/dL)		Ae ₂₄ (mg)		Cl _r (mL/min)	
	Day -1	Day 7	Day -1	Day 7	Day -1	Day 7
Subjects 18-40 years old (N=24)						
Mean	0.1663	1.2076	4.59	23.93	1.70	9.33
SD	0.1433	0.8695	3.74	10.60	1.34	5.02
Subjects ≥65 years old (N=24)						
Mean	0.1333	0.8436	3.49	20.93	1.62	9.47
SD	0.1088	0.3296	2.45	5.61	1.19	3.51
Male Subjects (N=24)						
Mean	0.2093	1.1988	5.50	25.57	2.23	11.11
SD	0.1339	0.7492	3.24	9.60	1.25	4.46
Female Subjects (N=24)						
Mean	0.0903	0.8524	2.57	19.29	1.09	7.70
SD	0.0872	0.5566	2.36	5.99	0.99	3.40

SD – Standard Deviation

Table 8. P-values from ANOVA for Percent Change in Serum Urate C_{mean,24} from Day -1 to Day 7 in Study TMX-01-016.

Parameter	ANOVA P-Values		
	Age Category	Gender	Age*Gender Interaction
%Change	0.572	0.001	0.912

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

Effect of Gender and Age on Serum Urate, Xanthine, and Hypoxanthine C_{mean,24}

The mean percent decrease from baseline in C_{mean,24} values for serum urate was slightly higher in females (59%) as compared to males (52%) (Table 6). The difference in the percent decrease of serum urate concentrations at 24 hour from Day -1 to Day 7 between the genders was statistically

significant ($p \leq 0.05$), but not between age groups (Table 8). Using weight or $AUC_{24,u}$ as a covariate, the difference in the percent decrease from baseline in serum urate $C_{mean,24}$ values between genders remained statistically significant as a linear relationship of weight or $AUC_{24,u}$ did not substantially account for the difference between genders observed for this parameter (data not shown). It should be noted, however, the mean baseline for serum urate $C_{mean,24}$ was lower by 1.374 mg/dL in female subjects as compared to male subjects. Although a higher % reduction in serum uric acid was observed in female subjects, the magnitude of uric acid reduction did not differ much between female and male subjects. Therefore, the difference in % reduction was not considered significant as it was related to the differing baseline used in the calculation.

The increase in serum xanthine $C_{mean,24}$ was slightly lower in younger subjects as compared to older subjects, and in female subjects as compared to male subjects. There appeared to be no substantial change in serum hypoxanthine in either age category, and male or female subjects after multiple dosing with TMX-67.

Discussion and Conclusion:

Gender: The plasma exposure to TMX-67 was greater in female subjects compared to male subjects following the administration of daily 80 mg oral doses of TMX-67 for 7 days. An average of 35% and 15% increase was observed for C_{max} and AUC_{24} in female subjects. Part of the difference could be accounted for by lower body weight for female subjects. The percent decrease in serum urate was also slightly greater in females as compared to males (59% vs. 52%) which was not accounted for by either body weight or $AUC_{24,u}$ of serum urate. It should be noted, however, that the baseline uric acid levels were also lower in female subjects. Although a higher % reduction was observed in female subjects, the magnitude of uric acid reduction did not differ much between female and male subjects. Therefore, the difference in % reduction was not considered significant as it was related to the differing baselines used in the calculation. No dose adjustment would be necessary based on gender differences.

Age: The plasma exposure to TMX-67 was similar between subjects 18-40 years and subjects ≥ 65 years following the administration of daily 80 mg oral doses of TMX-67 for 7 days. In addition, the percent decrease in serum urate was also similar between different age groups 18-40 years and ≥ 65 years (55% vs. 56%). Therefore, the pharmacokinetics and pharmacodynamics of TMX-67 did not appear to be substantially affected by age. As a result, no dose adjustment would be recommended based on differences in age.

Appendix.

Table A1. Summary of Race/Ethnicity, Age, Weight and Height Distribution for Subjects.

Demographic Characteristic	Males		Females	
	18-40 Years Old (N=12)	≥ 65 Years Old (N=12)	18-40 Years Old (N=12)	≥ 65 Years Old (N=12)
Race				
Black	1 (8%)	1 (8%)	0	1 (8%)
Caucasian	1 (8%)	6 (50%)	0	3 (25%)
Hispanic	10 (83%)	5 (42%)	12 (100%)	8 (67%)
Age (years)#				
18-29	4 (33%)	0	5 (42%)	0
30-40	8 (67%)	0	7 (58%)	0
65-69	0	3 (25%)	0	9 (75%)
≥70	0	9 (75%)	0	3 (25%)
Mean (SD)	30.8 (6.99)	71.7 (3.45)	32.8 (6.87)	68.2 (2.86)
Range	19-40	65-76	22-40	65-74
Weight (pounds)#				
Mean (SD)	174.8 (27.60)	180.2 (21.20)	147.5 (27.06)	153.3 (23.92)
Range	134-215	137-205	114-204	121-194
Height (inches)#				
Mean (SD)	67.5 (2.68)	67.9 (2.31)	62.3 (1.86)	61.3 (2.06)
Range	63-72	64-72	59-65	57-64

At baseline.

Table A2. 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

67M-1:

	t_{max} (h)	C_{max} (ng/mL)	AUC_1 (ng·h/mL)	AUC_{24} (ng·h/mL)	$t_{1/2}^a$ (h)	67M-1/TMX-67 AUC Ratio
Subjects 18-40 years old (N=24)						
Mean	1.37	85.256	224.044	225.410	7.6 (6.6)	0.029
SD	0.33	29.941	63.153	63.133	3.6	0.007
Subjects ≥65 years old (N=24)						
Mean	1.38	80.744	264.846	265.268	7.2 (6.7)	0.029
SD	0.40	28.580	84.495	84.136	1.9	0.006
Male Subjects (N=24)						
Mean	1.35	73.472	224.348	225.092	7.6 (6.7)	0.029
SD	0.38	26.008	68.451	67.942	3.4	0.008
Female Subjects (N=24)						
Mean	1.29	92.528	264.542	265.586	7.2 (6.6)	0.029
SD	0.36	29.291	80.423	80.136	2.3	0.005

^a Arithmetic Mean (Harmonic Mean)

SD - Standard Deviation

67M-2:

	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	AUC_{24} (ng-h/mL)	$t_{1/2}^a$ (h)	67M-2/TMX-67 AUC Ratio
Subjects 18-40 years old (N=24)						
Mean	1.33	65.940	228.328	229.113	9.0 (6.9)	0.030
SD	0.32	21.881	76.128	76.061	5.9	0.009
Subjects ≥65 years old (N=24)						
Mean	1.67	58.436	242.878	242.878	8.9 (8.1)	0.028
SD	0.35	18.511	68.651	68.651	3.0	0.009
Male Subjects (N=24)						
Mean	1.52	60.696	239.728	239.942	9.6 (7.7)	0.031
SD	0.43	23.913	81.457	81.355	5.8	0.010
Female Subjects (N=24)						
Mean	1.48	63.679	231.478	232.049	8.4 (7.3)	0.026
SD	0.31	16.564	62.835	62.818	3.2	0.006

^a Arithmetic Mean (Harmonic Mean)
SD - Standard Deviation

67M-4:

	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	AUC_{24} (ng-h/mL)	$t_{1/2}^a$ (h)	67M-4/67M-1 AUC Ratio
Subjects 18-40 years old (N=24)						
Mean	1.65	61.217	234.766	234.766	11.0 (9.1)	1.051
SD	0.31	22.974	76.666	76.666	6.7	0.238
Subjects ≥65 years old (N=24)						
Mean	1.81	58.929	269.557	269.687	10.0 (8.8)	1.017
SD	0.38	22.662	125.341	125.166	3.6	0.272
Male Subjects (N=24)						
Mean	1.71	52.017	223.258	223.388	11.0 (9.2)	1.013
SD	0.33	17.019	70.213	69.990	6.5	0.228
Female Subjects (N=24)						
Mean	1.75	68.129	281.065	281.065	10.0 (8.8)	1.055
SD	0.39	24.880	124.684	124.684	4.0	0.280

^a Arithmetic Mean (Harmonic Mean)
SD - Standard Deviation

Table A3. 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

67M-1:

	Free			Total	
	Ae_{24} (μg)	f_e	Cl_r (L/h)	Ae_{24} (μg)	f_e
Subjects 18-40 years old (N=24)					
Mean	3533	0.042	16.17	4762	0.057
SD	1089	0.013	4.46	1308	0.016
Subjects ≥65 years old (N=24)					
Mean	2975	0.035	11.70	4147	0.049
SD	1030	0.012	3.95	1262	0.015
Male Subjects (N=24)					
Mean	2826	0.034	13.38	3947	0.047
SD	1053	0.013	5.53	1149	0.014
Female Subjects (N=24)					
Mean	3683	0.044	14.49	4962	0.059
SD	959	0.011	3.85	1281	0.015

SD - Standard Deviation

67M-2:

	Free			Total	
	Ae ₂₄ (µg)	f _e	Cl _r (L/h)	Ae ₂₄ (µg)	f _e
Subjects 18-40 years old (N=24)					
Mean	2904	0.035	13.13	3514	0.042
SD	898	0.011	3.16	773	0.009
Subjects ≥65 years old (N=24)					
Mean	2194	0.026	9.30	2762	0.033
SD	728	0.009	2.72	804	0.010
Male Subjects (N=24)					
Mean	2342	0.030	11.11	3180	0.038
SD	1040	0.012	4.09	969	0.012
Female Subjects (N=24)					
Mean	2557	0.030	11.31	3096	0.037
SD	720	0.009	2.89	773	0.009

SD - Standard Deviation

67M-4:

	Free			Total	
	Ae ₂₄ (µg)	f _e	Cl _r (L/h)	Ae ₂₄ (µg)	f _e
Subjects 18-40 years old (N=24)					
Mean	2144	0.024	9.30	2294	0.026
SD	778	0.009	2.40	841	0.010
Subjects ≥65 years old (N=24)					
Mean	1846	0.021	7.40	2097	0.024
SD	676	0.008	2.18	693	0.008
Male Subjects (N=24)					
Mean	1845	0.021	8.44	2059	0.023
SD	759	0.009	2.63	789	0.009
Female Subjects (N=24)					
Mean	2145	0.024	8.26	2332	0.026
SD	697	0.008	2.34	739	0.008

SD - Standard Deviation

4.2.4 Food Effect Studies

4.2.4.1 Study C02-036: A Phase 1, Multiple-Dose Study: Pharmacokinetics and Pharmacodynamics of Febuxostat Under Fasting or Non-Fasting Conditions in Healthy Subjects

Study Period: December 18, 2002 to January 13, 2003

Sample Analysis Period: January 21, 2003 to February 26, 2003

Principle Investigator:

Study Center:

Analytical Sites:

/ / /

b(4)

Objective: To determine the effect of food on pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects following once daily multiple oral dosing with 80 mg of febuxostat for 6 days.

(Reviewer's Note: Per FDA guidance, the food effect study usually is conducted after a single dose. In this study, the Sponsor chose to conduct multiple dose study to assess the effect of food not only on pharmacokinetics but also on pharmacodynamics at steady-state.)

Study Design: This was a Phase I, single center, open-label, multiple-dose, randomized, two-period crossover study involving 24 subjects who received multiple 80 mg QD doses of febuxostat for 6 days in each period. Subjects were randomized to one of two regimen sequences. Subjects in Regimen Sequence I received Regimen A (fasting) in Period 1 and Regimen B (non-fasting) in Period 2. Subjects in Regimen Sequence II received Regimen B in Period 1 and Regimen A in Period 2. A 16-day interval separated the last dose of Period 1 from the first dose of Period 2.

Subjects were dosed from Day 1 to Day 6 of each period. Each subject received one 80 mg tablet of febuxostat with 240 mL of water each morning for 6 consecutive days in each period. Subjects under the non-fasting regimen received febuxostat approximately 30 minutes after a high fat meal. FDA recommended high fat breakfast was used. Subjects under the fasting (at least 10 hours) regimen did not receive breakfast on dosing days.

Twenty-four males and females were enrolled in Study C02-036. Twenty-three of the subjects (14 males and 9 females) completed the study. Subject 105 discontinued due to personal reason prior to dosing in Period 2. The mean age of the 23 subjects was 39 years (range: 20-55 years), the mean weight was 77.4 kg (range: 50.4-103.5 kg), and the mean height was 172.5 cm (range: 154.9-190.5 cm). Of the 23 subjects, 15 were Caucasian, 5 were Black, 2 were Hispanic, and 1 was Asian.

Test Articles:

80 mg febuxostat tablets (Abbott Formulation B1 80 mg tablet, Lot No. 86-064-4Q) _____
batch)

b(4)

Sample Collection: In each period, blood samples (7 mL) for the determination of febuxostat plasma concentrations were obtained in EDTA tubes on Day 6 at 0 (pre-dose), 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after febuxostat administration. The plasma samples were frozen at a nominal temperature of -20°C until analyzed.

In each period, venous blood samples for the determination of serum urate were obtained in specimen tubes on Day -1 at 24, 18 and 12 hours prior to dosing, and on Day 6 at 0 (pre-dose), 6, 12 and 24 hours post-dose. On Days 1 through 5, 0 hour (pre-dose) samples were obtained in both periods.

Sample Analysis: Concentrations of febuxostat in plasma were determined at _____
_____ using a validated high performance liquid chromatographic method

b(4)

(— Project 23150_1) with fluorescence detection. The lower limit of quantitation with a 0.5 mL plasma sample was 10 ng/mL for febuxostat.

Serum samples were analyzed at the _____ for uric acid according to _____ system method. The measurement of uric acid concentrations was performed by an enzymatic method with a colorimetric assay using a quinone di-irnine dye. The analytical range of this method was between 0.5 and 12 mg/dL. Manufacturer standards were used for calibration. Two levels of internal quality controls were run with each batch, and then assessed based upon an in-house SOP.

b(4)

Pharmacokinetic, Pharmacodynamic and Statistical Analysis: Pharmacokinetic parameters for febuxostat in plasma were determined by standard noncompartmental methods using WinNonlin® Professional V.3.1 computer software package (Pharsight Corporation, Mountain View, CA).

Pharmacodynamic parameters were estimated using serum urate concentration values. The pharmacodynamic parameters that were estimated included the 24-hour mean serum urate concentration ($C_{\text{mean}, 24}$) on both Day -1 and Day 6 of each period and the percent change of $C_{\text{mean}, 24}$ from baseline (Day -1) to Day 6 of each period.

Within the framework of the ANOVA model, the bioavailability of febuxostat under non-fasting conditions relative to fasting conditions was assessed by point estimates and 90% confidence intervals for the ratios of central values for C_{max} , AUC_t and AUC_{∞} . A conclusion of *no effect* of food on the pharmacokinetics of febuxostat was to be made if the 90% confidence intervals were completely contained within the interval (0.80, 1.25) for C_{max} , AUC_t , and AUC_{∞} .

Pharmacokinetic Results:

Plasma PK Profiles

The mean plasma concentration versus time profiles for febuxostat on linear and log-linear scales are shown in Figure 1.

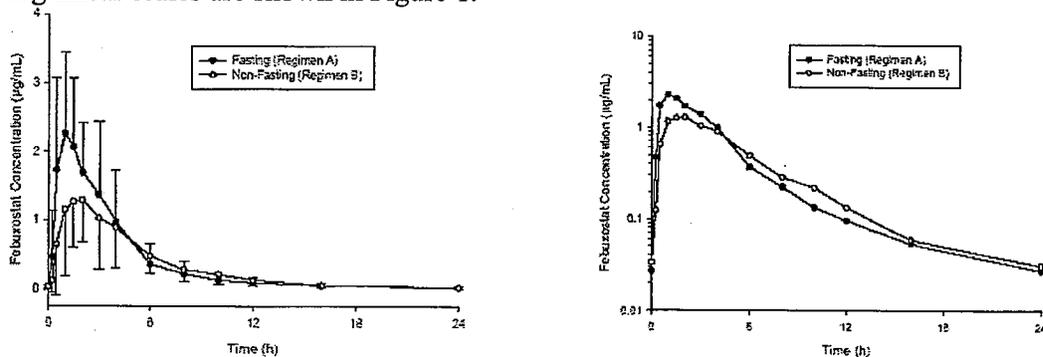


Figure 1. Mean Plasma Concentration-Time Profiles (Linear (□SD), Left and Log-Linear Format, Right) of Febuxostat Following Once Daily Multiple Oral Dosing with 80 mg of Febuxostat Under Fasting (Regimen A) or Non-Fasting (Regimen B) Conditions on Day 6 in Healthy Subjects.

Pharmacokinetic parameter estimates for febuxostat under fasting and non-fasting conditions are presented in Table 1.

Table 1. Summary of Pharmacokinetic Parameter Estimates for Febuxostat on Day 6 Following Once Daily Multiple Oral Dosing with 80 mg of Febuxostat Under Fasting or Non-Fasting Conditions in Healthy Subjects.

Regimen		t_{max} (h)	C_{max} ($\mu\text{g}/\text{mL}$)	AUC_t ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC_{24} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	$t_{1/2}^a$ (h)	Cl/F (L/h)	MRT (h)	$V_{w/F}$ (L)
Fasting	N	23	23	23	23	23	23	23	23
	Mean	1.63	3.2560	9.1941	9.2109	6.8 (5.9)	9.81	4.7	44.8
	SD	1.11	0.8403	3.6013	3.5886	2.7	3.42	1.3	19.9
Non-Fasting	N	23	23	23	23	23	23	23	23
	Mean	1.78	1.8004	7.6747	7.6747	5.9 (5.6)	11.88	6.0	71.7
	SD	1.03	0.8458	3.2914	3.2914	1.6	4.06	1.3	30.4

^a Arithmetic (Harmonic) mean

Following administration of febuxostat under non-fasting conditions (high fat meal), the t_{max} was delayed by approximately 10 minutes as compared to that under fasting conditions; however, this difference was not statistically significant ($p > 0.05$). Statistically significant differences ($p \leq 0.05$) between the means of the fasting and non-fasting regimens were observed for the natural logarithm of febuxostat C_{max} and AUC_{24} .

Ingestion of a high-fat meal did not appear to affect the apparent terminal phase elimination half-life ($t_{1/2}$) of febuxostat, and hence, a high-fat meal did not appear to affect the apparent elimination rate constant of febuxostat. The apparent volume of distribution of febuxostat appeared to increase by approximately 60% due to the increase in the oral clearance (Cl/F) estimation and the increase in the mean residence time (MRT) of febuxostat.

Relative Bioavailability

The point estimates and 90% confidence intervals for the ratio of the central values for C_{max} and AUC_{24} in the non-fasting regimen, relative to the fasting regimen, are presented in Table 2.

Table 2. Bioavailability of Febuxostat Under Non-fasting Conditions, Relative to Fasting Conditions.

Parameter	Point Estimate	90% Confidence Interval
C_{max}	0.512	(0.440 - 0.595)
AUC_{24}	0.824	(0.782 - 0.870)

There was a 49% decrease in mean C_{max} and an 18% decrease in mean AUC_{24} following administration of febuxostat 80 mg under the non-fasting conditions as compared to those under the fasting conditions. The 90% confidence intervals, for the ratio of the regimen central values, extended below the 0.80-1.25 range for both C_{max} and AUC_{24} .

Pharmacodynamic Results:

Steady-State

The mean pre-dose serum urate concentrations after febuxostat administration under fasting and non-fasting conditions are presented in Table 3. Based on the mean pre-dose serum urate

concentration data following once daily multiple dosing with febuxostat 80 mg, it appears that serum urate had reach its steady state by Day 4.

Table 3. Summary of Pre-dose Serum Urate Concentrations Prior to Oral Administration of an 80 mg Dose of Febuxostat to Healthy Subjects Under Fasting and Non-Fasting Conditions in Study C02-036.

Treatment		Pre-dose Serum Urate Concentration (mg/dL)						
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Fasting	Mean	5.096	3.787	3.243	2.896	3.030	2.952	2.883
	SD	1.560	1.592	1.572	1.442	1.349	1.382	1.419
	CV%	31	42	48	50	45	47	49
Non-Fasting	Mean	5.274	3.670	2.991	2.587	2.730	2.639	2.504
	SD	1.583	1.502	1.378	1.250	1.201	1.134	1.084
	CV%	30	41	46	48	44	43	43

Serum Urate Levels

The mean serum urate $C_{mean,24}$ estimates on Days -1 and 6, and its percent change from the baseline (Day -1) to Day 6 for each regimen are presented in Table 4.

Table 4. Summary of Mean Serum Urate $C_{mean,24}$ 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.

Treatment		$C_{mean,24}$ (mg/dL)		% Change from Baseline
		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	1.065	12.00

There was about 7% greater percent decrease in serum urate under non-fasting conditions than that under fasting conditions, and this difference was statistically significant ($p \leq 0.05$). This small difference in the pharmacodynamic effect of febuxostat was not considered clinically significant, even though it was statistically significant. This slight increase in effect was in spite of the decrease in the peak and total plasma exposure to febuxostat under non-fasting as compared to fasting conditions. As shown in Figure 1, although fed conditions resulted in decrease in peak and total exposure to febuxostat, exposure was higher in the 6 to 24 hour time interval under non-fasting conditions as compared to fasting conditions. Therefore, the concentrations of febuxostat under non-fasting conditions were higher than those under fasting conditions for a longer period of time. It is likely that the change in febuxostat plasma profile when administered under non-fasting condition may have contributed to this slightly higher percent decrease in serum urate despite lower peak and total plasma exposures to febuxostat under non-fasting conditions as compared to fasting conditions.

Discussion and Conclusion:

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. However, the lower rate and extent of absorption of febuxostat under non-fasting conditions was not accompanied by a diminished pharmacodynamic effect. Indeed, the percent decrease from baseline in serum urate $C_{mean,24}$ on Day 6 was slightly greater under non-fasting conditions (58.5%) than that under fasting conditions (51.2%). This small difference in the pharmacodynamic effect of febuxostat was not considered clinically significant, even though it was statistically significant. Based on the pharmacokinetic and pharmacodynamic results from this study, febuxostat can be administered without regard to meal intake.

4.2.4.2 Study C03-054: A Phase 1 Study to Assess the Effect of Food on the Pharmacokinetics of Febuxostat Following a Single Dose with One 120 mg Febuxostat Oral Tablet

Study Period: January 9, 2004 to January 16, 2004

Sample Analysis Period: February 13, 2004 to March 9, 2004

Principle Investigator:

Study Center:

Analytical Site:

b(4)

Objective: To determine the effect of food on the pharmacokinetics of febuxostat in healthy subjects following administration of one 120 mg oral tablet of febuxostat.

Study Design: This was a Phase 1, single-center, open-label, single-dose, randomized, two-period crossover study. Subjects were randomized to 1 of 2 regimen sequences. Subjects in Sequence 1 received Regimen A (one 120 mg febuxostat tablet administered under fasting condition) in Period 1 and Regimen B (one 120 mg febuxostat tablet administered under non-fasting condition) in Period 2 using the standard FDA high fat breakfast. Subjects in Sequence 2 received Regimen B in Period 1 and Regimen A in Period 2. A 7-day washout interval separated the dose in each period.

Twenty males and females were enrolled in Study C03-054. Nineteen of the subjects (8 males and 11 females) completed the study and they were included in the pharmacokinetic analysis. Subject 101 discontinued prior to receiving the fasting regimen because of an increased creatine phosphokinase (CPK) value at the admission visit for Period 2. The mean age of these 19 subjects was 36.5 years (range: 19-51 years), the mean weight was 69.3 kg (range: 55.8-86.3 kg), and the mean height was 166.4 cm (range: 149.9-177.8 cm). Of the 19 subjects that completed, 15 were Hispanic, 2 were Black and 2 were Caucasian.

Test Articles:

120 mg febuxostat tablets (Abbott Laboratories, Lot No. 02-077-4Q) (Abbott Formulation B1)

Sample Collection: In each period, venous blood samples (7 mL) for the determination of febuxostat plasma concentrations were obtained in EDTA tubes within 5 minutes prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after febuxostat administration.

Sample Analysis: Concentrations of febuxostat in plasma were determined at _____ using a validated high performance liquid chromatographic method (Project 23150_1) with fluorescence detection. The lower limit of quantitation with a 0.5 mL plasma sample was 10 ng/mL for febuxostat.

Pharmacokinetic and Statistical Analysis: Pharmacokinetic parameters for febuxostat in plasma were determined by standard noncompartmental methods using WinNonlin[®] Professional V.3.1 computer software package (Pharsight Corporation, Mountain View, CA).

Within the framework of the ANOVA model, the bioavailability of febuxostat under non-fasting conditions relative to fasting conditions was assessed by point estimates and 90% confidence intervals for the ratios of central values for C_{max} , AUC_t and AUC_{∞} . A conclusion of *no effect* of food on the pharmacokinetics of febuxostat was to be made if the 90% confidence intervals were completely contained within the interval (0.80, 1.25) for C_{max} , AUC_t , and AUC_{∞} .

Pharmacokinetic Results:

Plasma PK Profiles

The mean plasma concentration versus time profiles for febuxostat under fasting and non-fasting conditions on linear and log-linear scales are shown in Figure 1.

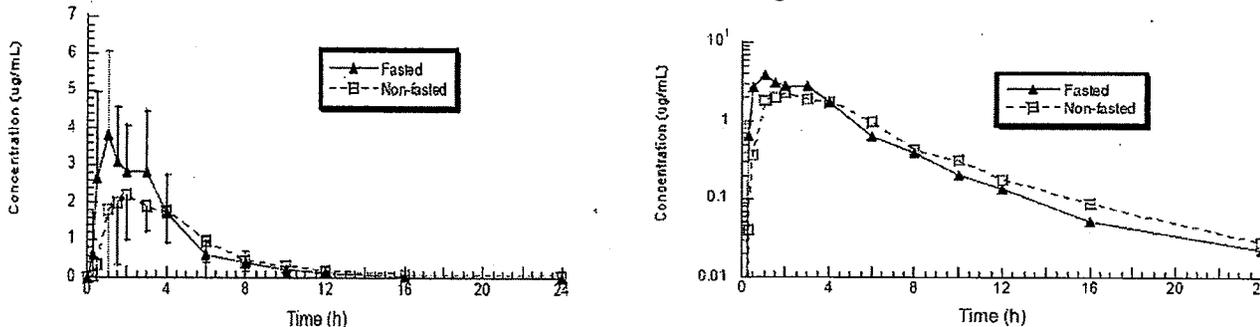


Figure 1. Mean Plasma Concentration-Time Profiles (Linear (\pm SD), Left and Log-Linear Format, Right) of Febuxostat in Healthy Subjects Following a Single 120 mg Oral Dose of Febuxostat Under Fasting and Non-Fasting Conditions in Study C03-054.

Mean pharmacokinetic parameter estimates for febuxostat under fasting and non-fasting conditions are presented in Table 1.

Table 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} ($\mu\text{g}/\text{mL}$)	AUC_t ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	$t_{1/2}^*$ (h)	Cl/F (h)	MRT (h)	V_{ss}/F (L)
A Fasting	n	19	19	19	19	19	19	19	19
	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 Non-fasting	n	19	19	19	19	19	19	19	19
	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

*Harmonic mean is in the parentheses.

Following administration of febuxostat under non-fasting conditions (high fat meal), the t_{max} was delayed by approximately 30 minutes as compared to that under fasting conditions. Statistically significant ($p \leq 0.05$) differences between the means of the fasting and non-fasting regimens were observed for natural log-transformed febuxostat pharmacokinetic parameters C_{max} , AUC_t and AUC_{∞} . The high fat meal caused an increase in mean t_{max} (~30 min), a decrease in C_{max} , AUC_t and AUC_{∞} . Ingestion of a high-fat meal did not appear to affect the apparent terminal elimination half-life of febuxostat. The apparent volume of distribution of febuxostat appeared to increase by approximately 69% due to the increase in the oral clearance (Cl/F) estimation and the increase in the mean residence time (MRT) of febuxostat with administering with food.

Relative Bioavailability

The point estimates and 90% confidence intervals for the ratio of the central values for C_{max} , AUC_t and AUC_{∞} in the non-fasting regimen, relative to the fasting regimen, are presented in Table 2.

Table 2. Bioavailability of Febuxostat Under Non-fasting Conditions, Relative to Fasting Conditions.

Parameter	Point Estimate	90% Confidence Interval
C_{max}	0.617	(0.515 - 0.738)
AUC_t	0.838	(0.782 - 0.898)
AUC_{∞}	0.843	(0.787 - 0.902)

For C_{max} , AUC_t and AUC_{∞} , the 90% confidence intervals for the relative bioavailability of febuxostat from Regimen B (one 120 mg tablet administered under non-fasting conditions) to Regimen A (one 120 mg tablet administered under fasting conditions) were not contained within the range of 0.80 and 1.25. On average, there was a 38% decrease for C_{max} , and 16% decrease for AUC_t and AUC_{∞} when administering 120 mg febuxostat tablet with food.

Discussion and Conclusion:

- Per FDA guidance, in general, the highest strength of a drug product intended to be marketed should be tested in a food effect study. This study studied food effect on the highest dose strength intended to be marketed, 120 mg tablet.
- Food decreased the rate and the extent of absorption of febuxostat. For C_{max} , AUC_t and AUC_{∞} , the 90% confidence intervals for the relative bioavailability of febuxostat under fed conditions to that under fasting conditions were not contained within the range of 0.80 and 1.25. On average, there was a 38% decrease for C_{max} , and 16% decrease for AUC_t and AUC_{∞} when administering 120 mg febuxostat tablet with food.
- Although there is a pharmacokinetic effect of food on febuxostat, the impact on pharmacodynamics may be little. Based on results from Study C02-036 (see Section 4.2.4.1), despite a decrease in the exposure to febuxostat, administering with food caused little changes in febuxostat pharmacodynamics (monitored by 24 hr serum uric acid reduction). Therefore, febuxostat may be administered without regard to food as the observed PK changes are not translated into a meaningful change in PD.

4.2.5 In Vivo Drug Interaction Studies

4.2.5.1 Study TMX-01-014: The Effect of an Antacid on the Pharmacokinetics of FEBUXOSTAT in Healthy Subjects

Study Objective

The objective of this study was to evaluate the effect of an antacid on the pharmacokinetics of FEBUXOSTAT in healthy subjects

Overall Study Design and Plan: Description

This was a Phase 1, open-label, single-center, randomized, 2-period crossover study. Twenty-four healthy adult volunteers were randomly assigned in equal numbers to 1 of 2 sequences. (An attempt was made to enroll equal numbers of each gender.)

Regimen A (80-mg [4 20-mg tablets] dose of FEBUXOSTAT with a 20-mL oral dose of antacid liquid administered (200 mg Magnesium Hydroxide and 225 mg Aluminum Hydroxide/5 mL) 5 minutes prior to FEBUXOSTAT

Regimen B (80-mg [4 20-mg tablets] dose of FEBUXOSTAT)

There was a 7-day washout between doses of the 2 periods. Subjects were confined in the Phase 1 testing facility from the afternoon of Day -1 until the morning of Day 2 for both periods. Twenty-four subjects were enrolled in the trial and completed all phases (16 females, 8 males). Interestingly 88% of the subjects were Hispanic (see below).

Demographic Characteristic	All Subjects (N=24)
Gender	
Male	10 (42%)
Female	14 (58%)
Race	
Black	2 (8%)
Caucasian	1 (4%)
Hispanic	21 (88%)
Age (years)#	
18-27	5 (21%)
28-37	8 (33%)
38-45	5 (21%)
46-55	6 (25%)
Mean (SD)	36.0 (9.34)
Range	19-55
Weight (pounds)#	
Mean (SD)	151.3 (28.78)
Range	101-221
Height (inches)#	
Mean (SD)	65.2 (3.69)
Range	58-75

On Day 1 of each period, venous blood samples for FEBUXOSTAT plasma concentrations were collected immediately prior to morning administration of study drugs and at 13 time points over the following 24 hours. Other procedures performed during the study included physical examination with fundoscopic eye exam, medical and social history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory examinations.

Results

Following administration of FEBUXOSTAT with an antacid, the mean time to maximum concentration was delayed by 55 minutes in comparison to FEBUXOSTAT alone. The mean values for C_{max}, AUC_t, and AUC_{inf} decreased by 31%, 15%, and 15%, respectively. Statistically significant ($p \leq 0.05$) differences between the means of Regimens A and B were observed for t_{max} and the natural logarithm of C_{max}, AUC_t, and AUC_{inf}. The mean apparent terminal half-life for FEBUXOSTAT remained unchanged following co-administration of an antacid with FEBUXOSTAT. The effects of period and sequence were not statistically significant ($p > 0.05$) for any of the pharmacokinetic parameters analyzed.

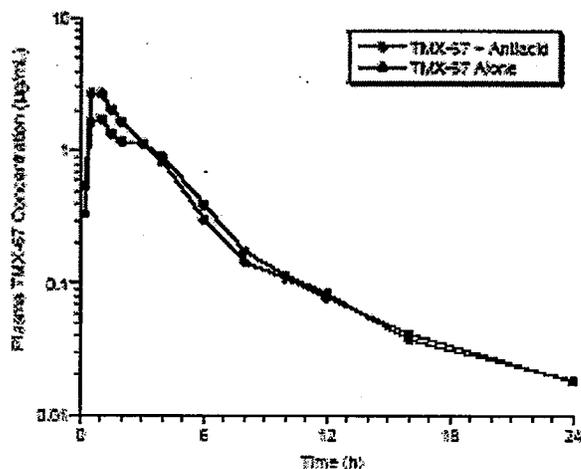
Table 11.4b Mean TMX-67 Pharmacokinetic Parameter Estimates Following Single Oral Dosing of TMX-67 with an Antacid and TMX-67 Alone in Healthy Subjects

Regimen	t _{max} (h)	C _{max} (µg/mL)	AUC _t (µg·h/mL)	AUC _∞ (µg·h/mL)	t _{1/2} ^a (h)	MRT (h)	V _d /F (L)
A ^b	1.77	2.2823	7.5082	7.7142	6.3 (5.3)	5.1	58.9
B ^c	0.85	3.2858	8.8215	9.0322	6.5 (5.5)	4.4	43.2

^a Arithmetic mean (harmonic mean)

^b Regimen A: 80 mg of TMX-67 with concurrent administration of 20 mL of an antacid liquid (200 mg magnesium hydroxide and 225 mg aluminum hydroxide per 5 mL)

^c Regimen B: 80 mg of TMX-67



The point estimates and 90% confidence intervals indicate that both the lower and upper bounds for C_{max} were outside the equivalence range of 0.80-1.25

Table 11.4c Bioavailability of TMX-67 Following Single Oral Doses of TMX-67 with an Antacid, Relative to TMX-67 Alone, in Healthy Subjects

Parameter	Point Estimate	90% Confidence Interval
C _{max}	0.676	0.581-0.786
AUC _t	0.849	0.802-0.899
AUC _∞	0.853	0.806-0.902

Note: The point estimates and confidence intervals were obtained from exponentiated differences obtained from analysis of the natural logarithm transformed data.

In the case of AUC_t and AUC_∞, their 90% confidence intervals were within range of 0.80-1.25. Therefore, although co-administration of an antacid with FEBUXOSTAT may affect C_{max} for FEBUXOSTAT, as the uric acid lowering effect of febuxostat appears to be related to the total exposure and not peak effect the observed difference should have no clinical consequences.

4.2.5.2 Study TMX-00-006: The Effect of Colchicine on the Pharmacokinetic Profile of FEBUXOSTAT

Study Objective:

The primary objective of this study was to evaluate the effect of colchicine on the pharmacokinetic profile of FEBUXOSTAT after multiple doses.

Overall Study design and Plan:Description

This was an open-label, multiple-dose, randomized, two-period complete crossover study. Twenty-four subjects were to be randomized to one of two regimen sequences.

Subjects in Regimen A were dosed with FEBUXOSTAT 40 mg once daily for seven days with the addition of colchicine 0.6 mg twice daily on days 4 through 7. Regimen B consisted of FEBUXOSTAT 40 mg once daily for seven days.

While the trial was originally designed to enroll 24 subjects, only 22 were enrolled, due to "recruitment problems". Of the 22 subjects enrolled all subjects completed the study.

Table 11.2a Summary of Demographic Characteristics

Variable	All Subjects (N=22)
Gender	
Male	16 (73%)
Female	6 (27%)
Age (yrs)†	
Mean ± S.D.	36.0 ± 12.3
Range	19.0-53.0
Race	
Asian	1 (5%)
Black	4 (18%)
Caucasian	16 (73%)
Hispanic	1 (5%)
Weight (lb)†	
Mean ± S.D.	163.4 ± 23.5
Range	126.5-209.5
Height (in)†	
Mean ± S.D.	67.3 ± 3.4
Range	59.0-71.5

Subjects were confined to the study unit on the night prior to study initiation (Day -1). Plasma samples (7ml) were taken pre-dose on day 1, and pre-dose on days 4, 5, and 6 (along with a 1hr post dose sample). On day 7 samples were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose.

Results

Following administration of FEBUXOSTAT with colchicine, the mean tmax was shortened by 18 minutes in comparison to the FEBUXOSTAT alone regimen. Slight decreases in mean T1/2, MRT, and Vss and increases in mean Cmax, AUCt and AUC24 for FEBUXOSTAT were observed when FEBUXOSTAT was administered with colchicine. Even so, parameters were within 14% of the respective mean parameter estimates for the FEBUXOSTAT alone regimen. Statistically significant (p<0.05) differences between the means of Regimens A and B were observed for tmax and the natural logarithm of AUC and AUC24 among the FEBUXOSTAT pharmacokinetic parameters analyzed.

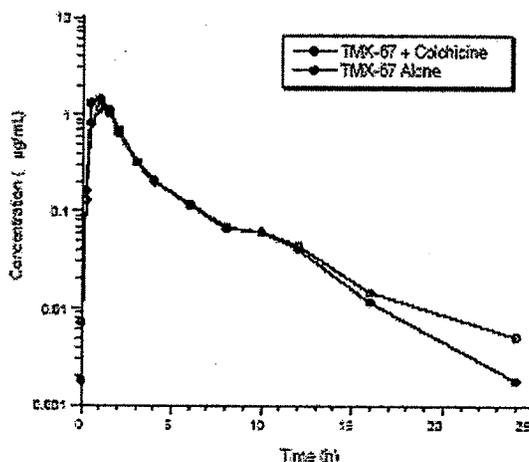
Table 11.4a Mean TMX-67 Pharmacokinetic Parameter Estimates Following Multiple Oral Doses of TMX-67 with Colchicine and TMX-67 Alone in Healthy Subjects

Regimen	t _{max} (h)	C _{max} (µg/mL)	AUC _t (µg·h/mL)	AUC ₂₄ (µg·h/mL)	t _{1/2} ^a (h)	MRT (h)	V _{ss} (L)
A ^b	0.84	1.6294	3.5422	3.6599	4.4 (3.8)	3.6	44.1
B ^c	1.14	1.4397	3.3396	3.4053	4.7 (4.0)	4.0	50.3

a Arithmetic mean (harmonic mean).

b TMX-67 (Days 1-7) and colchicine (Days 4-7).

c TMX-67 alone (Days 1-7).



The point estimates and 90% confidence intervals C_{max}, AUC_t, and AUC₂₄ in the FEBUXOSTAT and colchicine regimen (relative to the FEBUXOSTAT alone regimen) are presented below:

Parameter	Point Estimate	90% Confidence Interval
C _{max}	1.120	0.980-1.281
AUC _t	1.059	1.014-1.106
AUC ₂₄	1.070	1.025-1.117

While a slight difference in the C_{max} value is noted, the difference between the two regimens, based on the point estimates is ~12%. As the exposure, as measure by AUC, is unchanged (ie. within the 90% confidence interval) the changes noted here should be of little clinical impact.

4.2.5.3 Study C02-006: A Phase 1, Single-Center Study to Evaluate the Safety and the Effect of Febuxostat (FEBUXOSTAT) on the Pharmacokinetics of Colchicine at Steady State in Healthy Subjects

Study Objectives

The objective of this study was to evaluate the effect of febuxostat on the pharmacokinetics of colchicine at steady state in healthy subjects.

Overall Study Design and Plan: Description

The was an open-label, randomized, single-center, three-period crossover study designed to evaluate the effect of febuxostat on the pharmacokinetics of colchicines. A total of 33 healthy subjects (26 completers) were randomly assigned to receive each of the following treatments:

- Trt A-0.6 mg BID doses of colchicine with concurrent administration of once daily 120 mg oral doses of febuxostat (administered as six 20 mg tablets) for 14 days

Trt B-0.6 mg BID doses of colchicine with concurrent administration of once daily febusostat *placebo* for 14 days

Trt C-120 mg febusostat alone for 14 days in each study period.

(Note: The febusostat alone regimen was evaluated for safety only, not for pharmacokinetics.)

For treatments A & B, plasma samples were obtained for colchicine pre-dose at Day 1, 7, and 13. On Day 14 they were obtained pre-dose and 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 (pre-dose PM), 12.25, 12.5, 13.0, 13.5, 14.0, 15.0, 16.0, 18.0, and 24.0 hours post AM dose.

For treatments A, B, & C plasma samples were obtained for febusostat pre-dose at Day 1, 7, 13, and 14. No complete profiles were obtained for febusostat in this study.

Thirty-three subjects (19 males and 14 females) were enrolled in Study C02-006, and 27 subjects completed the study.

Demographic Characteristic	All Subjects (N=33)
Gender	
Male	19 (58%)
Female	14 (42%)
Race	
Caucasian	30 (91%)
Black	2 (6%)
Hispanic	1 (3%)
Age (years)#	
18-29	9 (27%)
30-39	16 (48%)
40-55	8 (24%)
Mean (SD)	33.2 (6.44)
Range	18-45
Weight (pounds)#	
Mean (SD)	162.7 (24.94)
Range	113-209
Height (inches)#	
Mean (SD)	67.7 (4.00)
Range	60-76

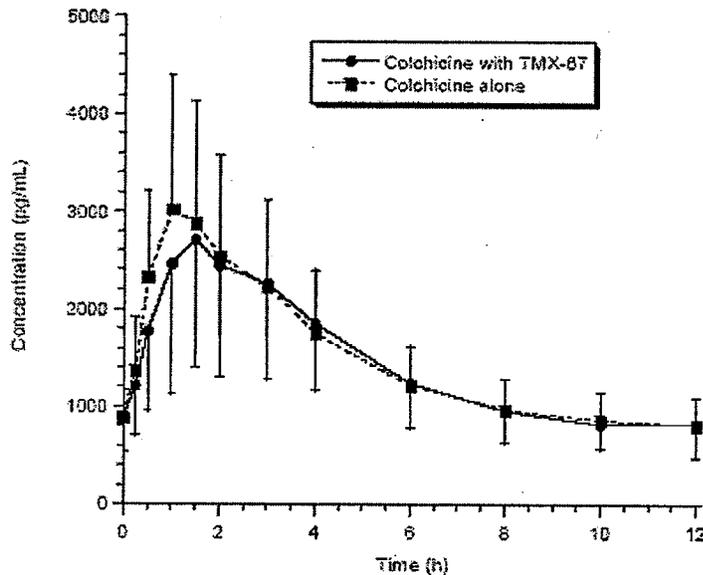
Results

Following multiple doses of colchicine with febusostat for 14 days, the colchicine pharmacokinetic parameters for both AM and PM C_{max} , AUC_{12} , $t_{1/2}$, and AUC_{24} , the means for the coadministered colchicine and febusostat regimen differed by no more than approximately 11% from the means of the respective parameters in the colchicine alone regimen.

Table 11.4b Mean Colchicine Pharmacokinetic Parameter Estimates on Day 14 Following Multiple Oral Doses of Colchicine with Febuxostat or Colchicine Alone

Regimen		t_{max} (h)	C_{max} (pg/mL)	AUC_{12} (pg-h/mL)	AUC_{14} (pg-h/mL)	$t_{1/2}$ ^a (h)	CL/F (L/h)	$V_{d/F}$ (L)
Colchicine & Febuxostat (AM Dose)	Mean	1.8	2895.7	17386.5	-	9.5 [8.3]	38.7	507.1
	SD	0.9	1380.7	6428.6	-	4.0	12.5	284.9
	%CV	49	48	37	-	43	32	56
Colchicine Alone (AM Dose)	Mean	1.3	3253.8	17933.4	-	10.1 [8.9]	37.0	505.9
	SD	0.6	1449.7	6055.9	-	3.9	11.7	267.2
	%CV	43	45	34	-	38	32	53
Colchicine & Febuxostat (PM Dose)	Mean	2.40	2746.9	16434.1	33766.8	8.1 [6.8]	39.9	493.8
	SD	1.15	1203.3	5400.5	11559.2	4.5	11.6	294.7
	%CV	48	44	33	34	55	29	60
Colchicine Alone (PM Dose)	Mean	2.19	2626.4	16479.7	34410.3	8.1 [7.3]	39.2	489.0
	SD	1.03	817.7	4502.4	10320.0	3.0	11.4	210.1
	%CV	47	31	27	30	38	29	43

a Arithmetic mean [harmonic mean]
Cross Reference: Appendix 16.5.



In general, there does not appear to be a significant interaction between colchicine and febuxostat in terms of their effects on the pharmacokinetics of either drug. The presence of a pharmacodynamic interaction was not assessed as these studies were done in otherwise healthy subjects.

4.2.5.4 Study-C02-005: A Phase I Study to Assess the Effect of Multiple Dosing of Febuxostat on the Pharmacokinetics of Desipramine

Objectives

The objective of this study was to determine the effect of febuxostat on the pharmacokinetics of desipramine, a CYP2D6 substrate, in healthy subjects.

Overall Study Design and Plan: Description

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.

VARIABLE	All Subjects (N = 22)
GENDER	
MALE	10 (45%)
FEMALE	12 (55%)
RACE	
CAUCASIAN	20 (91%)
HISPANIC	2 (9%)
AGE (yr) #	
18-29	9 (41%)
30-39	5 (23%)
40-55	8 (36%)
N	
MEAN	33.7
SD	11.25
MEDIAN	33.0
MIN-MAX	19-51
WEIGHT (lb) #	
N	22
MEAN	159.2
SD	26.14
MEDIAN	161.9
MIN-MAX	117-214
HEIGHT (in) #	
N	22
MEAN	67.2
SD	2.97
MEDIAN	66.9
MIN-MAX	63-72

Regimen A: 120 mg QD dose of febuxostat for 9 consecutive days, from Day 1 to Day 9, with 25 mg of desipramine on Day 6

Regimen B: Placebo for the 120 mg QD dose of febuxostat for 9 consecutive days, from Day 1 to Day 9, with 25 mg of desipramine on Day 6

Results

The co-administration of febuxostat with desipramine increased the mean desipramine C_{max} , AUC_t 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 (C/F).

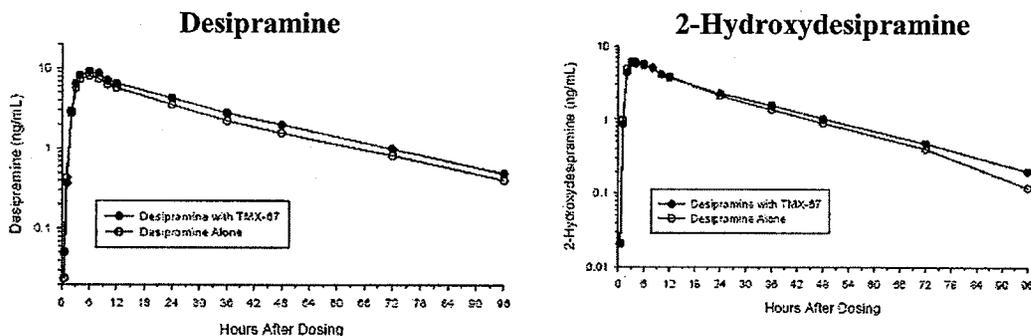
Parameter	Units	Desipramine				2-Hydroxydesipramine			
		Desipramine with Febuxostat		Desipramine Alone		Desipramine with Febuxostat		Desipramine Alone	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
t_{max}	(h)	6.6	1.3	6.0	1.0	4.2	1.5	4.0	1.2
C_{max}	(ng/mL)	9.62	3.46	8.35	3.24	6.19	1.96	6.57	2.31
AUC_t	(ng·h/mL)	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
k_{el}	(1/h)	0.0367	0.0116	0.0390	0.0140	0.0346	0.0132	0.0374	0.0158
C/F	(L/h)	124.4	101.7	157.4	137.2	-	-	-	-
AUC_{∞} Ratio ^b		0.7362	0.4046	0.8852	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.



With regards to the 90% CIs, the desipramine C_{max} was within the 0.80-1.25 range, but the upper bound of the 90% CIs for AUC_t 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 C_{max} , AUC_t , and AUC_{∞} parameters were all within the 0.80-1.25 range, suggesting that the changes seen with the concomitant administration of desipramine and febuxostat are related to the formation rate of 2-hydroxydesipramine and not its elimination.

Parameter	Point Estimate	90% Confidence Interval
<u>Desipramine</u>		
C _{max}	1.163	(1.0967 - 1.2324)
AUC ₀₋₁	1.242	(1.1369 - 1.3570)
AUC _{0-∞}	1.220	(1.1059 - 1.3459)
AUC Ratio ^a	0.832	(0.7629 - 0.9069)
<u>2-Hydroxydesipramine</u>		
C _{max}	0.959	(0.9026 - 1.0183)
AUC ₀₋₁	1.059	(1.0089 - 1.1122)
AUC _{0-∞}	1.015	(0.9277 - 1.1102)

^a AUC ratio means 2-hydroxydesipramine AUC_{0-∞} to desipramine AUC_{0-∞}.

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.

4.2.5.5 Study C03-059: A Phase 1 Study to Evaluate the Effect of Hydrochlorothiazide on the Pharmacokinetics and Pharmacodynamics of Febuxostat in Healthy Subjects

Objectives:

The objective of this study was to evaluate the effect of hydrochlorothiazide on the pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects.

Overall Study Design and Plan: Description

This was a single-center, open-label, single-dose, randomized, two-period crossover study performed to evaluate the effect of hydrochlorothiazide on the pharmacokinetics and pharmacodynamics (uric acid levels) of febuxostat in healthy subjects. A total of 36 subjects were enrolled and 33 were available for analysis.

Demographic Characteristics	All Subjects (N=36)	Subjects Included in PK/PD Analyses (N=33)
Gender		
Male	20 (56%)	19 (58%)
Female	16 (44%)	14 (42%)
Race		
Caucasian	22 (61%)	21 (64%)
Black	7 (19%)	7 (21%)
Hispanic	6 (17%)	4 (12%)
Asian	1 (3%)	1 (3%)
Age (years) ²		
Mean (SD)	32.6 (9.00)	32.9 (9.12)
Range	19 - 51	19 - 51
Weight (pounds) ³		
Mean (SD)	158.8 (25.09)	160.8 (24.84)
Range	104 - 201	104 - 201
Height (inches) ²		
Mean (SD)	67.3 (3.56)	67.5 (3.13)
Range	58 - 73	60 - 73

Subjects were randomly assigned to receive either an 80 mg oral dose of febuxostat (administered as a single 80 mg tablet) with co-administration oral administration of 50 mg hydrochlorothiazide or an 80 mg oral dose of febuxostat in each study period.

Blood samples (7 mL) for febuxostat were collected during Day 1 of both periods at time 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-dose and on Day 2 at 16 and 24 hours post-dose. Hydrochlorothiazide levels were not determined in this trial.

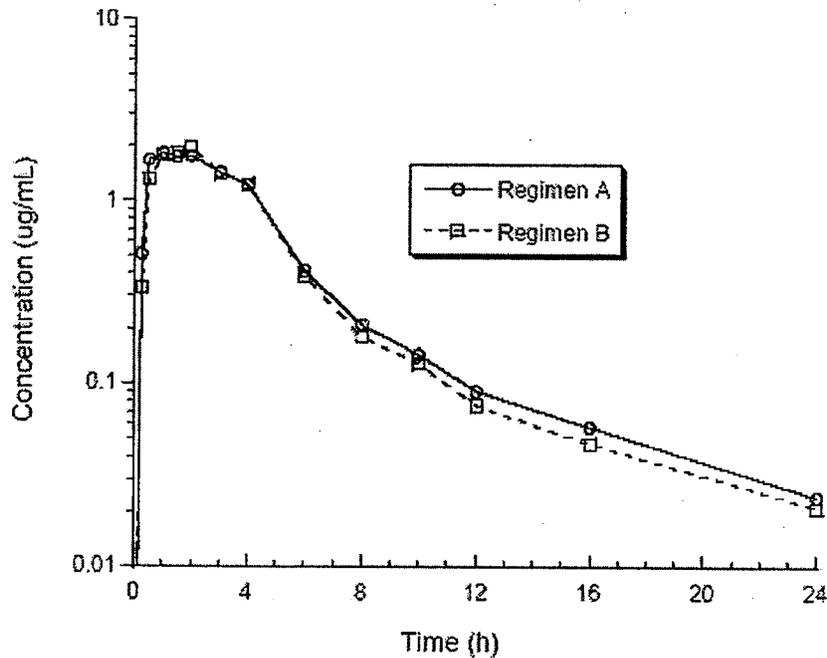
Results

Following administration of febuxostat with or without co-administration of hydrochlorothiazide, mean febuxostat C_{max}, AUC_t, and AUC₂₄ were all within 4% of those in the febuxostat alone regimen.

Table 11.4a Summary of Pharmacokinetic Parameter Estimates for Febuxostat Following 80 mg Dose of Febuxostat + 50 mg Hydrochlorothiazide or 80 mg Febuxostat Alone in Healthy Subjects

Regimen		t _{max} (h) (N=33)	C _{max} (µg/mL) (N=33)	AUC _t (µg·h/ mL) (N=33)	AUC _∞ (µg·h/ mL) (N=33)	t _{1/2z} ^a (h) (N=33)	CL/F (L/h) (N=33)	V _{ss} /F (L) (N=33)
	Febuxostat 80 mg + Hydrochlorothiazide 50 mg	Mean	1.93	2.924	9.346	9.597	6.5 (5.8)	8.82
SD		1.43	1.378	2.564	2.570	2.2	2.01	17.0
Febuxostat 80 mg	Mean	1.98	2.932	9.085	9.292	6.1 (5.7)	9.28	43.8
	SD	1.28	1.439	2.575	2.606	1.6	2.53	16.0

^a Arithmetic mean (harmonic mean)



The 90% CIs for these parameters were all within the acceptance interval of 0.80-1.25.

Parameter	Point Estimate	90% Confidence Interval
C _{max}	1.001	(0.8593 - 1.1664)
AUC ₀₋₁	1.033	(0.9758 - 1.0943)
AUC _{0-∞}	1.038	(0.9833 - 1.0968)

With regards to pharmacodynamic measures the mean 24 and 48 hour serum urate concentration (C_{mean,24}; C_{mean,48}) following the administration of hydrochlorothiazide with febuxostat were approximately 6.5% and 7.9% higher, respectively, than those following administration of febuxostat alone. The mean urinary uric acid Cl_r and Ae₂₄ values were approximately 9.5% and 4.4% lower, respectively, following co-administration of hydrochlorothiazide with febuxostat.

Table 11.4c Summary of Serum Urate and Urine Uric Acid Parameter Estimates of 80 mg Dose of Febuxostat + 50 mg Hydrochlorothiazide or 80 mg Febuxostat Alone in Healthy Subjects

Regimen		Serum		Urine	
		C _{mean,24} (mg/dL) (N=30) ^a	C _{mean,48} (mg/dL) (N=30) ^a	Cl _r (mL/min) (N=30) ^a	Ae ₂₄ (mg) (N=33)
Febuxostat 80 mg + Hydrochlorothiazide 50 mg	Mean	3.63	3.67	9.11	434.2
	SD	1.305	1.279	2.793	82.79
Febuxostat 80 mg	Mean	3.41	3.40	10.07	454.2
	SD	1.204	1.144	2.842	114.25
P-value ^b		<<0.001***	=0.001***	0.003**	0.129

a. Period 2 parameter could not be calculated for Subjects 105, 110, and 117 due to missing data.

b. P-value for testing hydrochlorothiazide effect, from ANOVA with terms for sequence, subject (sequence), period, and regimen.

, * Statistical significance at 0.01 and 0.001 levels, respectively

While the differences in Ae₂₄ were not statistically significant, the differences in C_{mean,24}, C_{mean,48}, and Cl_r were statistically significant. However, the differences in the mean pharmacodynamic parameters estimates between regimens were small and are unlikely to be clinically relevant, at these doses. Based on the combined PK/PD results of this study, no dose-adjustment for febuxostat appears to be necessary when administered with hydrochlorothiazide at these doses.

4.2.5.6 Study TMX-02-017: Assessment of Potential Effect of Indomethacin on the Pharmacokinetics of FEBUXOSTAT and the Potential Effect of FEBUXOSTAT on the Pharmacokinetics of Indomethacin at Steady State in Healthy Subjects

Objective:

The objective of this study was to assess the potential effect of indomethacin on the pharmacokinetics of FEBUXOSTAT and the potential effect of FEBUXOSTAT on the pharmacokinetics of indomethacin at steady state in healthy subjects.

Overall Study Design and Plan: Description

This study was an open-label, randomized, single-center, three-period complete crossover study. It was designed to evaluate the effect of indomethacin on the pharmacokinetics of febuxostat,

and the effect of febuxostat on the pharmacokinetics of indomethacin at steady-state in healthy subjects. Subjects were randomly assigned to receive each of the following treatments in a random order:

- Trt A. 80 mg oral doses of febuxostat alone (administered as four 20 mg tablets) for 5 days
- Trt B. 80 mg oral doses of febuxostat with concurrent oral administration of 50 mg indomethacin BID for 5 days
- Trt C. 50 mg indomethacin BID alone for 5 days in each study period.

A total of 27 subjects were enrolled in the trial and 26 completed all phases of the trial.

VARIABLE	ALL SUBJECTS (N = 27)
GENDER	
MALE	13 (48%)
FEMALE	14 (52%)
RACE	
CAUCASIAN	4 (15%)
HISPANIC	23 (85%)
AGE (yr) #	
18-27	5 (19%)
28-37	7 (26%)
38-45	12 (44%)
46-55	3 (11%)
N	27
MEAN	36.7
SD	8.73
MEDIAN	39.0
MIN-MAX	21-52
WEIGHT (lb) #	
N	27
MEAN	160.1
SD	19.06
MEDIAN	159.0
MIN-MAX	128-210
HEIGHT (in) #	
N	27
MEAN	65.3
SD	3.72
MEDIAN	65.0
MIN-MAX	59-73

Blood samples (5 mL) for febuxostat (Trt. A & B) were collected according to the following schedule:

Days 1-4, time 0 (pre-dose)

Day 5, time 0 (pre-dose) and , 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

Blood samples for indomethacin (Trt B & C) were collected according to the following schedule:

Days 1-4, time 0 (pre-dose)

Day 5, time 0 (pre-dose) 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (pre-evening dose), 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, and 24 hours post-dose

The sequence of the dose and subsequent procedures for a given subject was maintained so that the time intervals for these activities were the same for that subject throughout the study. Any collection of blood that coincided with other study procedures took precedence over other study activities.

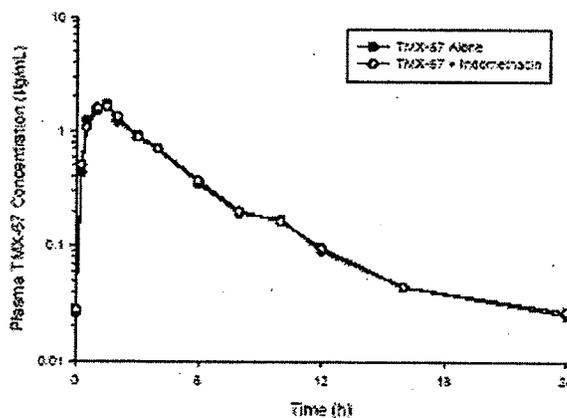
Results

Following administration of febuxostat with indomethacin for 5 days, the changes in mean febuxostat pharmacokinetic parameters, including t_{max} , C_{max} , AUC_t , AUC_{24} , $t_{1/2}$, and V_{ss}/F for the febuxostat with indomethacin regimen were all within 11% of the respective parameters in the febuxostat alone regimen. Both C_{max} and MRT were essentially unchanged, indicating that absorption rate was not significantly affected.

Table 11.4b Summary of Pharmacokinetic Parameter Estimates for TMX-67 Following Multiple Oral Doses of TMX-67 Alone or TMX-67 with Indomethacin in Healthy Subjects

Regimen		t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_t ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{24} ($\mu\text{g}\cdot\text{h/mL}$)	$t_{1/2}$ ^a (h)	MRT (h)	V_{ss}/F (L)
TMX-67 Alone	N	26	26	26	26	25	26	25
	Mean	1.25	1.9989	7.1272	7.1343	6.0 (5.2)	5.2	60.2
	SD	0.67	0.9431	1.9754	1.9716	2.5	1.9	16.1
TMX-67 & Indomethacin	N	26	26	26	26	25	25	25
	Mean	1.31	1.7818	7.1768	7.1950	6.0 (5.2)	5.2	60.0
	SD	0.55	0.4916	1.8079	1.8073	2.1	0.7	15.7

^a Arithmetic mean (harmonic mean)



As expected, the 90% CIs for both febuxostat C_{max} and AUC_{24} were within the 0.80-1.25 range, although the C_{max} value was close. Given that they are contained in the acceptance interval, and that the CI contains "1", we can conclude that indomethacin has no significant effect on the bioavailability of febuxostat.

Table 11.4d Bioavailability of TMX-67 Following Multiple Oral Doses of TMX-67 with Indomethacin, Relative to TMX-67 Alone, in Healthy Subjects

Parameter	Point Estimate	90% Confidence Interval
C_{max}	0.931	(0.8189 - 1.0579)
AUC_{24}	1.017	(0.9739 - 1.0610)

Note: The results are based on the ANOVA of the natural logarithm of C_{max} and AUC_{24} .

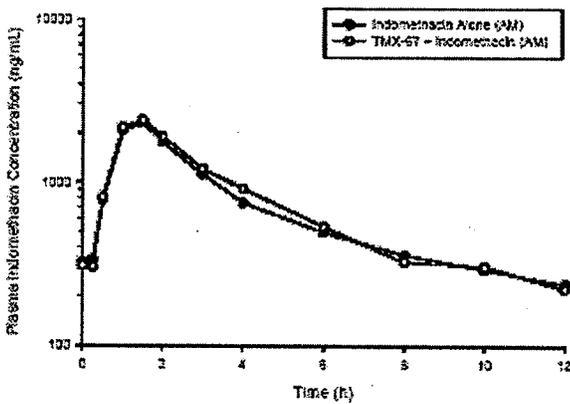
As for indomethacin, following administration of indomethacin with FEBUXOSTAT, the changes in the mean indomethacin pharmacokinetic parameters, including t_{max} , C_{max} , AUC_{12} , and AUC_{24} , were all within 12% of the respective parameters in the indomethacin alone regimen for both AM and PM doses.

Table 11.4c Summary of Pharmacokinetic Parameter Estimates for Indomethacin Following Multiple Oral Doses of Indomethacin Alone or TMX-67 with Indomethacin in Healthy Subjects

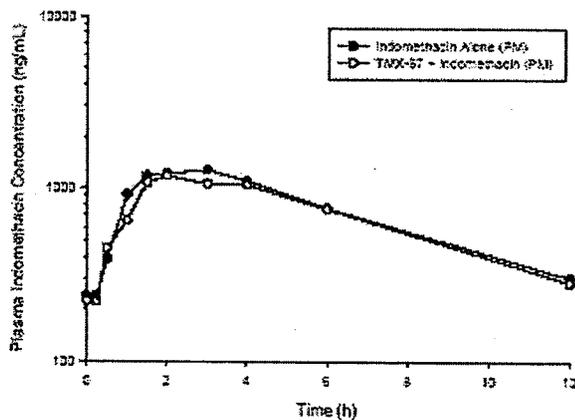
Regimen		t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_{12} ($\text{ng}\cdot\text{h/mL}$)	AUC_{24} ($\text{ng}\cdot\text{h/mL}$)	$t_{1/2\alpha}$ (h)	MRT (h)	V_d/F (L)
Indomethacin Alone (AM Dose)	N Mean SD	26 1.37 0.61	26 2757.6 536.2	26 8709.0 2062.3	- - -	26 7.2 (5.2) 4.1	26 7.6 2.8	26 22.54 9.04
Indomethacin Alone (PM Dose)	N Mean SD	26 2.56 1.47	26 1916.4 646.8	26 9094.1 1964.0	26 17803.1 3797.6	26 4.9 (4.2) 2.4	26 7.7 2.0	26 22.10 7.03
TMX-67 & Indomethacin (AM Dose)	N Mean SD	26 1.52 0.66	26 2743.8 680.9	26 9261.9 1798.4	- - -	26 5.7 (5.2) 1.7	26 6.2 1.3	26 17.18 4.69
TMX-67 & Indomethacin (PM Dose)	N Mean SD	26 2.27 1.19	26 1770.2 627.2	26 8430.0 1912.4	26 17692.0 3359.7	26 5.7 (4.4) 3.4	26 8.6 2.9	26 32.12 40.27

a Arithmetic mean (harmonic mean)

Log Concentration Indomethacin AM Dosing



Log Concentration Indomethacin PM Dosing



A statistically significant ($p < 0.05$) change was detected in the mean AM AUC_{12} values between the two regimens (8709 vs. 9261 $\text{ng}\cdot\text{hr/ml}$), numerically it represents a 6% change and is

unlikely to be clinically significant and is more related to the overall power of the trial being able to resolve small differences. The effects of period and sequence were assessed in the trial and not statistically significant ($p > 0.05$) for any of the pharmacokinetic parameters analyzed with the exception of the period and sequence on AM AUC₁₂, which were statistically significant ($p < 0.05$). It is unclear what the impact of this would be clinically, however, it matches up with the previous observation regarding the detected 6% difference in these values. Again it is not anticipated that these findings are clinically significant.

This is supported by the confidence interval analysis which demonstrates bioequivalence between both the AUC₁₂ and AUC₂₄ values.

Table 11.4e Bioavailability of Indomethacin Following Multiple Oral Doses of TMX-67 with Indomethacin, Relative to Indomethacin Alone, in Healthy Subjects

Parameter	Point Estimate	90% Confidence Interval
C _{max}	0.981	(0.9117 - 1.0564)
AUC ₁₂	1.070	(1.0405 - 1.1011)
AUC ₂₄	0.997	(0.9629 - 1.0322)

Note: The results are based on the ANOVA of the natural logarithm of C_{max}, AUC₁₂, and AUC₂₄.

Thus, while a period and sequence effect was detected, the overall conclusion is that there is not a meaningful pharmacokinetic interaction between indomethacin and febuxostat.

4.2.5.7 Study C02-013: Assessment of Potential Effect of Naproxen on the Pharmacokinetics of Febuxostat (FEBUXOSTAT) and the Potential Effect of Febuxostat on the Pharmacokinetics of Naproxen at Steady State in Healthy Subjects

Objectives:

The objective of this study was to assess the potential effect of naproxen on the pharmacokinetics of febuxostat (FEBUXOSTAT) and the potential effect of febuxostat on the pharmacokinetics of naproxen at steady state in healthy subjects.

Overall Study Design and Plan: Description

This was an open-label, randomized, single-center, three-period complete crossover study performed to evaluate the effect of naproxen on the pharmacokinetics of febuxostat, and the effect of febuxostat on the pharmacokinetics at steady-state. Subjects were randomly assigned to receive each of the following treatments in a random order:

- Trt. A 80 mg oral doses of febuxostat alone (administered as four 20 mg tablets) for 7 days
- Trt. B 80 mg oral doses of febuxostat with concurrent oral administration of 500 mg naproxen BID for 7 days
- Trt. C 500 mg naproxen BID alone for 7 days in each study period.

A total of 27 healthy subjects were enrolled in the trial and 25 completed both phases and were available for analysis.

Demographic Characteristic	All Subjects (N=27)
Gender	
Male	12 (44%)
Female	15 (56%)
Race	
Caucasian	3 (11%)
Hispanic	24 (89%)
Age (years)#	
18-27	4 (15%)
28-37	7 (26%)
38-45	10 (37%)
46-55	6 (22%)
Mean (SD)	38.7 (9.16)
Range	21-53
Weight (pounds)#	
Mean (SD)	157.6 (22.70)
Range	107-198
Height (inches)#	
Mean (SD)	65.55 (3.995)
Range	59-74

Blood samples (5 mL) for febuxostat were collected during Trt. A & B according to the following schedule:

Days 1, 3, 6: time 0 (pre-dose)

Day 7: time 0 (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose

Blood samples (5 mL) for naproxen were collected during Trt. B & C according to the following schedule:

Days 1, 3, 6: time 0 (pre-dose)

Day 7: time 0 (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (Pre-evening dose), 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, and 24 hours post-dose

The sequence of the dose and subsequent procedures for a given subject was maintained so that the time intervals for these activities were the same throughout the study. Any collection of blood that coincided with other study procedures took precedence over other study activities.

Results

Following administration of febuxostat with naproxen for 7 days, febuxostat C_{max}, AUC_t and AUC₂₄ mean values were approximately 28%, 40%, and 40% higher, respectively, than the febuxostat alone regimen.

Table 11.4b Summary of Pharmacokinetic Parameter Estimates for Febuxostat Following Multiple Oral Doses of Febuxostat Alone or Febuxostat with Naproxen in Healthy Subjects

Regimen		t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_t ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{24} ($\mu\text{g}\cdot\text{h/mL}$)	$t_{1/2}^a$ (h)	Cl/F (L/h)	MRT (h)	V_d/F (L)
Febuxostat Alone	N	25	25	25	25	24	25	24	24
	Mean	1.52	1.7504	6.8753	6.8807	6.2 (5.6)	12.31	4.8	58.6
	SD	0.78	0.3776	1.5632	1.5576	1.8	3.35	0.6	15.0
Febuxostat & Naproxen	N	25	25	25	25	24	25	24	24
	Mean	1.56	2.2473	9.6852	9.6892	7.8 (6.7)	8.91	5.6	49.3
	SD	0.71	0.5633	2.6330	2.6298	4.1	2.70	1.1	14.1

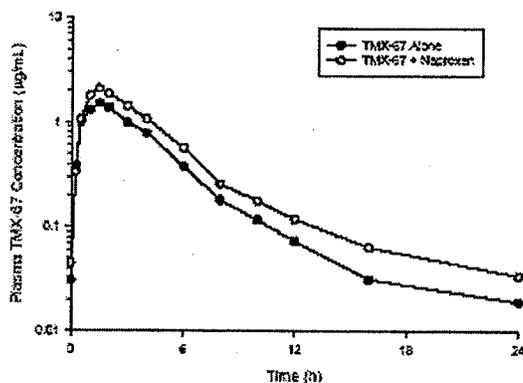
a Arithmetic mean (harmonic mean)

In addition, the 90% CIs each of these parameters extended beyond the upper 1.25 acceptance limit.

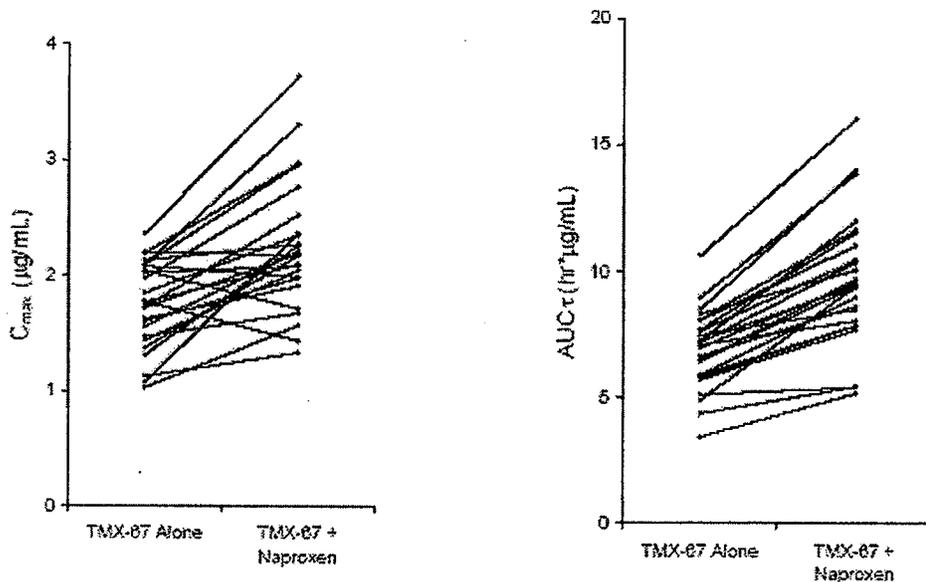
Table 11.4c Bioavailability of Febuxostat Following Multiple Oral Doses of Febuxostat with Naproxen, Relative to Febuxostat Alone, in Healthy Subjects

Parameter	Point Estimate	90% Confidence Interval
C_{max}	1.280	(1.1812 - 1.3674)
AUC_t	1.396	(1.3337 - 1.4621)
AUC_{24}	1.396	(1.3325 - 1.4621)

This increase in febuxostat levels is readily apparent from the mean plasma level time profile:



A plot of the individual values for AUC_t and C_{max} reveal that the majority of the subjects had increased febuxostat levels, and that these results are not being affected by a subset of individuals.



According to the sponsor, this observed increase in febuxostat exposure was most likely due to a decrease in febuxostat elimination as a result of the inhibitory effect of naproxen on glucuronidation of febuxostat.

While this is plausible, it does not alter the fact that both the peak plasma levels and exposure of febuxostat is markedly increased. The data clearly indicates that patients receiving the 80 mg dose will in fact be exposed to levels (based on AUC) more akin to 110 mg, and patients receiving 120 mg will be exposed to levels approaching 150 mg.

/ / / /

b(4)

Unlike the changes seen in febuxostat pharmacokinetics, the plasma levels of naproxen are relatively unchanged following concomitant administration with febuxostat.

Table 11.4d Summary of Pharmacokinetic Parameter Estimates for Naproxen Following Multiple Oral Doses of Naproxen Alone or Febuxostat with Naproxen in Healthy Subjects

Regimen		t_{max} (h)	C_{max} (ng/mL)	AUC_0-24 (ng·h/mL)	AUC_{0-12} (ng·h/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2\alpha}$ ^a (h)	CVF (L/h)	MRT (h)	V_d/F (L)
Naproxen Alone (AM Dose)	N	24	24	24	24	-	24	24	24	24
	Mean	1.9	93.7	791.5	791.5	-	11.3 (10.4)	0.636	16.4	10.39
	SD	0.9	7.1	66.0	66.0	-	3.8	0.053	4.2	2.49
Naproxen Alone (PM Dose)	N	24	24	24	24	24	24	24	24	24
	Mean	2.9	86.9	777.5	777.5	1569.0	13.6 (13.1)	0.649	21.5	13.94
	SD	1.3	8.9	71.2	71.2	128.3	2.9	0.065	4.9	3.34
Febuxostat & Naproxen (AM Dose)	N	24	24	24	24	-	24	24	24	24
	Mean	1.9	93.8	801.6	801.6	-	10.2 (9.2)	0.628	14.9	9.27
	SD	0.8	6.3	67.0	67.0	-	3.1	0.052	3.7	2.23
Febuxostat & Naproxen (PM Dose)	N	24	24	24	24	24	24	24	24	24
	Mean	3.6	83.6	760.9	760.9	1562.4	13.5 (12.5)	0.661	21.9	14.50
	SD	1.5	10.3	57.8	57.8	118.2	4.1	0.053	6.9	4.84

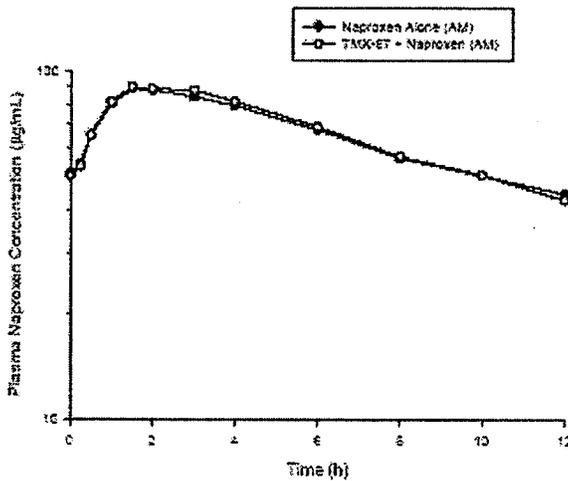
^a Arithmetic mean (harmonic mean)

No period or sequence effects were found in the study and the 90% confidence intervals were within the acceptance interval for naproxen.

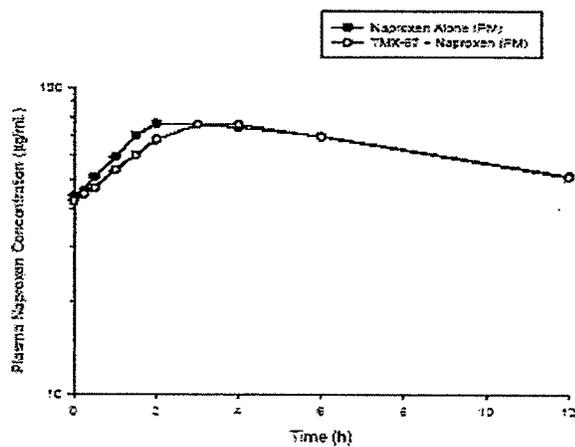
Parameter	Point Estimate	90% Confidence Interval
C_{max}	1.001	(0.9733 - 1.0272)
AUC_0-24	1.013	(0.9927 - 1.0332)
AUC_{0-12}	1.013	(0.9927 - 1.0332)
AUC_{0-24}	0.996	(0.9801 - 1.0127)

Unlike the results of the indomethacin drug-drug interaction trial, there was no difference in the naproxen pharmacokinetic profile between the AM and the PM dosing regimen:

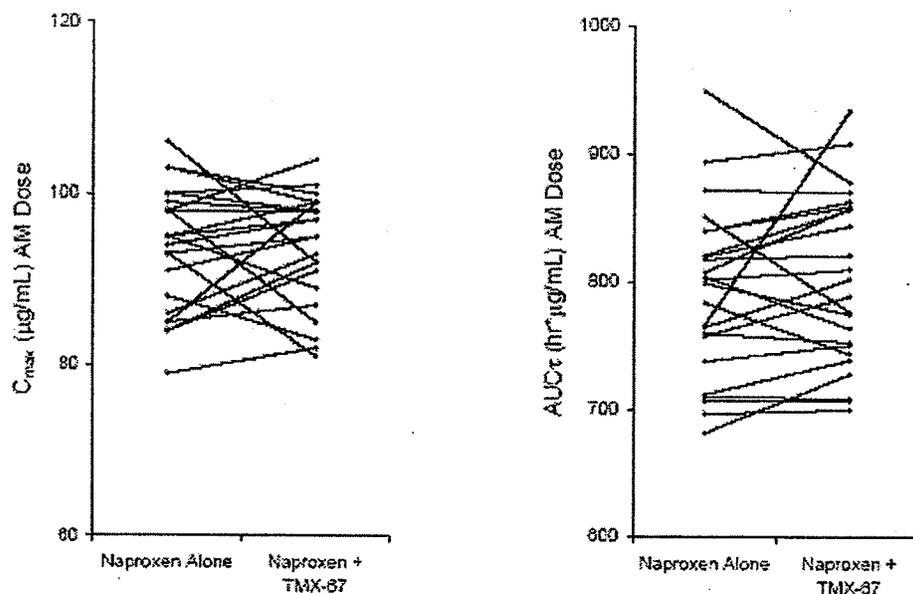
Log Concentration Naproxen AM Dosing



Log Concentration Naproxen PM Dosing



The observed pattern from the naproxen data shows that the differences in the C_{max} and AUC_t data is of a more random nature than that seen with febuxostat, indicating the lack of a significant interaction of febuxostat with naproxen's pharmacokinetics.



4.2.5.8 Study C03-057: A Phase 1 Two-way Crossover Study to Assess the Effect of Multiple Oral Doses of Febuxostat on the Pharmacokinetics and Pharmacodynamics of Warfarin Following Multiple Oral Doses of Warfarin

Objectives:

The objective of this study was to determine the effect of multiple doses of febuxostat on the pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin in healthy male and female subjects following multiple oral doses of warfarin.

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 (120 mg QD) 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.

Demographic Characteristics	All Subjects (N=22)	Crossover Period Subjects (N=21)	PK/PD Analysis Subjects (N=13)
Gender			
Male	21 (95.5%)	20 (95.2%)	13 (100%)
Female	1 (4.5%)	1 (4.8%)	0 (0%)
Race			
Caucasian	13 (59.1%)	12 (57.1%)	8 (61.5)
Black	6 (27.3%)	6 (28.6%)	3 (23.1)
Hispanic	1 (4.5%)	1 (4.5%)	0 (0%)
Asian	1 (4.5%)	1 (4.5%)	1 (7.7%)
Other	1 (4.5%)	1 (4.8%)	1 (7.7%)
Age(years)^a			
Mean (SD)	33.0 (11.82)	32.3 (11.55)	27.8 (9.56)
Range	19 - 55	19 - 55	19 - 49
Weight (pounds)^a			
Mean (SD)	177.9 (28.71)	177.3 (29.29)	176.9 (25.96)
Range	125 - 236	125 - 236	140 - 235
Height (inches)^a			
Mean (SD)	69.5 (3.29)	69.3 (3.21)	69.8 (3.29)
Range	64 - 76	64 - 76	64 - 76

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 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).

Blood Collection Time for R- and S-Warfarin Relative to Time of Dosing

Crossover Periods	Day	Blood Sample Collection
1 and 2	12 & 13	0 (predose)
1 and 2	14	0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose

Blood Collection Time for INR Determinations Relative to Time of Dosing

Periods	Day	Blood Sample Collection
Warfarin Lead-in	1	0 (predose) and 12 hours postdose
Warfarin Lead-in	2-9	12 hours postdose
Crossover Period 1 and 2	1, 3, 5, 7, 9, 11, 12 & 13	0 (predose)
Crossover Period 1 and 2	14	0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose

Blood Collection Time for Factor VII Determinations Relative to Time of Dosing

Periods	Day	Blood Sample Collection
Warfarin Lead-in	1	0 (predose)
Crossover Period 1 and 2	12 & 13	0 (predose)
Crossover Period 1 and 2	14	0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose

Results-Pharmacokinetic

Following administration of warfarin with febuxostat co-administration of febuxostat with warfarin increased the estimated C_{max} 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 _d /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 AUC₂₄ and AUC_t were equal in all subjects in both periods.

b Arithmetic mean (harmonic mean).

The 90% CIs for C_{max} 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 AUC₂₄ and AUC_t were equal in all subjects in both periods.

Based on the point estimates, co-administration of febuxostat with warfarin increased the estimated C_{max} and AUC₂₄ central values by less than 3% for R-warfarin and less than 5% for S-warfarin. The 90% confidence intervals of the ratio of the regimen central values were within the acceptance interval (0.80-1.25) for C_{max} and AUC₂₄ with respect to R- and S-warfarin. From a pharmacokinetic perspective, there is no evidence of a drug-drug interaction between warfarin and febuxostat in the subjects who completed the trial.

Results-Pharmacodynamic

With regards to the pharmacodynamics of warfarin, [the time to reach maximum international normalized ratio (INR_{max}), the 24-hour mean international normalized ratio (INR_{mean,24}), and the 24-hour mean Factor VII (F-VII_{mean,24})] were within 7% of those for warfarin alone.

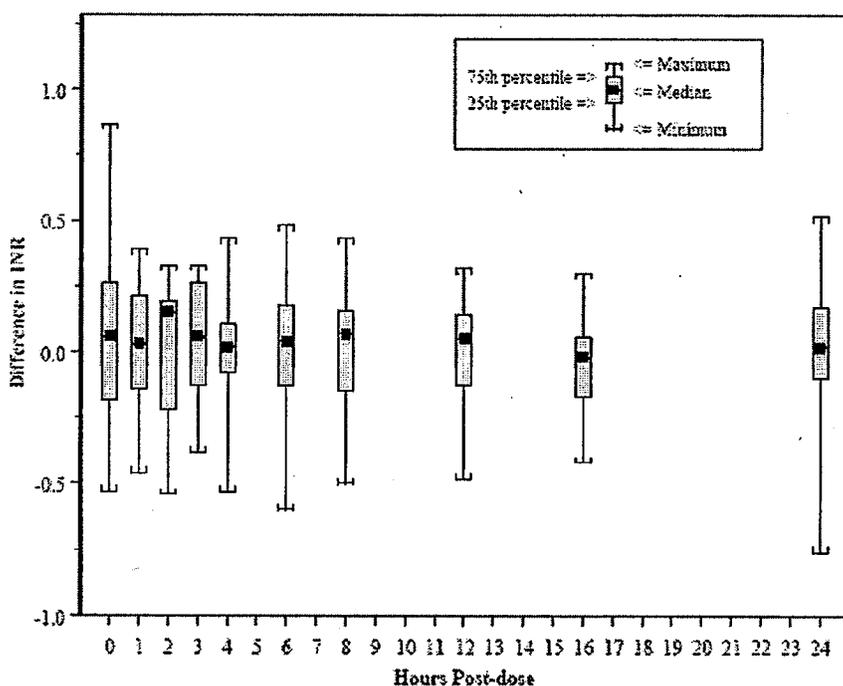
Regimen		INR _{max} (N=13) ^a	INR _{mean,24} (N=13) ^a	F-VII _{mean,24} (%) (N=13) ^a
Warfarin QD + Febuxostat QD	Mean	1.87	1.70	39.60
	SD	0.408	0.372	12.501
Warfarin QD + Placebo QD	Mean	1.80	1.71	37.16
	SD	0.493	0.468	12.063
P-value ^b		0.4582	0.7482	0.2912

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.

It is the sponsor's conclusion, based on the data above, and a comparison of the differences in INR between the two treatments, obtained over 24-hours on Day 14 (see below), that there were negligible within-subject differences (febuxostat - placebo) for INR values, indicating no quantifiable interaction of febuxostat on warfarin.

Figure 11.4a Distribution of Differences in International Normalized Ratio by Hours Postdose Day 14 (Febuxostat - Placebo)

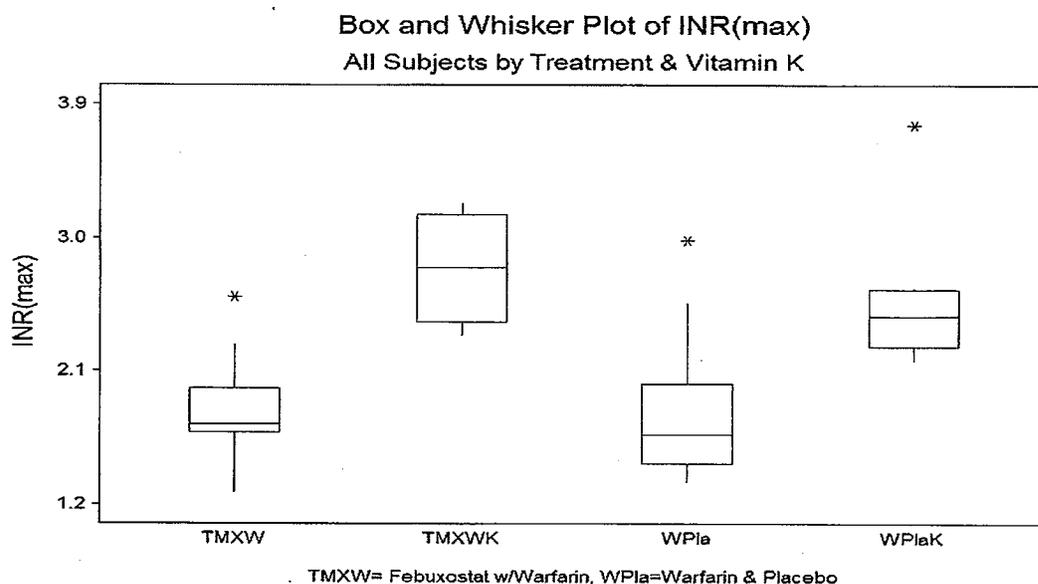


It should be noted that the Agency does not agree with the sponsor as the results from this study were censored by the removal of subjects from the trial due to increases in INR. This is especially troubling as increases in INR are exactly the side effect one would expect if an interaction was to have taken place.

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 were 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. The same cannot be said for the febuxostat subjects.



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.

Of further concern is the way in which the trial was conducted. Subject 119 had consistently high INR values through out both phases of the trial with their INR peaking at 3.09, and yet they did not receive vitamin K until 11 days later-following study closure:

Subject Number	Study Drug Taken	Date	Study Day	INR	
				Sample Time	Value Vitamin K
119	Warfarin 5.5 mg: Placebo	25FEB2004	17	8:45	2.02
	Warfarin 5.5 mg: Febuxostat 120 mg	27FEB2004	19	8:45	2.89
	Warfarin 5.5 mg: Febuxostat 120 mg	29FEB2004	21	8:45	3.06
	Warfarin 5.5 mg: Febuxostat 120 mg	01MAR2004	22	8:45	2.95
	Warfarin 5.5 mg: Febuxostat 120 mg	02MAR2004	23	8:45	2.89
	Warfarin 5.5 mg: Febuxostat 120 mg	04MAR2004	25	8:45	2.54
	Warfarin 5.5 mg: Febuxostat 120 mg	06MAR2004	27	8:45	2.26
	Warfarin 5.5 mg: Febuxostat 120 mg	08MAR2004	29	8:47	2.25
	Warfarin 5.5 mg: Febuxostat 120 mg	09MAR2004	30	8:45	2.26
	Warfarin 5.5 mg: Febuxostat 120 mg	10MAR2004	31	8:45	2.30
	Warfarin 5.5 mg: Febuxostat 120 mg	11MAR2004	32	8:45	2.26
		11MAR2004	32	9:15	2.33
		11MAR2004	32	9:45	2.25
		11MAR2004	32	10:45	2.27
		11MAR2004	32	11:45	2.60
		11MAR2004	32	12:45	2.24
		11MAR2004	32	14:45	2.22
		11MAR2004	32	16:45	2.35
	11MAR2004	32	20:45	2.43	
		12MAR2004	33	8:45	2.55
		12MAR2004	33	8:45	2.37
		13MAR2004	34	8:10	1.23

Clearly this patient was being adequately followed (note the 18 INR determinations) between their highest value and vitamin K administration. Even so this case raises troubling issues with study administration and monitoring as this patient clearly qualified for vitamin K administration according to the study protocol itself:

Excerpt from section 5.1 of the protocol (pg 17)

If a subject's INR is >1.8 at Day 15 of Period 2, the subject will be assessed for any signs of bleeding and will remain in the unit for an additional day. At the investigator's discretion, the subject may be treated with Vitamin K. On the morning of Day 16 of Period 2, the subject will have a repeat PT and INR. If the repeat INR remains >1.8, the subject will stay in the unit an additional day until the INR is <1.8 or the subject is treated with Vitamin K. PT and INR is then to be repeated daily until INR is <1.8 upon which the subject can be discharged from the unit.

The fact that this patient was allowed to continue in the study with consistent INR values above 1.8 was inappropriate, even according to their own protocol.

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 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,

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4.2.6 QT Prolongation Study

4.2.6.1 Study C02-023 (Part A): A Phase 1, Double-Blind Study to Evaluate the Safety and Tolerability of 300 mg of TMX-67, and a Double-Blind, Crossover Study to Evaluate the Potential Effect of TMX-67 on the QTc in Healthy Subjects After Multiple Doses Using (moxifloxacin hydrochloride) as the Active Control

b(4)

Study Period: August 7, 2002 to August 13, 2002

Sample Analysis Period: August 16, 2002 to January 8, 2003

Principle Investigator: _____

Study Center:

Analytical Sites: / / / /

protein binding)

b(4)

Reviewer's Note: This was a Phase 1, 2-part study, designed, in the interest of safety, so that Part A (assessment of the safety of the 300 mg QD dose of febuxostat) was completed prior to the initiation of Part B (assessment of once daily multiple dosing of 80 mg and 300 mg of febuxostat on the QTc). Only results for Part A are reviewed in this report. Results for Part B are reviewed in a separate report. See Section 4.2.6.2.

Study Rationale: Part B of Study C02-023 was designed to assess the effect of once daily multiple dosing of 80 mg and 300 mg of febuxostat on the QTc. The 300 mg dose was selected to provide a several fold safety margin (based on the area under the plasma concentration versus time curve [AUC]) for the febuxostat doses in development (i.e., 80 and 120 mg). The safety as well as pharmacokinetics and pharmacodynamics of once daily 300 mg multiple oral doses of febuxostat in healthy volunteers were evaluated (Part A of Study C02-023) before using this dose to study QT prolongation (Part B of Study C02-023). The maximum dose of 300 mg QD of febuxostat was expected to result in an AUC 6 times the AUC of the optimal uric acid lowering dose (80 mg) and 4 times the AUC of the maximum dose (120 mg) in clinical studies.

Objectives:

- To assess the safety of febuxostat (TMX-67) 300 mg once daily (QD) in healthy subjects
- To determine the pharmacokinetics/pharmacodynamics for febuxostat 300 mg QD in healthy subjects

Study Design: Part A of Study C02-023 was a double-blind, placebo-controlled, randomized, single-center study designed to evaluate the safety and pharmacokinetic/pharmacodynamic profile of febuxostat 300 mg QD. The study included 12 healthy subjects; 10 received febuxostat 300 mg QD for 7 days and 2 received placebo QD for 7 days. 300 mg dose were given as three 80 mg tablets plus three 20 mg tablets.

Safety evaluations during confinement included the performance of electrocardiograms (ECGs), vital signs, blood and urine clinical laboratory evaluations, drug and alcohol screening, serum pregnancy testing, physical examinations, and adverse event assessments.

Twelve subjects (6 males and 6 females) were enrolled and completed Part A of Study C02-023 (Table 1). Subjects were excluded if they were being treated for heart rhythm disturbances with any antiarrhythmic medicines or had a screening QT_{FC} of 480 msec or greater. All 10 subjects (4 males and 6 females) receiving febuxostat 300 mg QD were included in the pharmacokinetic and pharmacodynamic analyses. Data from all 12 subjects were included in the safety analyses. Subjects 101 and 112 (both males) were administered placebo and their data were not included in the summary statistics.

Table 1. Summary of Demographic Characteristics.

Demographic Characteristic	All Subjects (N=12)	Febuxostat 300 mg (N=10)	Placebo (N=2)
Gender			
Male	6 (50%)	4 (40%)	2 (100%)
Female	6 (50%)	6 (60%)	0 (0%)
Race			
Caucasian	1 (8%)	1 (10%)	0 (0%)
Hispanic	11 (92 %)	9 (90%)	2 (100%)
Age			
Mean (SD)	39.7 (9.16)	40.8 (9.65)	34.0 (2.83)
Range	26-61	26-61	32-36
Weight (pounds)			
Mean (SD)	164.4 (22.75)	162.1 (23.87)	176.0 (15.56)
Range	135-215	135-215	165-187
Height (inches)			
Mean (SD)	65.1 (3.48)	64.5 (3.41)	68 (2.83)
Range	61-71	61-71	66-70

Test Articles:

Test Product	Dose/Tablet	Manufacturer	Finishing Lot Number (Manufacturer's Lot Number)
Febuxostat	20 mg	Abbott Laboratories	86-061-4Q
Placebo for 20 mg tablets	NA	Abbott Laboratories	82-462-AR
Febuxostat	80 mg	Abbott Laboratories	86-064-4Q
Placebo for 80 mg tablets	NA	Abbott Laboratories	83-465-AR

Febuxostat (80 and 120 mg) are Formulation B1 (production size).

Sample Collection: Plasma, serum, and urine samples were collected for the determination of febuxostat and its metabolites (67M-1, 67M-2, and 67M-4), uric acid (urate), xanthine, and hypoxanthine concentrations. Plasma was also collected for protein binding. The collections are outlined in the following table:

Analyte	Matrix	Samples Collected		
Febuxostat & Metabolites	Plasma		Days 1-7: Predose	Day 7: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 & 24 hours post-dose
Febuxostat & Metabolites	Urine	12-0 hours prior to Day 1 dose		Day 7: 0-6, 6-12 & 12-24 hours post-dose
Uric Acid, Xanthine & Hypoxanthine	Serum	24, 18 & 12 hours prior to Day 1 dose	Days 1-7: Predose	Day 7: 6, 12 & 24 hours post-dose
Uric Acid, Xanthine & Hypoxanthine	Urine	24-18, 18-12 & 12-0 hours prior to Day 1 dose		Day 7: 0-6, 6-12 & 12-24 hours post-dose
Protein Binding	Plasma		Day 1: Prior to dosing	

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

Sample Analysis: Samples for PK and PD analysis were conducted at _____ . Same validation analytical methods used for samples 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 b(4) details.

Plasma protein binding samples were analyzed using an equilibrium dialysis technique performed by _____

Pharmacokinetic and Pharmacodynamic Analysis: Pharmacokinetic parameters for febuxostat and its metabolites in plasma were determined by standard noncompartmental methods using WinNonlin® Professional V.3.1 computer software package (Pharsight Corporation, Mountain View, CA). b(4)

Pharmacodynamic parameters were estimated using the serum and urine concentration values.

Pharmacokinetic Results:

Protein Binding

The *in vitro* protein binding of [¹⁴C] febuxostat at a nominal concentration of 1 µg/mL was determined in predose plasma samples obtained from each subject using an equilibrium analysis technique. The mean ± SD free fraction calculated from the samples collected from the subjects who received febuxostat was 0.007 ± 0.001 which shows that [¹⁴C] febuxostat was highly bound to plasma proteins in the subject samples analyzed (99.3%).

Plasma PK Profiles

Based on the predose plasma concentrations of febuxostat and its metabolites, febuxostat and its metabolites appear to have reached steady state around Day 4 (Figure 1).

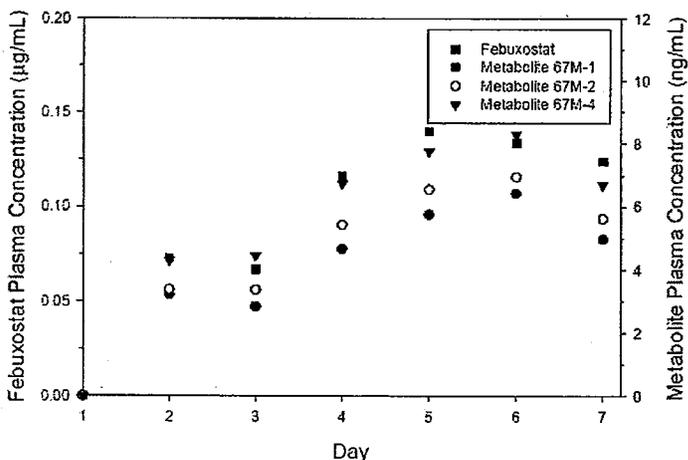


Figure 1. Mean Febuxostat and Metabolites 67M-1, 67M-2 and 67M-4 Predose Plasma Concentrations Following Daily Oral Administration of Febuxostat (300 mg QD) to Subjects in Study C02-023, Part A.

Pharmacokinetic parameter estimates for febuxostat and its metabolites on Day 7 are presented in Tables 2 and 3.

Table 2. Summary of Pharmacokinetic Parameters of Febuxostat on Day 7 Following Oral Administration of Febuxostat (300 mg QD).

Analyte		t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	C_{max} (ng/mL)	AUC_{τ} ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{τ} (ng·h/mL)	$t_{1/2}^a$ (h)	V_z/F (L)	Cl/F (L/h)	Cl/F _n (L/h)	C_{max}/D (L ⁻¹)	AUC_{τ}/D (h/L)
Febuxostat	Mean	1.00	14.2547	100.6877	48.3557	339.1953	6.3 (5.9)	31.7	6.80	1025.18	0.0475	0.1612
	SD	0.33	5.4405	45.6143	15.7048	129.0214	1.6	10.4	2.11	439.12	0.0181	0.0523

N=10

a Arithmetic Mean (Harmonic Mean)

Table 3. Summary of Pharmacokinetic Parameters of 67M-1, 67M-2, and 67M-4 on Day 7 Following Oral Administration of Febuxostat (300 mg QD).

Analyte		t_{max} (h)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)	$t_{1/2}^a$ (h)	C_{max}/D (10 ⁻³ L ⁻¹)	AUC_{τ}/D (10 ⁻³ h/L)	AUC Ratio ^b
67M-1	Mean	1.65	398.182	1503.998	7.4 (6.9)	1.327	5.013	0.031
	SD	0.34	165.229	551.923	2.3	0.551	1.840	0.006
67M-2	Mean	1.85	306.339	1364.678	8.5 (7.6)	1.021	4.549	0.029
	SD	0.47	153.165	400.943	3.1	0.511	1.336	0.006
67M-4	Mean	2.25	219.236	1202.274	8.6 (8.3)	0.731	4.008	0.811
	SD	0.54	77.605	417.769	1.8	0.259	1.393	0.127

N=10

a Arithmetic Mean (Harmonic Mean)

b Ratios are 67M-1/febuxostat, 67M-2/febuxostat and 67M-4/67M-1

The total mean exposure to febuxostat (AUC_{τ}) following oral administration of febuxostat 300 mg QD for 7 days was 48.36 $\mu\text{g}\cdot\text{h/mL}$, approximately 6 times the observed mean total plasma exposures with 80 mg of febuxostat in previous studies in healthy subjects (7.49-8.16 $\mu\text{g}\cdot\text{h/mL}$ AUC_{τ}). The AUC_{τ} of febuxostat from the 300 mg dose group was 4 times that from the 120 mg dose group (11.96 $\mu\text{g}\cdot\text{h/mL}$).

There was no substantial change in the mean dose-normalized AUC_{τ} when the dose was increased from 240 mg QD to 300 mg QD (0.1457 ± 0.0413 h/L to 0.1612 ± 0.0523 h/L). The febuxostat mean oral clearances were similar following the 240 mg and 300 mg oral doses (7.28 ± 1.74 L/h vs. 6.80 ± 2.11 L/h, respectively). In addition, the dose-normalized C_{max} and AUC of the metabolites did not appear to change compared with the mean values for the 240 mg dose group values. Also, the 300 mg febuxostat QD metabolite to parent drug ratios were similar to those of the 240 mg dose group. Therefore, there were no substantial changes in disposition of febuxostat and its metabolites when increasing the dose from 240 mg QD to 300 mg QD.

The harmonic mean of the apparent $t_{1/2z}$ for febuxostat and its metabolites was shorter for the 300 mg QD dose group as compared with the harmonic mean value of the 240 mg QD dose group due to the biphasic nature of the terminal phase and the different sampling regimens between the 2 studies (sampling up to 24 hours in this study vs. sampling up to 48 hours in the dose-escalation study) which led to different terminal phase intervals being used for estimation of the $t_{1/2}$ between the 2 dose groups (12-24 hour mean interval for the 300 mg vs. 19-40 hour mean interval for the 240 mg). The harmonic mean half-life values, however, were comparable to

those observed for the lower doses of febuxostat in the studies where similar intervals were used for their estimation.

Ae_{24} , fraction of dose excreted (f_e) in urine, and Cl_r of unchanged and total febuxostat, 67M-1, 67M-2, and 67M-4 on Day 7 following oral administration of febuxostat (300 mg QD) are presented in Table 4.

Table 4. Mean of Total Daily Urinary Excretion (Ae_{24}), Fraction of Dose Excreted in Urine (f_e), and Renal Clearance (Cl_r) of Unchanged and Total Febuxostat, 67M-1, 67M-2, and 67M-4 on Day 7 Following Oral Administration of Febuxostat (300 mg QD).

Analyte		Unchanged			Total	
		Ae_{24} (μ g)	f_e	Cl_r (L/h)	Ae_{24} (μ g)	f_e
Febuxostat	Mean	3934	0.013	0.09	104368	0.348
	SD	1274	0.004	0.04	30217	0.101
67M-1	Mean	19870	0.063	14.04	27942	0.089
	SD	5348	0.017	3.57	5667	0.018
67M-2	Mean	13824	0.044	10.49	18139	0.058
	SD	3156	0.010	2.25	4176	0.013
67M-4	Mean	8896	0.027	7.69	10018	0.030
	SD	2458	0.007	1.65	2649	0.008

N=10

The mean Ae_{24} , fraction of the dose excreted in urine (f_e), and Cl_r of febuxostat and its metabolites were generally within the range of means observed with the lower doses of febuxostat.

Pharmacodynamic Results:

The mean predose serum concentrations of uric acid, xanthine and hypoxanthine on Days 1-7 are presented in Figure 2. Based on the predose serum concentrations, xanthine and hypoxanthine appear to have reached steady state by Day 4 and serum uric acid appears to have reached steady state by Day 6.

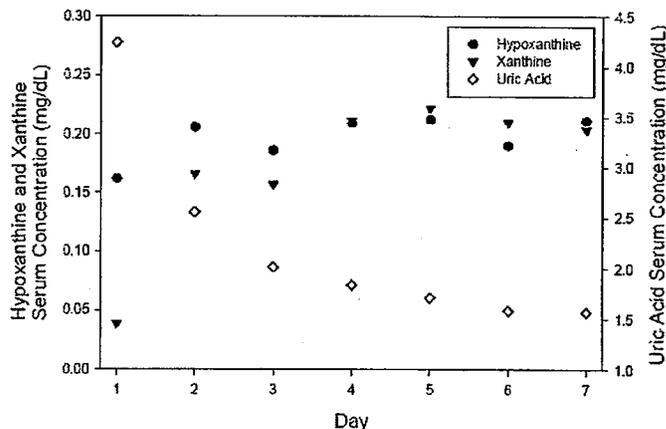


Figure 2. Mean Uric Acid, Xanthine and Hypoxanthine Predose Serum Concentrations Following Daily Oral Administration of Febuxostat (300 mg QD) to Subjects in Study C02-023, Part A.

Serum Urate, Xanthine, and Hypoxanthine Levels

A summary of the mean serum uric acid, xanthine, and hypoxanthine $C_{\text{mean},24}$ values on Day -1 and Day 7, and the percent change from baseline is presented in Table 5.

Table 5. Summary of 24-Hour Mean Serum Uric Acid, Xanthine, and Hypoxanthine Concentrations and Percent Change from Baseline in the 24-Hour Mean Serum Uric Acid Concentrations on Day 7 Following Oral Administration of Febuxostat (300 mg QD).

Analyte		$C_{\text{mean},24}$ (mg/dL)		% Change
		Day -1	Day 7	
Uric Acid	Mean	4.068	0.577	-86.97
	SD	1.152	0.403	7.00
Xanthine	Mean	0.0396	0.2289	
	SD	0.0094	0.0664	
Hypoxanthine	Mean	0.1844	0.1917	
	SD	0.0727	0.0463	

N=10

Following oral administration of febuxostat 300 mg QD for 7 days, the 24-hour mean uric acid concentrations decreased by approximately 87% (Table 5), which was slightly higher than the predicted value (76%), based on the baseline E_{max} model which was used to fit the data from the dose-escalation study (Study TMX-99-001, Section 4.2.2.1). The mean xanthine serum concentrations increased to 0.229 mg/dL, which was equal to the predicted value (0.229 mg/dL) based on the baseline E_{max} model used to fit the xanthine data from the dose-escalation study. As in the dose-escalation study, there appeared to be no substantial change (only a 4% increase in this study) in the 24-hour mean serum hypoxanthine concentrations following multiple dosing with 300 mg of febuxostat.

Urine Uric Acid, Xanthine, and Hypoxanthine Levels

The summary for the 24-hour amount excreted in urine (Ae_{24}), urinary $C_{\text{mean},24}$, and Cl_r of uric acid, xanthine, and hypoxanthine on Days -1 and 7 following oral administration of 300 mg QD febuxostat are presented in Table 6.

Table 6. Summary of 24-Hour Amount Excreted (Ae_{24}), Mean Concentration ($C_{\text{mean},24}$) and Renal Clearance (Cl_r) of Uric Acid, Xanthine, and Hypoxanthine in Urine on Days -1 and 7 Following Oral Administration of Febuxostat 300 mg.

Analyte		Day -1			Day 7		
		Ae_{24} (mg)	$C_{\text{mean},24}$ (mg/dL)	Cl_r (mL/min)	Ae_{24} (mg)	$C_{\text{mean},24}$ (mg/dL)	Cl_r (mL/min)
Uric Acid	Mean	521.60	18.131	4.58	35.59	1.353	1.06
	SD	147.98	7.000	1.91	43.11	1.479	1.40
Xanthine	Mean	10.30	0.330	7.60	260.8	10.567	35.93
	SD	8.37	0.212	3.06	45.6	2.781	13.53
Hypoxanthine	Mean	6.90	0.237	1.39	45.40	1.760	8.15
	SD	3.51	0.137	0.76	13.69	0.358	3.65

Following oral administration of 300 mg QD of febuxostat for 7 days, the urinary $C_{\text{mean},24}$ declined by approximately 93% from 18.131 mg/dL on Day -1 to 1.353 mg/dL on Day 7. Similarly, uric acid mean Ae_{24} also decreased by approximately 93% following multiple dosing

with 300 mg QD of febuxostat. The extent of decrease in urine uric acid $C_{\text{mean},24}$ and Ae_{24} , however, may have been slightly overestimated since some of the concentrations of uric acid in urine samples on Day 7 were below the lower limit of quantitation and hence were reported as zero. In comparison to Day 1 mean Clr, the Day 7 mean Clr was lower by approximately 77%, most likely due to the underestimation of urine uric acid $C_{\text{mean},24}$ and Ae_{24} on Day 7, which would lead to underestimation of Clr on Day 7. In previous studies, renal clearance of uric acid appeared not to be affected by febuxostat.

Following multiple dosing with 300 mg QD of febuxostat, xanthine $C_{\text{mean},24}$, Ae_{24} , and Clr on Day 7 increased to 32, 25, and 5 times its baseline values, respectively. The extent of increase in the xanthine Ae_{24} was slightly higher with the 300 mg QD dose group as compared with the 240 mg QD dose group; however, the urine xanthine $C_{\text{mean},24}$ appeared to be lower due to higher urine output for the 300 mg dose group as compared with the 240 mg dose group. The slightly higher Ae_{24} exhibited by the 300 mg dose group may have been partly due to a slightly higher baseline total uric acid, xanthine, and hypoxanthine Ae_{24} for the 300 mg dose group as compared with the 240 mg dose group. The hypoxanthine urine $C_{\text{mean},24}$, Ae_{24} , and Clr on Day 7 increased to 7, 7, and 6 times its baseline values, respectively.

Conclusion:

- Febuxostat 300 mg QD for 7 days resulted in an exposure (AUC) that was approximately 6 times that obtained after multiple dosing with 80 mg of febuxostat and 4 times that with 120 mg of febuxostat and was in line with the pre-study predictions.
- There was no substantial change in the pharmacokinetics of febuxostat within the 240 mg QD to 300 mg QD dosage range. Following multiple dosing with febuxostat 300 mg QD, there appeared to be a greater pharmacodynamic effect than was observed with febuxostat 240 mg QD.
- In Part A of Study C02-023, the 300 mg dose of febuxostat QD was found to be safe and generally well tolerated in this limited dataset of 12 subjects. The results of this study supported proceeding to Part B of Study C02-023.

4.2.6.2 *Study C02-023 (Part B): A Phase 1, Double-Blind Study to Evaluate the Safety and Tolerability of 300 mg of TMX-67, and a Double-Blind, Crossover Study to Evaluate the Potential Effect of TMX-67 on the QTc in Healthy Subjects After Multiple Doses Using (moxifloxacin hydrochloride) as the Active Control*

b(4)

Study Periods: August 27, 2002 to October 9, 2002
Sample Analysis Periods: October 22, 2002 to January 8, 2003 (Febuxostat)
October 16, 2002 to October 22, 2002 (Moxifloxacin)
Principle Investigators:
Study Centers: / / / /
Analytical Sites:

b(4)

Reviewer's Note: This was a Phase 1, 2-part study, designed, in the interest of safety, so that Part A (assessment of the safety of the 300 mg QD dose of febuxostat) was completed prior to the initiation of Part B (assessment of once daily multiple dosing of 80 mg and 300 mg of febuxostat on the QTc). Only results for Part B are reviewed in this report. Results for Part A are reviewed in a separate report. See Section 4.2.6.1.

Background and Study Rationale: Febuxostat was screened for cardiac safety using *in vitro* models of human hERG (Human Ether-a-go-go, a potassium ion channel) test and isolated dog Purkinje fibers. Preclinical cardiovascular safety telemetry studies also were conducted. There was an agonistic effect noted in the hERG assay and a loss of excitability in the action potential duration at high doses. These studies and findings did not show or indicate a prolongation in the length of time it takes the electrical system in the heart to repolarize adjusted for heart rate (normal 350-440 milliseconds) (QTc) with febuxostat.

Clinical data did not show any apparent QT prolongation (length of time it takes the electrical system in the heart to repolarize) effects leading to ECG abnormalities, and except for subjects with pre-existing or concurrent diseases, ECG tracings in the Phase 1 and Phase 2 studies were homogeneous and within normal limits. Part B of this study was designed to assess the effect of once daily multiple dosing of 80 mg and 300 mg of febuxostat on the QTc. The 300 mg dose was selected to provide a several fold safety margin (based on the area under the plasma concentration versus time curve [AUC]) for the febuxostat doses in development (i.e., 80 mg and 120 mg).

Objectives: To assess the potential for a prolongation of the QTc interval after multiple doses of febuxostat (TMX-67) in healthy subjects.

Study Design: Part B of Study C02-023 was a multicenter, randomized, blinded (febuxostat and placebo only), 4-period crossover trial using multiple doses of 80 mg of febuxostat, 300 mg of febuxostat, placebo, and 400 mg of — moxifloxacin (active control). Forty-four (44) healthy subjects were randomly assigned in equal numbers to the 4 regimen sequences (Table 1). Each period consisted of 4 days of QD dosing. There was a 7-day washout interval between the last dose in a period and the first dose of the subsequent period.

b(4)

Table 1. Study Regimen Sequences.

Regimen Sequence	Number of Subjects	Period 1	Period 2	Period 3	Period 4
I	11	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	— 400 mg
II	11	Febuxostat 300 mg	Placebo	— 400 mg	Febuxostat 80 mg
III	11	Febuxostat 80 mg	— 400 mg	Placebo	Febuxostat 300 mg
IV	11	— 400 mg	Febuxostat 300 mg	Febuxostat 80 mg	Placebo

b(4)

Throughout the study, ECG, pharmacokinetic, and safety data were collected. The safety of the study drug was monitored using physical examinations, ECGs, laboratory evaluations, adverse events, concomitant medications, and vital signs.

Forty-four subjects (32 males and 12 females) were enrolled in Part B of Study C02-023; 43 subjects completed at least 1 period and 41 (29 males and 12 females) completed all 4 periods of the study. Subject 205 (Male, Hispanic) discontinued after receiving study drug (febuxostat 300 mg) on Day 1 of Period 1. The reason for discontinuation was given as "withdrawn consent." Subjects 225 (Male, Black) and 230 (Male, Caucasian) discontinued after receiving study drug (febuxostat 80 mg) and completing Period 1. Subject 225 was discontinued for "personal reasons; too many blood draws." Subject 230 discontinued due to an adverse event of increased laboratory values (amylase of 329 U/L, lipase of 601 U/L).

Data from all 44 subjects were analyzed for safety, and data from 41 subjects were included in the primary ECG analysis. Qualifying data were included in the descriptive statistics for pharmacokinetic analysis.

The mean age of the 44 subjects was 41 years (range: 25-65 years), the mean weight was 168.2 pounds (range: 135-221 pounds), and the mean height was 67.5 inches (range: 60-75 inches). Twenty-two (22) of the subjects were Hispanic (50%), 18 were Caucasian (41%), 3 were Black (7%) and 1 was Asian (2%).

Test Articles:

Study Drug	Dose/Tablet	Manufacturer	Finishing Lot Number (Manufacturer's Lot Number)
Febuxostat	20 mg	Abbott Laboratories	86-061-4Q
Placebo for 20 mg tablets	NA	Abbott Laboratories	82-462-AR
Febuxostat	80 mg	Abbott Laboratories	86-064-4Q
Placebo for 80 mg tablets	NA	Abbott Laboratories	83-463-AR
— (moxifloxacin hydrochloride)	400 mg	—	25004SL

b(4)

Febuxostat (80 and 120 mg) are Formulation B1 (production size).

Blood Collection for PK Analyses: Blood samples (5 mL) for febuxostat assays were collected on Day 1 pre-dose and at 33, 63, 93, 123, and 243 minutes post-dose; on Days 2 and 3 pre-dose; and on Day 4 pre-dose and at 18, 33, 48, 63, 78, 93, 108, 123, 138, 153, 168, 183, 243, and 363 minutes post-dose.

Blood samples (3 mL) for moxifloxacin assays were collected on Day 1 pre-dose and at 33, 63, 93, 183, and 363 minutes post-dose; on Days 2 and 3 pre-dose; and on Day 4 pre-dose and at 33, 63, 93, 123, 153, 183, 243, and 363 minutes post-dose.

(Reviewer's Note: The Sponsor did not collect blood beyond 6 hr in this study.)

ECG and Blood Pressure Measurements:

- A resting 12-lead ECG was obtained during screening
- On Day -1 (the day before dosing), ECGs were obtained at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 240, 360, 480 minutes, and at 12 hrs
- On Day 1, ECGs were obtained 30 minutes prior to dosing, and at 30, 60, 90, 120, 150, 180, and 240 minutes post-dose
- On Days 2 and 3, ECGs were obtained 1 hour post-dose

- On Day 4, ECGs were obtained 30 minutes prior to dosing and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 240, 360, and 480 minutes; and at 12 and 24 hours post-dose.

For each ECG, the following parameters were measured: heart rate, PR interval, QRS complex duration, QT interval, QT_{Fc}, RR interval, and ST segment. In addition, T and U wave morphology was recorded. Additional ECG parameters were evaluated as appropriate.

_____ ECG machines (model: _____, were used to obtain the ECG tracings at both clinical study sites. A subject was to be discontinued from the study if a QT_{Fc} ≥ 520 msec was observed.

b(4)

PK Sample Analysis: Concentrations of febuxostat in plasma were determined at _____ using a validated high performance liquid chromatographic method (Project 23150_1) with fluorescence detection. The lower limit of quantitation with a 0.5 mL plasma sample was 0.01 µg/mL for febuxostat.

b(4)

Blood samples collected after administration of the placebo tablets were not analyzed for febuxostat content.

Concentrations of moxifloxacin in plasma were determined at _____ using a validated high performance liquid chromatographic method (Method LC 335) with UV detection. Moxifloxacin and the internal standard _____ were The lower limit of quantitation with a 0.25 mL plasma sample was 25.0 ng/mL.

b(4)

Pharmacokinetic Analysis: The pharmacokinetic parameters estimated from the plasma concentration data for both febuxostat and moxifloxacin included the maximum observed plasma concentration (C_{max}) and time to the observed maximum concentration (t_{max}). Due to the limited blood sampling at the later time points, no other pharmacokinetic parameters were estimated. Assay results below the lower limit of quantitation were treated as zero in calculations. Nominal times for the blood samples were used in reporting the data.

Electrocardiographic Analyses: The following ECG variables were summarized and analyzed: QT interval, PR interval, QRS duration, and heart rate. QT intervals were corrected using Fridericia's formula (QT_{Fc} = QT/RR^{1/3}). The Fridericia's corrected QT was used as the primary assessment of QT prolongation.

The differences between active doses and placebo with respect to QT_{Fc} on Days 1 and 4 were assessed based on the maximum and the time-averaged QT_{Fc} intervals defined as follows:

1. The maximum QT_{Fc} interval was defined as the maximum of the post-dose QT_{Fc} values in each day (Days 1 and 4) for each subject. This analysis reflects the largest effect on the QT interval regardless of whether it corresponds to the time C_{max} of febuxostat or moxifloxacin was observed.
2. The time-averaged QT_{Fc} interval was defined as the average of all post-dose QT_{Fc} values in each day (Days 1 and 4) for each subject.

Pharmacokinetic Results:Febuxostat

Based on the pre-dose febuxostat mean concentration data, the steady state concentrations of febuxostat have been achieved by Day 4 for both 80 mg and 300 mg once daily doses of febuxostat (Table 2).

Table 2. Predose Concentrations (Mean \pm SD, $\mu\text{g/mL}$) of Febuxostat on Days 2, 3, and 4.

	Day 2	Day 3	Day 4
80 mg (N=43)	0.0193 \pm 0.0123	0.0197 \pm 0.0122	0.0146 \pm 0.0099
300 mg (N=41)	0.1183 \pm 0.072	0.1028 \pm 0.056	0.0866 \pm 0.047

Because of limited blood sampling at the later time points, only C_{max} and T_{max} values for febuxostat were listed in Table 3.

Table 3. Pharmacokinetic Parameters after Administration of Febuxostat 80 or 300 mg for 1 or 4 Days.

	Febuxostat 80 mg				Febuxostat 300 mg			
	Day 1		Day 4		Day 1		Day 4	
	t_{max} (h)	C_{max} ($\mu\text{g/mL}$)						
Mean	2.72	1.8353	2.38	2.4566	3.01	6.8816	2.75	10.4120
SD	1.13	1.0822	0.92	1.0507	1.24	4.6649	0.97	3.9445
%CV	41	59	39	43	41	68	35	38
Median	2.05	1.6499	2.55	2.5961	4.05	7.2509	2.80	10.6272
Minimum	0.55	0.3320	0.30	0.5768	0.55	0.4978	0.55	2.1138
Maximum	4.05	4.8699	6.05	5.6384	4.05	18.8887	6.05	18.2606
N	43	43	43	43	41	41	41	41

After administration of 300 mg febuxostat for 4 days, the mean C_{max} (10.4120 $\mu\text{g/mL}$) was approximately 4 times that observed after administration of 80 mg febuxostat for 4 days (2.4566 $\mu\text{g/mL}$).

Moxifloxacin

Based on the pre-dose concentration data from Days 2, 3, and 4, the steady-state concentration of moxifloxacin was reached by Day 4 for — 400 mg QD (Table 4). b(4)

Table 4. Mean Predose Concentrations (ng/mL) of Moxifloxacin on Days 2, 3, and 4.

	Day 2 (N=41)	Day 3 (N=40)	Day 4 (N=41)
400 mg	677 \pm 152	854 \pm 196	825 \pm 221

Descriptive statistics for the moxifloxacin T_{max} and C_{max} following administration of — 400 mg are given in Table 5. b(4)

Table 5. Moxifloxacin Pharmacokinetic Parameters from Daily Dosing of 400 mg for 1 or 4 Days.

	400 mg			
	Day 1		Day 4	
	t_{max} (h)	C_{max} (ng/mL)	t_{max} (h)	C_{max} (ng/mL)
Mean	3.47	2780	3.06	3490
SD	1.26	828	1.33	679
%CV	36	30	43	19
Median	3.05	2800	3.05	3410
Minimum	0.55	838	1.05	2100
Maximum	6.05	4600	6.05	5190
N	41	41	41	41

b(4)

The T_{max} values obtained in this study were similar to the mean T_{max} values of approximately 1-3 hours as reported in the package insert. The mean values for C_{max} from single or multiple doses were also consistent with those reported in the package insert (single dose, 3100 ng/mL; multiple dose, 3600-4600 ng/mL).

b(4)

ECG Results:

Maximal and Time-Averaged QT_{Fc} Intervals

The mean of the maximum post-dose QT_{Fc} interval values and the time-averaged values for 400 mg was statistically significantly greater than placebo (p<0.001) on Day 1 and Day 4, respectively, while there were no statistically significant differences between either of the febuxostat dose regimens and placebo (Tables 6 and 7).

b(4)

Table 6. Comparison of Maximum QT_{Fc} Intervals.

	Mean of Maximum QT _{Fc} (msec)				Difference from Placebo (msec)		
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	400 mg	Febuxostat 80 mg	Febuxostat 300 mg	400 mg
Baseline	406.0	407.1	405.7	404.3	1.1	-0.3	-1.7
Day 1	396.5	398.6	398.5	406.8***	2.1	2.0	10.3
Day 4	402.9	403.7	405.1	415.9***	0.8	2.2	13.0

*** Indicates statistically significant difference from placebo at the 0.001 level.

b(4)

Table 7. Comparison of Time-Averaged QT_{Fc} Intervals.

	Mean of Time-Averaged QT _{Fc} (msec)				Difference from Placebo (msec)		
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	400 mg	Febuxostat 80 mg	Febuxostat 300 mg	400 mg
Baseline	387.6	389.6	389.7	387.2	2.0	2.1	-0.4
Day 1	384.1	384.9	385.4	389.9***	0.8	1.3	5.8
Day 4	384.5	383.6	386.5	395.6***	-0.9	2.0	11.1

*** Indicates statistically significant difference from placebo at the 0.001 level.

Categorical Analyses of QT_{Fc} Intervals

The numbers of subjects with increases from baseline to maximum post-dose QT_{Fc} intervals in categories of <30 msec, 30-60 msec, and >60 msec are shown in Table 8. 400 mg had the most % of patients showed 30-60 msec QT_{Fc} increases from baseline on both Day 1 and Day 4 and there was 1 patient (Subject 239, male, Caucasian) had an increase for more than 60 msec

when dosed with — 400 mg on Day 1. Both 80 and 120 mg groups of febuxostat had similar % of patients as the placebo group for all the categories.

b(4)

Table 8. Number and Percentage of Subjects with Increases from Baseline to Maximum Post-dose QT_{FC} Interval.

Day/Category		Placebo N (%)	Febuxostat 80 mg N (%)	Febuxostat 300 mg N (%)	— 400 mg N (%)
Day 1	<30 msec	40 (98)	43 (100)	41 (98)	35 (85)
	30-60 msec	1 (2)	0	1 (2)	5 (12)
	>60 msec	0	0	0	1 (2)
Day 4	<30 msec	39 (95)	42 (98)	38 (93)	22 (54)
	30-60 msec	2 (5)	3 (7)	3 (7)	19 (46)
	>60 msec	0	0	0	0

b(4)

The shifts of QT_{FC} interval values from baseline relative to the categories of normal (<430 msec), borderline (>430 msec and <450 msec), or prolonged (>450 msec) are shown in Table 9.

Table 9. Shifts of QT_{FC} Interval Values from Baseline Relative to the Categories of Normal, Borderline, or Prolonged.

		Placebo			Febuxostat 80 mg			Febuxostat 300 mg			— 400 mg		
		Baseline			Baseline			Baseline			Baseline		
		N	B	P	N	B	P	N	B	P	N	B	P
Day 1	N	39	2	0	42	1	0	37	2	0	33	1	0
	B	0	0	0	0	0	0	2	1	0	6	1	0
	P	0	0	0	0	0	0	0	0	0	0	0	0
Day 4	N	37	1	0	40	1	0	34	2	0	28	1	0
	B	2	1	0	2	0	0	4	1	0	11	1	0
	P	0	0	0	0	0	0	0	0	0	0	0	0

b(4)

N = "Normal (<=430 msec)", B = "Borderline (>430 to <=450 msec)", and P = "Prolonged (>450 msec)".

Number of subjects per group: Placebo = 41, Febuxostat 80 mg = 43, Febuxostat 300 mg = 42, and — 400 mg = 41.

The numbers of subjects with QT_{FC} shift from normal to borderline on Day 1 were 0, 2 (5%), and 6 (15%) for febuxostat 80 mg, 300 mg, and — 400 mg, respectively, as compared with 0 for placebo (Table 9). The numbers of subjects with QT_{FC} shift from normal to borderline on Day 4 were 2 (5%), 4 (10%), and 11 (27%) for febuxostat 80 mg, 300 mg, and — 400 mg, respectively, as compared with 2 (5%) for placebo. No subject in any regimen had prolonged QT_{FC} intervals (> 450 msec) either on Day 1 or Day 4.

b(4)

In terms of QT_{FC} shift from normal to borderline on Day 1 and Day 4, it appears that 80 mg febuxostat group was similar to the placebo group, while the 300 mg febuxostat had higher % of patients shifted and — 400 mg had the highest % of patients shifted.

Box plot of QT_{FC} intervals versus time on Baseline (Day -1), Day 1, and Day 4 were produced for each regimen (see Appendix, Figures A.1 and A.3).

Analyses of Uncorrected QT, PR, QRS Intervals, and Heart Rates

Uncorrected QT interval, PR interval, QRS interval, and heart rate were analyzed using maximum and time-averaged post-dose values on Days 1 and 4. The results from the analyses are presented in Tables 10 and 11, respectively.

Table 10. Maximum Uncorrected QT, PR, QRS Intervals, and Heart Rates.

	Mean of Maximum Values				Difference from Placebo		
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	400 mg	Febuxostat 80 mg	Febuxostat 300 mg	400 mg
Uncorrected QT (msec)							
Baseline	404.2	407.6	404.3	402.5	3.3	0.1	-1.7
Day 1	391.0	394.8	392.0	399.3***	3.8	1.0	8.3
Day 4	391.6	392.7	392.2	405.4***	1.1	0.6	13.8
PR Interval (msec)							
Baseline	183.5	175.4	173.6	175.8	-8.1	-9.9	-7.7
Day 1	175.6	165.2	163.7	163.8*	-10.4	-11.9	-11.8
Day 4	167.8	166.0	186.3	180.1	-1.8	18.5	12.3
QRS Interval (msec)							
Baseline	97.9	97.8	98.9	99.4	-0.1	1.0	1.5
Day 1	95.9	95.6	94.5	94.1	-0.3	-1.4	-1.8
Day 4	98.0	95.7	96.0	96.0	-2.3	-2.0	-2.0
Heart Rate (bpm)							
Baseline	72.0	71.9	71.4	72.2	-0.1	-0.6	0.2
Day 1	70.2	68.4	69.1	71.5	-1.8	-1.1	1.3
Day 4	76.3	75.6	77.6	75.0	-0.7	1.3	-1.3

*, ***, indicates statistically significant difference from placebo at the 0.05 and 0.001 level, respectively.

The mean of the maximum post-dose uncorrected QT values for 400 mg was statistically significantly greater than placebo with mean increases of 8.3 and 13.8 msec (p<0.001) on Day 1 and Day 4, respectively. There was no statistically significant difference between either of the febuxostat dose regimens and placebo on either Day 1 or Day 4. For the PR interval, the means of the maximum post-dose values on Day 1 for febuxostat 300 mg and 400 mg were statistically significantly less than placebo with mean differences of -11.9 and -11.8 msec, (p=0.037 and p=0.038), respectively.

The differences between each of the active regimens and placebo for QRS intervals and heart rate were not statistically significant.

Table 11. Time-Averaged Uncorrected QT, PR, QRS Intervals, and Heart Rates.

	Mean of Time-Averaged Values				Difference from Placebo		
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	400 mg	Febuxostat 80 mg	Febuxostat 300 mg	400 mg
Uncorrected QT (msec)							
Baseline	384.3	387.4	386.8	384.1	3.1	2.5	-0.2
Day 1	378.1	381.4	379.8	382.2	3.3	1.7	4.1
Day 4	373.4	372.3	372.9	384.5***	-1.1	-0.5	11.1
PR Interval (msec)							
Baseline	159.7	159.7	157.4	158.4	0	-2.3	-1.3
Day 1	159.1	158.7	157.7	157.1	-0.4	-1.4	-2.0
Day 4	158.9	158.9	160.7	160.1	0	1.8	1.2
QRS Interval (msec)							
Baseline	91.5	92.5	93.1	91.0	1.0	1.6	-0.5
Day 1	91.4	91.2	90.8	90.5	-0.2	-0.6	-0.9
Day 4	91.0	90.7	91.4	91.0	-0.3	0.4	0
Heart Rate (bpm)							
Baseline	62.3	61.7	62.2	62.2	-0.6	-0.1	-0.1
Day 1	63.7	62.3	63.3	64.4	-1.4	-0.4	0.7
Day 4	66.4	66.4	67.5	66.1	0	1.1	-0.3

*, ***, Indicates statistically significant difference from placebo at the 0.05 and 0.001 level, respectively.

The mean of the time-averaged post-dose uncorrected QT values for 400 mg was statistically significantly greater than placebo with mean increases of 4.1 and 11.1 msec ($p < 0.001$) on Day 1 and Day 4, respectively.

For the PR and QRS intervals on both Days 1 and 4, there were no statistically significant differences between each of the active dose regimens and placebo in the analyses of time-averaged post-dose values. There was a statistically significant difference between febuxostat 80 mg and placebo in the analyses of time-averaged post-dose heart rates (62.3 versus 63.7 bpm; $p = 0.036$) on Day 1.

T Wave and U Wave Morphology

Table 12. Frequency of Subjects with T Wave Abnormality

	Placebo n (%)	Febuxostat 80 mg n (%)	Febuxostat 300 mg n (%)	400 mg n (%)
Baseline	4 (10)	2 (5)	2 (5)	2 (5)
Day 1	2 (5)	4 (9)	1 (2)	3 (7)
Day 4	3 (7)	6 (14)	6 (15)	3 (7)

All abnormal T waves were classified as nonspecific T wave abnormalities; none were described as being clinically significant.

Evaluations for the U wave for all subjects were recorded as "Absent."

Conclusion:

- Based on the individual and mean pharmacokinetic data at steady state, ECG recordings were obtained at or near the time of maximum febuxostat and moxifloxacin plasma concentrations.
- As compared with placebo, the analysis of ECG recording data demonstrated that there were no QT_{Fc} interval prolongations for the febuxostat regimens, whereas 400 mg significantly prolonged QT_{Fc} interval.
- Subjects with abnormal T waves were found in all the dose regimens (including placebo). All abnormal T waves were classified as nonspecific T wave abnormalities and none were described as being clinically significant.

Appendix. Exploratory Analyses

Box plots of QT_{Fc} intervals versus time on Baseline (Day -1), Day 1, and Day 4 were produced for each regimen (Figures A.1 to A.3). Some degree of time-dependency of the QT_{Fc} intervals was observed, especially on Day 4. The dependency appears to be stronger for the 400 mg regimen as compared with the febuxostat regimens or placebo.

(Reviewer's Note: There are four plots in Figures A.1 to A.3. They are arranged as top left 80 mg febuxostat, top right febuxostat 300 mg, bottom left placebo, and bottom right 400 mg)

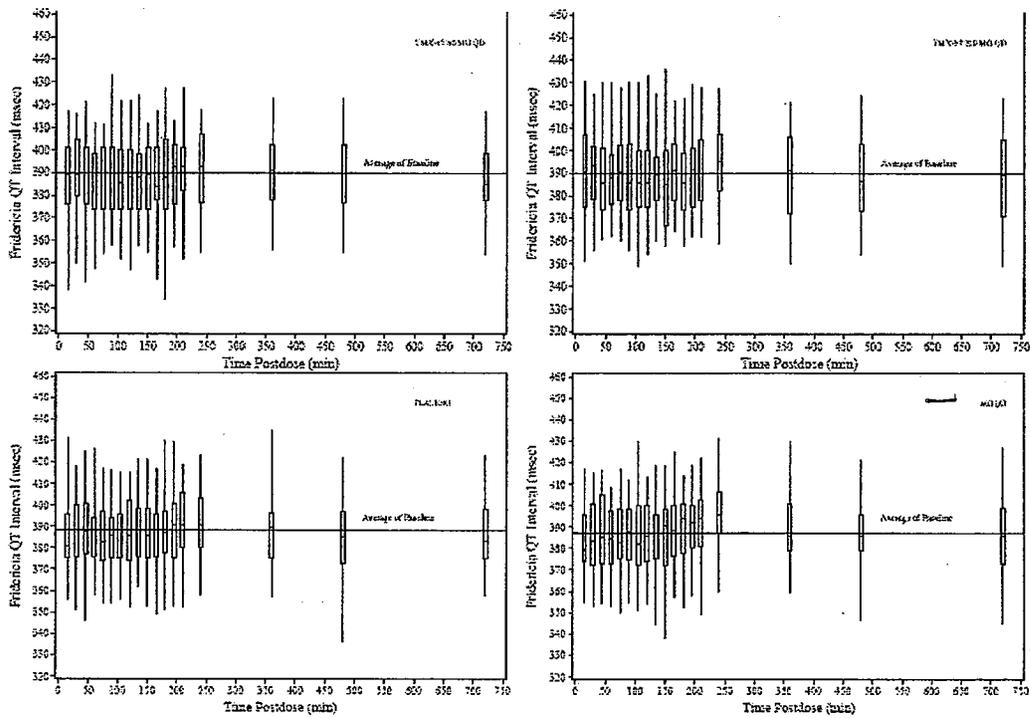


Figure A.1. Box Plot of Fridericia QT Interval versus Time for Baseline.

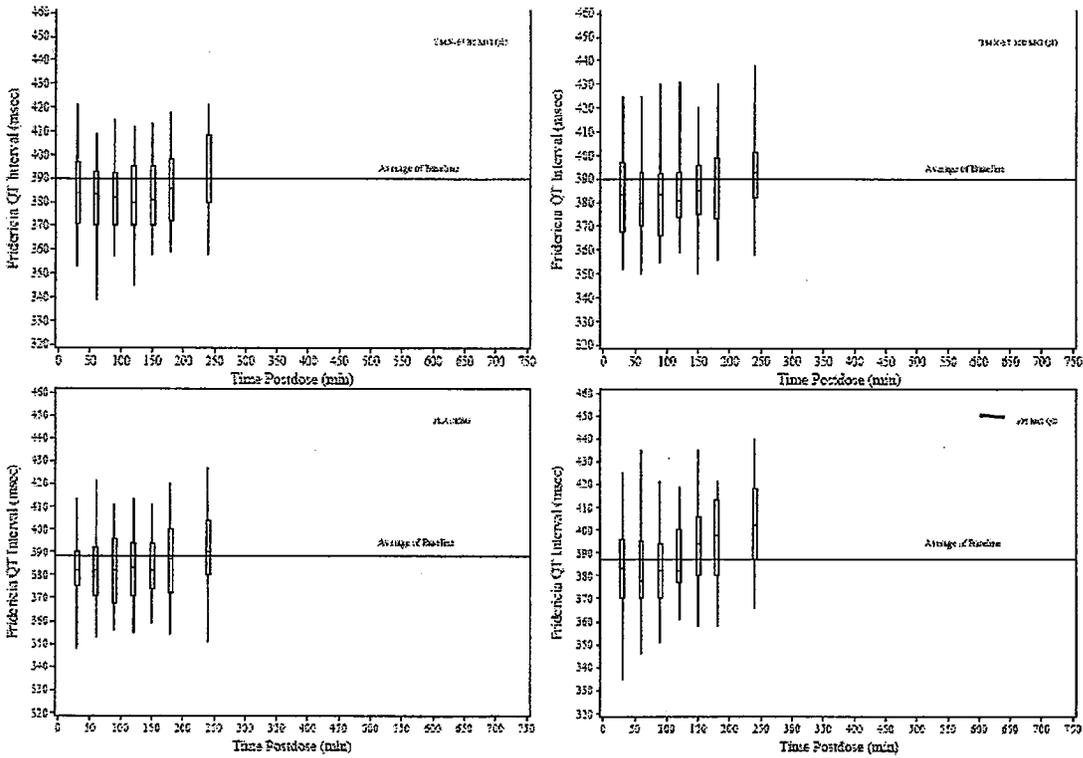


Figure A.2. Box Plot of Fridericia QT Interval versus Time for Day 1.

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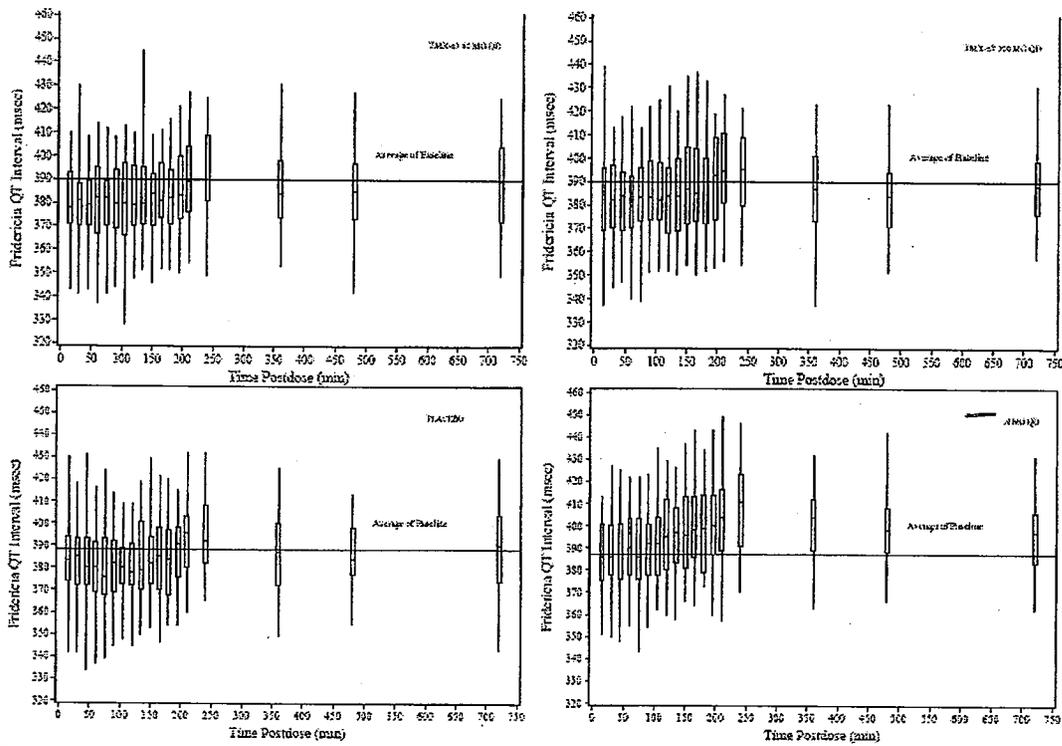


Figure A.3. Box Plot of Fridericia QT Interval versus Time for Day 4.

The association between QT intervals and RR interval was assessed using scatter plots of the QT intervals versus RR interval for each regimen. The scatter plots showed that there was a highly positive correlation between the uncorrected QT interval and RR interval and that there was no correlation between the Fridericia's QT interval and RR interval (Figures A.4 and A.5). This result supports the selection of Fridericia's QT as the primary assessment for QT prolongation.

(Reviewer's Note: There are four plots in Figures A.4 and A.5. They are arranged as top left 80 mg febuxostat, top right febuxostat 300 mg, bottom left placebo, and bottom right 400 mg

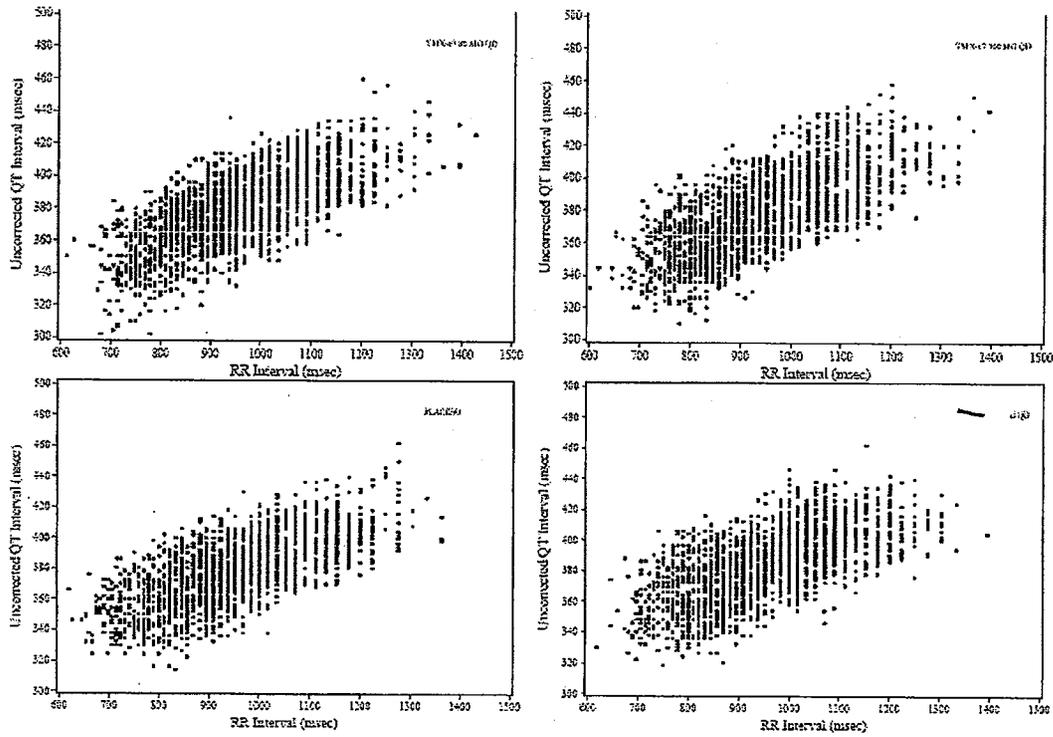


Figure A.4. Scatter Plot of Uncorrected QT Interval versus RR Interval.

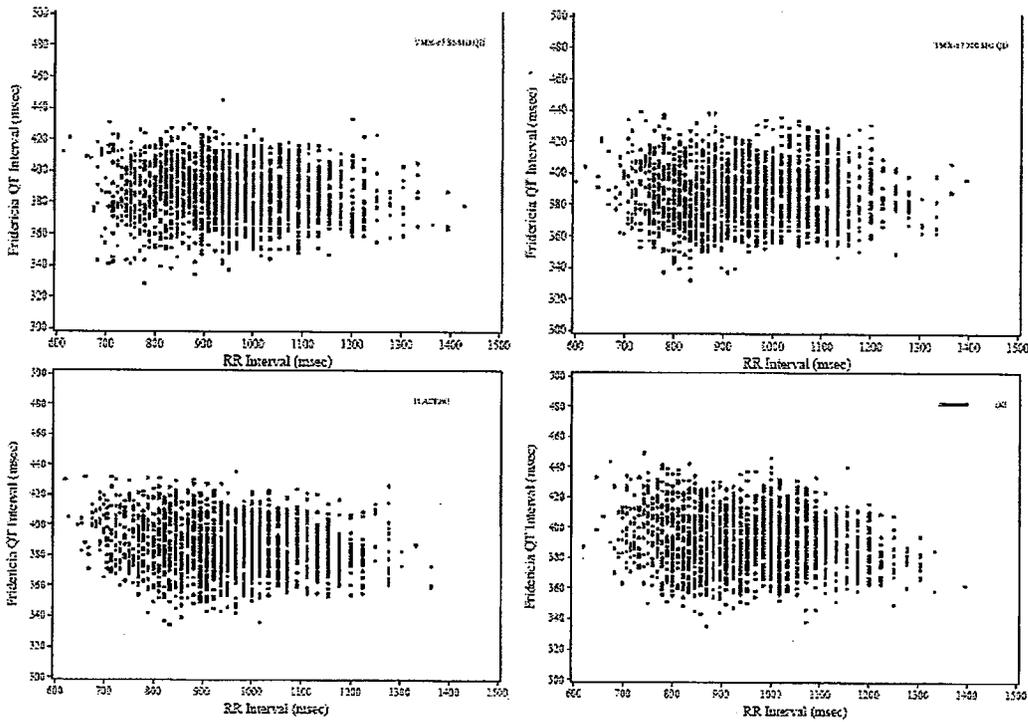


Figure A.5. Scatter Plot of Fridericia QT Interval versus RR Interval.

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4.2.7 Bioequivalence Studies

4.2.7.1 Study TMX-02-018: A Phase 1 Study to Assess the Relative Bioavailability of Abbott Formulation B1 TMX-67 Coated Tablets to Teijin Tablets

Study Period: February 22, 2002 to March 16, 2002

Sample Analysis Period: March 20, 2002 to April 9, 2002

Principle Investigator:

Study Center:

Analytical Site:

b(4)

Background: Twenty (20) mg is the highest strength of the TMX-67 tablets manufactured by Teijin Ltd. The 20 mg tablets have been used in previous Phase I studies conducted with TMX-67 in the US, and was used as a reference formulation in this study. Both 20 mg and 80 mg TMX-67 coated tablets, Formulation B1, are being manufactured at Abbott Laboratories and were used in later studies evaluating TMX-67 for the treatment of hyperuricemia.

Objective: The primary objective of this study was to compare the bioavailability of Abbott Formulation B1 TMX-67 coated tablets to Teijin TMX-67 tablets. Additionally, this study assessed the bioavailability of TMX-67 Formulation B1 4 x 20 mg coated tablets relative to 80 mg Formulation B1 coated tablets manufactured by Abbott Laboratories and dose proportionality from 20 mg to 80 mg.

Study Design: This was a Phase 1, single-center, open-label, single-dose, randomized, 4-period complete crossover study. Twenty-eight (28) healthy adult volunteers were randomly assigned in equal numbers to 1 of 4 dose regimen sequences. An attempt was made to enroll equal numbers of each gender. There was a 6-day washout between doses in each successive period. On each dosing day (Day 1 of each period), after at least a 10-hour fast, subjects received a single oral dose of TMX-67 with 240 mL of water at approximately 8:00 a.m. and no food was served until after the 4-hour blood sample collection.

Regimen A: 20 mg TMX-67 as 1 20 mg tablet of Teijin Ltd. (Teijin Ltd. 20 mg tablet)

Regimen B: 20 mg TMX-67 as 1 20 mg tablet of Abbott Formulation B1 (Abbott 20 mg tablet)

Regimen C: 80 mg TMX-67 as 1 80 mg tablet of Abbott Formulation B1 (Abbott 80 mg tablet)

Regimen D: 80 mg TMX-67 as 4 20 mg tablets of Abbott Formulation B1 (Abbott 20 mg tablet)

Twenty-eight healthy adult subjects (14 males, 14 females) were enrolled in the study, twenty-six of which completed the study (13 males and 13 females). Subject #109 prematurely discontinued due to "other" reasons (elected to withdraw) after receiving the Abbott 80 mg tablet regimen and the Teijin 20 mg tablet regimen. Subject #114 prematurely discontinued due to personal reasons after receiving the Teijin 20 mg tablet regimen. Data for these 2 subjects were subsequently excluded from all of the descriptive statistics and statistical analyses. The mean values for age, height, and weight of the 26 subjects completing the study were 26 years (range: 18 to 50 years), 170 cm (range: 155 to 196 cm), and 70 kg (range: 49 to 90 kg), respectively. Of the subjects completing this study, 25 were Caucasian, and 1 was Black.

Test Articles:

Study Drug	Formulation (Tablets)	Manufacturer	Finishing Lot Number (Manufacturer's Lot Number)
TMX-67	20 mg	Teijin	76-302-AL
TMX-67	20 mg	Abbott Laboratories	82-463-AR
TMX-67	80 mg	Abbott Laboratories	83-466-AL

The quantitative composition of these TMX-67 tablet formulations is listed in Table 1.

b(4)

Table 1. Composition of TMX-67 Tablets.

Ingredients	Teijin 20 mg Tablet mg/tablet	Abbott Formulation B1 20 mg Tablet mg/tablet	Abbott Formulation B1 80 mg Tablet mg/tablet
TEI-6720 (A-319198.0)	20.00	20.00	80.00
Lactose, Monohydrate, NF			
Cellulose, Microcrystalline, NF	/	/	/
Hydroxypropyl Cellulose, NF	/	/	/
Hydroxypropyl Cellulose, JP	/	/	/
Croscarmellose Sodium, NF	/	/	/
Magnesium Stearate, NF			
Magnesium Stearate, JP			
Silicon Dioxide, NF			
Opadry II, Green			
Total			520.0

b(4)

Sample Collection: In each period, venous blood samples were obtained prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing.

Sample Analysis: Concentrations of TMX-67 in plasma samples were determined at _____ using a high-performance liquid chromatography (HPLC) method with fluorescence detection (← Project 23150_1). The plasma assay had a lower limit of quantitation (LLOQ) of 10.0 ng/mL.

b(4)

Pharmacokinetic and Statistical Analysis: The relative bioavailability of the Abbott B1 20 mg tablet (Regimen B) to that of the Teijin 20 mg tablet (Regimen A) and of the 80 mg Abbott B1 tablet (Regimen C) to that of four Abbott B1 20 mg tablets (Regimen D) was assessed via point estimates and 90% confidence intervals for the ratio of regimen central values obtained within the framework of the ANOVA model. Bioequivalence was concluded if the 90% confidence intervals were completely contained within the interval (0.80, 1.25). Additionally, for C_{max} , AUC_t , and AUC_{∞} , point estimates and 90% confidence intervals for the ratio of central values

from the Abbott B1 80 mg tablet (Regimen C) to the central value of four times the parameter estimates of the Abbott B1 20 mg tablet (Regimen B) were also provided as described above.

Pharmacokinetic Results:

Plasma PK Profiles

The mean plasma concentration versus time profiles for febuxostat on linear and log-linear scales are shown in Figure 1.

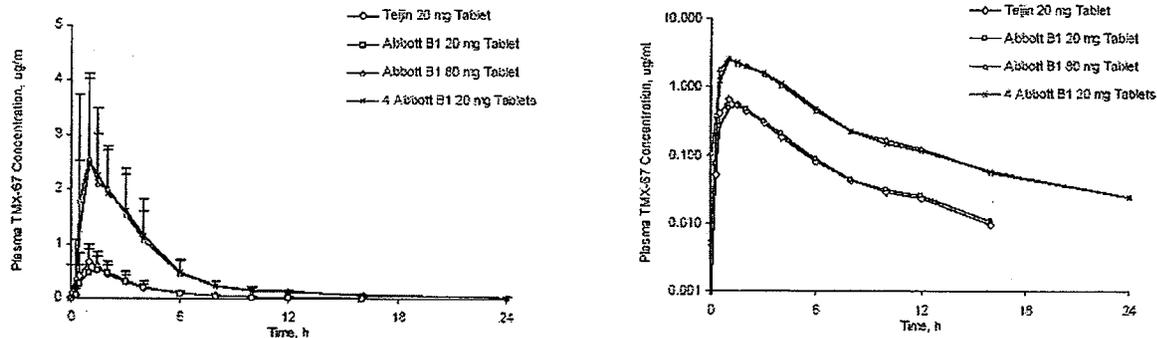


Figure 1. Mean Plasma Concentration-Time Profiles (Linear (\pm SD), Left and Log-Linear, Right) of TMX-67 Following Single Oral Dosing of TMX-67 to Healthy Subjects in Study TMX-02-018.

Noncompartmental pharmacokinetic parameter estimates for Regimens A, B, C and D are summarized in Table 2.

Table 2. A Summary of Descriptive Statistics for TMX-67 Pharmacokinetic Parameter Estimates Following Single Oral Doses of TMX-67 in Different Study Regimens in Healthy Subjects.

Regimen		t_{max} (h)	C_{max} (μ g/mL)	$AUC_0-\infty$ (μ g·h/mL)	AUC_{0-24} (μ g·h/mL)	$t_{1/2}^a$ (h)	λ_2 (h^{-1})	Cl/F (L/h)
A ^a	N	26	26	26	26	26	26	26
	Mean	1.37	0.8466	2.0618	2.1659	4.9 (4.4)	0.157	9.95
	SD	0.77	0.2955	0.6099	0.6274	1.5	0.055	2.66
B ^b	N	26	26	26	26	26	26	26
	Mean	1.58	0.8106	2.0195	2.1443	5.6 (4.8)	0.143	10.08
	SD	0.84	0.2791	0.6505	0.6489	2.3	0.056	2.68
C ^c	N	26	26	26	26	26	26	26
	Mean	1.52	3.5984	10.1824	10.4205	5.7 (5.0)	0.139	8.10
	SD	0.99	1.3670	2.4523	2.4753	3.0	0.045	1.90
D ^d	N	26	26	26	26	26	26	26
	Mean	1.48	3.2816	10.1186	10.3460	5.5 (5.0)	0.139	8.33
	SD	1.05	1.1342	2.8567	2.8773	1.9	0.044	2.31

a Teijin 20 mg tablet

b Abbott B1 20 mg tablet

c Abbott B1 80 mg tablet

d Four Abbott B1 20 mg tablets

e Arithmetic mean (harmonic mean)

Relative Bioavailability

The point estimates and 90% confidence intervals for the ratio of test and reference central values for the pharmacokinetic parameters tested are presented in Table 3.

Table 3. Bioavailability of TMX-67 Following Single Oral Doses of the Test Regimens (Abbott B1 20 mg Tablet, Abbott B1 80 mg Tablet), Relative to the Reference Regimens (Teijin 20 mg Tablet, Four Abbott B1 20 mg Tablets, Abbott B1 20 mg Tablet).

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
Abbott B1 80 mg Tablet vs. Abbott B1 20 mg Tablet (Dose-corrected C_{max} & AUC)	C_{max}	1.093	0.9651 – 1.2380
	AUC_t	1.290	1.2245 – 1.3586
	AUC_{∞}	1.236	1.1772 – 1.2986

Note: The point estimates and confidence intervals were obtained from exponentiated differences obtained from analysis of the natural logarithm transformed data.

In the case of Abbott B1 20 mg tablet relative to the Teijin 20 mg tablet, the 90% confidence intervals for the regimen central value ratios were within the acceptable 0.80-1.25 range for C_{max} , AUC_t , and AUC_{∞} . Therefore, the Abbott B1 20 mg tablet was bioequivalent to the Teijin 20 mg tablet. When comparing the Abbott B1 80 mg tablet to four Abbott B1 20 mg tablets, the 90% confidence intervals for the regimen central value ratios were also within the acceptable range of 0.80-1.25 for C_{max} , AUC_t and AUC_{∞} . Therefore, the Abbott B1 80 mg tablet was bioequivalent to four Abbott B1 20 mg tablets.

The dose-corrected comparison between the Abbott B1 20 mg tablet and the Abbott B1 80 mg tablet was assessed by evaluating the bioavailability of the Abbott B1 80 mg tablet with respect to the Abbott B1 20 mg tablet for dose-corrected C_{max} , AUC_t , and AUC_{∞} . The 90% confidence intervals of the regimen central values assessing the bioavailability of the Abbott B1 80 mg tablet relative to that of the Abbott B1 20 mg tablet were within the 0.80-1.25 range with respect to dose-corrected C_{max} but not with respect to dose-corrected AUC_t and AUC_{∞} .

Conclusion:

- The Abbott B1 20 mg tablet was bioequivalent to the Teijin 20 mg tablet.
- The Abbott B1 80 mg tablet was bioequivalent to four Abbott B1 20 mg tablets. *(Reviewer's Note: Because 20 and 80 mg Abbott B1 tablets _____ and previous PK study suggested that PK was dose-proportional between 20 and 80 mg, bioequivalence between four 20 mg tablets and one 80 mg tablet is evident. An in vitro dissolution study would be sufficient to demonstrate BE.)*
- The confidence intervals of the regimen central value ratios for assessing the bioavailability of Abbott B1 80 mg tablet relative to that of Abbott B1 20 mg tablet were within the 0.80-1.25 range with respect to dose-corrected TMX-67 C_{max} , but not with respect to dose-

corrected TMX-67 AUC_t and AUC_∞. Dose-corrected AUC_t and AUC_∞ for Abbott B1 80 mg tablet were higher by 26% and 21%, respectively, than those for the Abbott B1 20 mg tablet. This may be due to the plasma levels were below detection limit (10 ng/mL) for the 20 mg dose at later timepoints (after 18 hours).

4.2.7.2 Study C02-034: A Phase 1 Study to Assess the Relative Bioavailability of TMX-67 from an 80 mg ([redacted] batch size) Tablet to that from an 80 mg ([redacted] batch size) Tablet

b(4)

Study Period: December 13, 2002 to December 20, 2002

Sample Analysis Period: February 11, 2003 to February 27, 2003

Principle Investigator: [redacted]

Study Center: [redacted]

Analytical Site: [redacted]

b(4)

Background: The Abbott Formulation B1 80 mg febuxostat tablets of [redacted] batch size (representative of commercial batches) would be used in later clinical studies (Note: [redacted]). Therefore, it would be important to demonstrate that 80 mg febuxostat tablets of the [redacted] batch size (representative of commercial batches) are bioequivalent to the 80 mg febuxostat tablets of the [redacted] batch size (pilot plant batch size) that were used in earlier clinical studies.

b(4)

(Reviewer's Note: This would be considered a Level 1 batch size change according to SUPAC. Therefore, an in vitro dissolution study would have been sufficient to demonstrate bioequivalence between 80 mg [redacted] tablet and 80 mg [redacted] tablet using the logic of the SUPAC guidance document. The study is reviewed because the [redacted] tablet represents the to-be-marketed batch and its BE to earlier formulation used in clinical studies is important.)

b(4)

Objective: To assess the bioavailability of febuxostat (TMX-67) from an 80 mg [redacted] batch size) tablet relative to an 80 mg ([redacted] batch size) tablet of febuxostat.

b(4)

Study Design: This was a Phase 1, single-center, open-label, single-dose, randomized, 2-period, crossover study. Subjects were randomly assigned to 1 of 2 regimen sequences (see table below). Thirty-six healthy adult subjects were selected to participate in this study. An attempt was made to enroll equal numbers of subjects of each gender. On each dosing day (Day 1 of each period), after at least a 10-hour fast, subjects received a single oral dose of TMX-67 with 240 mL of water at approximately 8:00 a.m. and no food was served until after the 4-hour blood sample collection. There was a 7-day interval between the doses of the 2 study periods.

Regimen A: One 80-mg febuxostat tablet [redacted] batch size administered orally

Regimen B: One 80-mg febuxostat tablet [redacted] batch size administered orally

b(4)

Thirty-six healthy adult subjects (10 males, 26 females) were enrolled and completed the study. The mean values for age, height, and weight of the 36 subjects were 43 years (range: 18 to 54

The mean plasma concentration versus time profiles for febuxostat on linear and log-linear scales are shown in Figure 1.

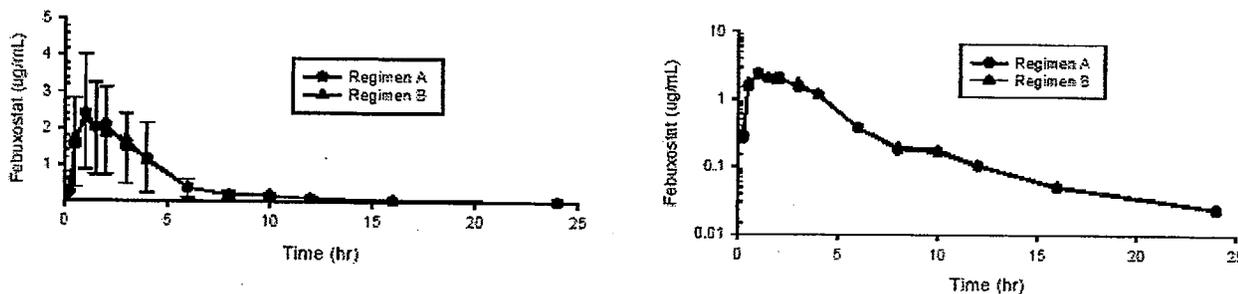


Figure 1. Mean Linear (\pm SD, Left) and Log-linear (Right) Plasma Concentration-Time Profiles Following Single Oral Dosing of Febuxostat (Regimen A and B) to Healthy Subjects in Study C02-034.

Noncompartmental pharmacokinetic parameter estimates for Regimens A and B are summarized in Table 2.

Table 2. A Summary of Descriptive Statistics for Febuxostat Pharmacokinetic Parameter Estimates Following Single Oral Doses of Febuxostat in Regimen A and Regimen B in Healthy Subjects.

Regimen		t_{max} (h)	C_{max} (μ g/mL)	AUC_t (μ g·h/mL)	AUC_{∞} (μ g·h/mL)	AUC_{∞} % Extrap	$t_{1/2}^*$ (h)	λ_z (h^{-1})	CL/F (L/h)
A ^a	N	36	36	36	34	34	34	34	34
	Mean	1.81	3.3106	9.8223	10.2171	3	6.0 (5.4)	0.127	8.90
	SD	1.15	1.4005	3.8870	4.0003	1	1.9	0.044	3.11
B ^b	N	36	36	36	34	34	34	34	34
	Mean	1.53	3.4873	9.8510	10.1633	3	5.9 (5.4)	0.129	8.32
	SD	0.93	1.4068	3.6318	3.7142	1	1.3	0.046	3.05

* Arithmetic mean (harmonic mean)

^a One Abbott B1 80 mg tablet: —

^b One Abbott B1 80 mg tablet: —

(Reviewer's Notes: Terminal half-life was not determinable for one of the dosing period for Subjects 126 and 129 because the plasma level for the 24 hr sample was about the same as that for the 16 hr sample. Therefore, the Sponsor did not calculate AUC_{∞} and CL/F for these two subjects and data for these two subjects were excluded for the final statistical analysis for AUC_{∞} , etc.. Excluding data from these two subjects is acceptable because mean AUC_{∞} values from 34 subjects and mean AUC_t values from 36 subjects were very close. Excluding AUC_{∞} data from these 2 subjects is not expected to have big impact on the final conclusion.)

Relative Bioavailability

The point estimates and 90% confidence intervals for the ratio of test (Abbott B1 80 mg tablet, —), and reference (Abbott B1 80 mg tablet, —), regimen central values for the febuxostat pharmacokinetic parameters tested are presented in Table 3.

b(4)

Table 3. Relative Bioavailability of Febuxostat from One Abbott B1 80 mg tablet to One Abbott B1 80 mg tablet

Comparison Formulation B1	Pharmacokinetic* Parameter	Relative Bioavailability	
		Point Estimate	90% Confidence Interval
One Abbott B1 80 mg tablet vs. One Abbott B1 80 mg tablet	C _{max}	0.937	0.8368-1.0500
	AUC _t	0.989	0.9531-1.0262
	AUC _∞	0.997	0.9616-1.0333

b(4)

* N = 36 for C_{max} and AUC_t
N = 34 for AUC_∞

The 90% confidence intervals for the ratio of test and reference regimen central values were within the 0.80-1.25 range for febuxostat C_{max}, AUC_t and AUC_∞.

Conclusion:

One Abbott B1 febuxostat 80 mg tablet manufactured in a _____ was bioequivalent to one Abbott B1 febuxostat 80 mg tablet manufactured in a _____

b(4)

4.2.7.3 Study C03-044: A Phase 1 Study to Assess the Relative Bioavailability of 1 Febuxostat 120 mg Tablet to 1 Febuxostat 80 mg Tablet and 1 Febuxostat 40 mg Tablet

Study Period: July 26, 2003 to August 9, 2003
Sample Analysis Period: August 14 to September 12, 2003
Principle Investigator: _____
Study Center: _____
Analytical Site: _____

b(4)

Background: In order to achieve a febuxostat dose of 120 mg, previous clinical studies have used a combination of an 80 mg febuxostat tablet plus a 40 mg febuxostat tablet. A new 120 mg dose tablet has been developed and is the highest tablet strength that is planned to be marketed. As a result, it was necessary to show that a single 120 mg dose tablet was bioequivalent to a combination of 1 febuxostat 80 mg tablet plus 1 febuxostat 40 mg tablet (all Formulation B1).

Objective: To assess the relative bioavailability of 1 febuxostat Formulation B1 120 mg tablet to that from 1 febuxostat Formulation B1 80 mg tablet plus 1 febuxostat Formulation B1 40 mg tablet.

Study Design: This was a Phase 1, single-center, open-label, single-dose, randomized, 2-period, crossover study. Subjects were randomly assigned to 1 of 2 regimen sequences (see table below). Thirty-six subjects aged 18-55, inclusive, and in general good health, were selected to participate in this study. On each dosing day (Day 1 of each period), after at least a 10-hour fast, subjects received a single oral dose of TMX-67 with 240 mL of water at approximately 8:00 a.m. and no food was served until after the 4-hour blood sample collection. There was a washout interval of at least 6 days between the dose in each of the 2 periods.

Regimen A: One febuxostat 120 mg tablet

Regimen B: One febuxostat 80 mg tablet plus one febuxostat 40 mg tablet

Thirty-six subjects were enrolled in the study. One subject (126) prematurely discontinued from the study after Day 1 in Period 1 due to personal reasons not related to study drug. This subject was excluded from all pharmacokinetic analyses. Thirty-five subjects (21 males and 14 females) completed dosing with both regimens. The mean values for age, height, and weight of the 35 subjects completing the study were 32 years (range: 18 to 53 years), 174 cm (range: 155 to 193 cm), and 74 kg (range: 54 to 94 kg), respectively. Of the subjects completing this study, 18 were Caucasian, 10 were Black, and 7 were Hispanic.

Test Articles:

Study Drug	Regimen		
	A (Test) Febuxostat	B (Reference) Febuxostat	B (Reference) Febuxostat
Dosage Form	Coated Tablet	Coated Tablet	Coated Tablet
Formulation	B1	B1	B1
Batch Size			
Dose (mg)	120	80	40
Lot Number	02-077-4Q	86-064-4Q	91-071-4Q

a Representative of the commercial batch size

The quantitative composition of these TMX-67 tablet formulations is listed in Table 1. Formulation B1 40, 80 and 120 mg tablets (to-be-marketed formulation)

Table 1. Composition of Febuxostat Tablets.

Ingredients of Febuxostat Tablets	Abbott B1 40 mg tablet	Abbott B1 80 mg tablet	Abbott B 120 mg tablet
Lactose, Monohydrate, NF	/	/	/
Cellulose, Microcrystalline, NF (/	/	/
TEL-6720 (A-319198.0) [Febuxostat]	40	80	120
Hydroxypropyl Cellulose, NF	/	/	/
Croscarmellose Sodium, NF	/	/	/
Magnesium Stearate, NF,	/	/	/
Silicon Dioxide, NF	/	/	/
Opadry II, Green,	/	/	/
Total Tablet Weight	260.42	520.84	/

(Reviewer's Note: Because 40, 80 and 120 mg Abbott Formulation B1 tablets, and previous PK study suggested that PK was dose-proportional up to 120 mg, bioequivalence between one 120 mg tablets and one 80 mg tablet plus one 40 mg tablet is evident. This study is reviewed because as the 80 and 120 mg tablets represent the to-be-marketed formulation, it is important to show dosage-form equivalence between different dose strengths.)

Sample Collection: In each period, venous blood samples were obtained prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing.

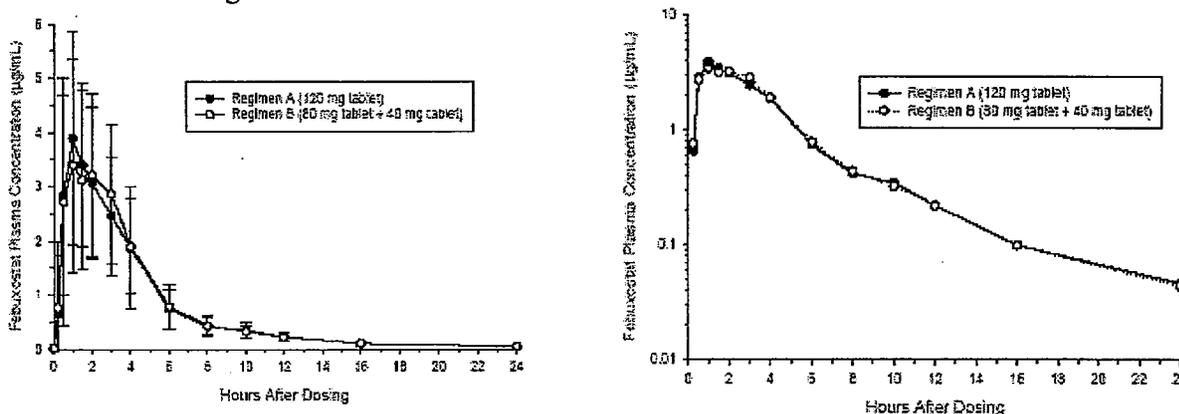
Sample Analysis: Concentrations of TMX-67 in plasma samples were determined at _____ using a high-performance liquid chromatography (HPLC) method with fluorescence detection (Project 23150_1). The plasma assay had a lower limit of quantitation (LLOQ) of 10.0 ng/mL.

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Pharmacokinetic Results:

Plasma PK Profiles

The mean plasma concentration versus time profiles for febuxostat on linear and log-linear scales are shown in Figure 1.



Mean (±SD) Plasma Concentration-Time Profile of Febuxostat (Linear) and Mean Plasma Concentration-Time Profile of Febuxostat (Log-Linear) Following Single Oral Dosing of Febuxostat to Healthy Subjects in Study C03-044

Figure 1.

Noncompartmental pharmacokinetic parameter estimates for Regimens A and B are summarized in Table 2.

Table 2. A Summary of Descriptive Statistics for Febuxostat Pharmacokinetic Parameters Following Single Oral Doses of 120 mg Febuxostat in Different Regimens in Healthy Subjects.

Regimen		t_{max} ^a (h)	C_{max} (µg/mL)	AUC_t (µg/mL)	$AUC_{0-∞}$ (µg·h/mL)	$AUC_{0-∞}$ % Extrap	$t_{1/2}$ ^a (h)	λ_z (h ⁻¹)	Cl/F (L/h)
A ^b	N	35	35	35	35	35	35	35	35
	Mean	1.48	4.9843	16.8864	17.2441	2	5.4 (5.3)	0.131	7.50
	SD	0.92	1.6542	4.4007	4.4457	1	0.7	0.017	2.23
B ^c	N	35	35	35	35	35	35	35	35
	Mean	1.74	5.0288	17.0925	17.4443	2	5.5 (5.3)	0.130	7.42
	SD	1.13	1.7549	4.6613	4.6911	1	1.2	0.022	2.18

- a Arithmetic mean (harmonic mean)
- b 1 febuxostat 120 mg tablet
- c 1 febuxostat 80 mg tablet plus 1 febuxostat 40 mg tablet

Relative Bioavailability

The point estimates and 90% confidence intervals for the ratio of 1 febuxostat 120 mg tablet (test) and 1 febuxostat 80 mg tablet plus 1 febuxostat 40 mg tablet (reference) regimen central values for the pharmacokinetic parameters tested are presented in Table 3.

Table 3. 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

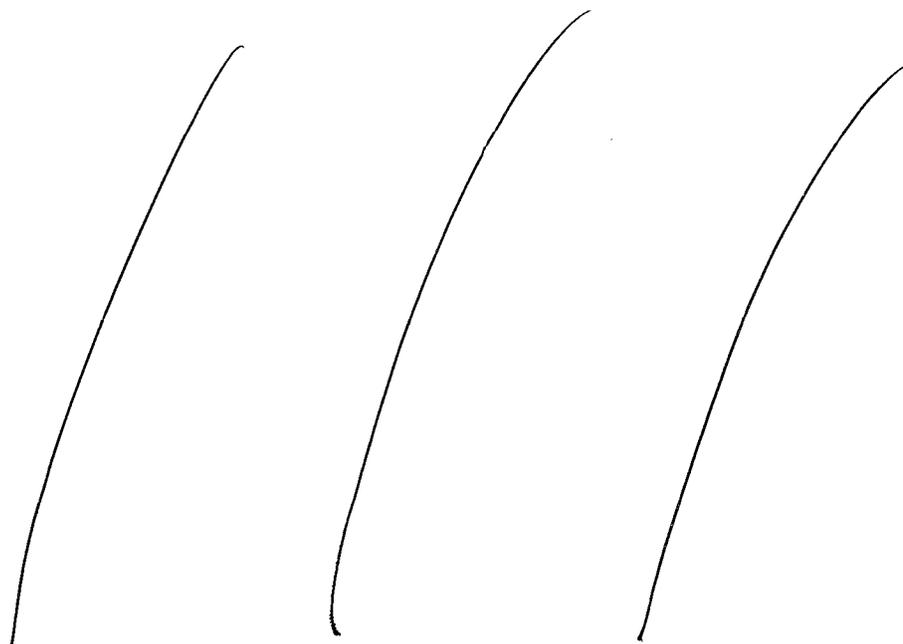
^a N=35

The 90% confidence intervals for febuxostat were within the acceptable 0.80-1.25 range for C_{max}, AUC_t, and AUC_∞.

Discussion and Conclusion:

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. 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.

4.2.7.4 *BE Studies not Reviewed*



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Trade Secret / Confidential (b4)

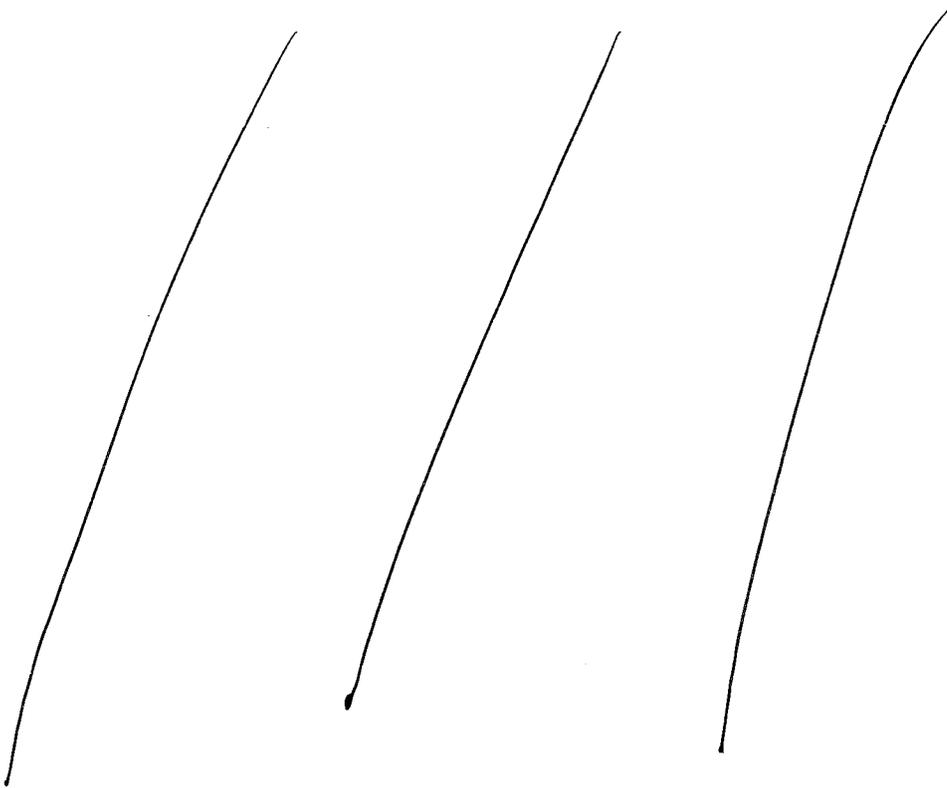
Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

4.2.8 Dissolution Studies

Dissolution method was developed using the registration lots of 80 mg (lots 86-064-4Q, 86-065-4Q, and 86-066-4Q) and 120 mg (lots 02-076-4Q, 02-077-4Q, and 02-078-4Q) tablets, different dissolution media of pH ranging from 1.0 to 7.5, different dissolution apparatus, and agitation speeds. The proposed dissolution method and acceptance criterion for febuxostat tablets are listed in Table 1.



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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

[Redacted content]

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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.

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4.3 Pharmacometric Review

Office of Clinical Pharmacology and Biopharmaceutics Pharmacometrics Review

NDA	21856
Drug	Febuxostat
Primary Reviewer	Venkatesh Atul Bhattaram
Team Leader	Joga Gobburu

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Executive Summary

TAP Pharmaceuticals is seeking approval for febuxostat to lower serum urate levels in patients with hyperuricemia. Sponsor has conducted extensive studies in healthy subjects and patients aimed at examining relationship between dose/concentration-serum urate levels. In the pivotal trials, three dose levels of febuxostat (80, 120 and 240 mg), placebo and allopurinol were tested in patients whose baseline serum urate levels were greater than 8 mg/dL. The primary endpoint (response rate) that was agreed upon by the Agency and the sponsor was "Proportion of patients whose last three visit serum urate levels are below 6 mg/dL". The response rates (combined from two trials) were 51%, 63%, 69% at 80, 120 and 240 mg dose groups respectively. The response rate was 22% for allopurinol group. In terms of risk, there is no dose-safety (non-cardiovascular) events relationship at 80 and 120 mg which would necessitate substantial dose adjustments. However, as noted by the safety medical officer, there are higher incidences of cardiovascular risk events in the febuxostat arm in comparison to allopurinol. The question then was "What do we know about benefit at lower doses, although one would expect safety related risk(s) would be lower or similar to the tested doses?" Based on PK/PD modeling and simulations, a lower dose (40 mg), the response rate is projected to be about 22% which is similar to allopurinol. However, it is not possible to comment on any lower risk of cardiovascular events in comparison to doses tested in clinical trials. The current dosing recommendations proposed by the sponsor _____ Is it better to initiate treatment in patients with 40 mg dose and increase the dose based on measured serum urate levels at specific time interval? This is a debatable issue. However, if the regulatory decision is to approve the drug for its higher response rates, then the 40 mg dose level could also offer benefit similar to allopurinol and could be either used to initiate treatment _____

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Introduction

The underlying metabolic disorder in gout is hyperuricemia, which is best defined as an elevation in serum urate to >7.0 mg/dL. This value just exceeds the limit of solubility of urate in extracellular fluids (6.8 mg/dL). The solubility of monosodium urate, however, is dependent on various factors, including pH, temperature, sodium ion concentration, and protein concentration. In the extremities, areas such as the metatarsal joints and knees, temperature may range at times as low as 26°C to 33°C. At normal body temperature (37°C), in vitro studies have shown that urate concentration is soluble at 6.8 mg/dL. However, at lower temperatures (35°C), the limit of solubility is 6.0 mg/dL or lower. The annual incidence of gout ranges from 0.20 to 0.35 per thousand in various populations with an overall prevalence of 1.6 to 13.6 per thousand. Gout is at least 5 times more common in men than in women. This disease is associated with a number of comorbidities such as obesity, alcohol consumption, renal dysfunction, insulin resistance, and hypertension.

Urate-lowering pharmacotherapy is important in the management of patients with gout and frequent attacks of gouty arthritis, chronic gouty arthropathy, chronic tophaceous gout, renal impairment, or uric acid urolithiasis. The choice of urate-lowering agents has been restricted to

uricosuric drugs, which enhance renal uric acid excretion, and the xanthine oxidase (XO) inhibitor, allopurinol, which reduces uric acid production. Allopurinol is effective in reducing serum urate; however, achieving normal serum urate may be difficult in patients with impaired renal function or in transplant recipients. An uncommon but significant limitation of allopurinol use is the risk, more common in elderly individuals, of reactions that may include: rashes, some severe; hematologic cytopenias; hepatitis; vasculitis; and the potentially life-threatening allopurinol hypersensitivity syndrome. Febuxostat is a potent, non-purine selective inhibitor of XO that inhibits the formation of uric acid from xanthine. It potently inhibits both the oxidized and reduced forms of the enzyme. In contrast, allopurinol and its active metabolite, oxypurinol, have been shown to only inhibit 1 of the forms. More importantly, unlike allopurinol and its metabolites, febuxostat has minimal effect on other enzymes (guanine deaminase, hypoxanthine-guanine phosphoribosyl-transferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase, and purine nucleoside phosphorylase) involved in purine and pyrimidine metabolism. The enzyme redox state-independency of the inhibition and selectivity demonstrated by febuxostat may be key in the differentiation of febuxostat from allopurinol.

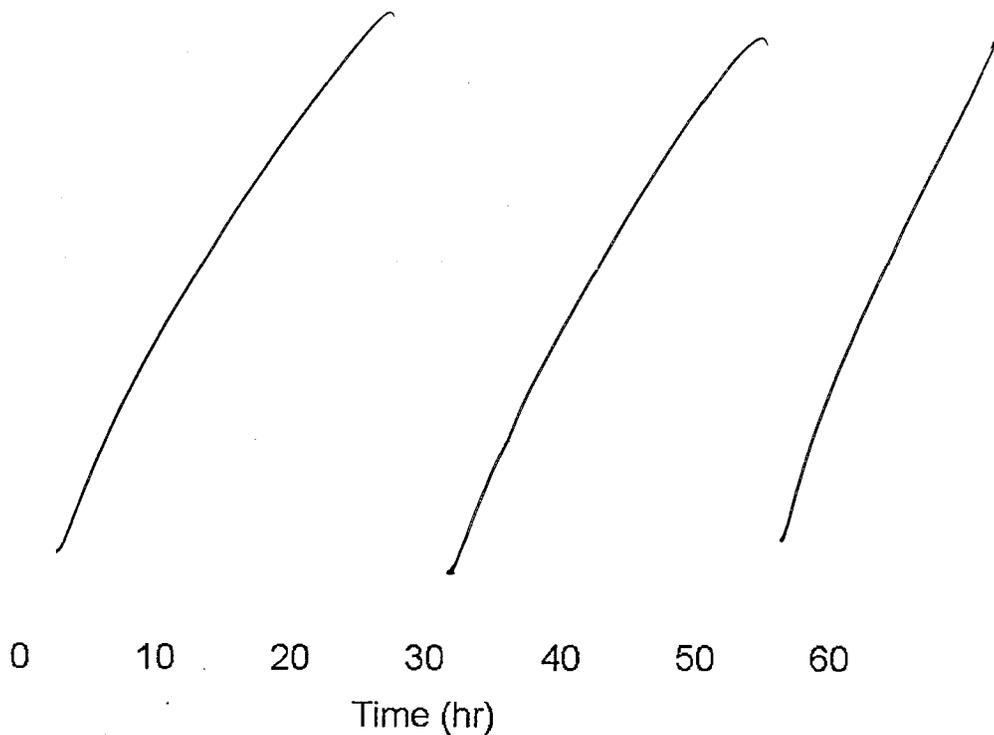
As a part of drug development strategy for febuxostat, the sponsor conducted extensive PK/PD studies examining the concentration-effect (serum urate level lowering) relationships. Dose selection for the pivotal trials was based on dose ranging study conducted in patients with hyperuricemia. The current review will describe the findings of the sponsor and also the work done by the reviewer to explain the relationship between dose/concentration-effect relationships. Also the benefit/risks of the doses sought for approval will be discussed.

Question Based Review

1. Is the dose/dosing regimen proposed by the sponsor acceptable?

Dosing regimen: Yes, the dosing regimen proposed by the sponsor is reasonable. Sponsor proposed once-a-day dosing schedule for febuxostat and is well reflected in the time course of serum urate levels as shown in Figure 1 below:

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Figure 1. Time course of serum febxostat and urate concentrations after single oral doses of 40, 80, 120 and 240 mg.

Dose: The sponsor conducted extensive studies to characterize dose-response relationship (Figure 2). Three dose levels (80, 120 and 240 mg) were tested in the pivotal trials. The effects on the primary endpoint (Proportion of patients whose last three visit serum urate levels < 6 mg/dL) in the pivotal trials were twice higher than that observed with allopurinol (active-control). The time course of serum uric acid as observed in pivotal trials is shown in Figure 3 below.

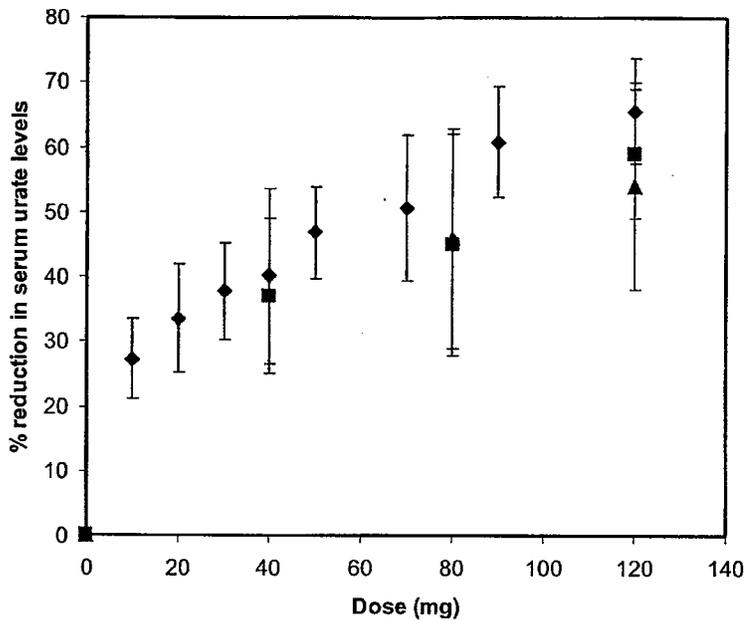


Figure 2. % reduction (Mean±SD) in serum urate levels (pre-dose) in healthy subjects (♦) patients (Phase II-■; Phase III-▲)

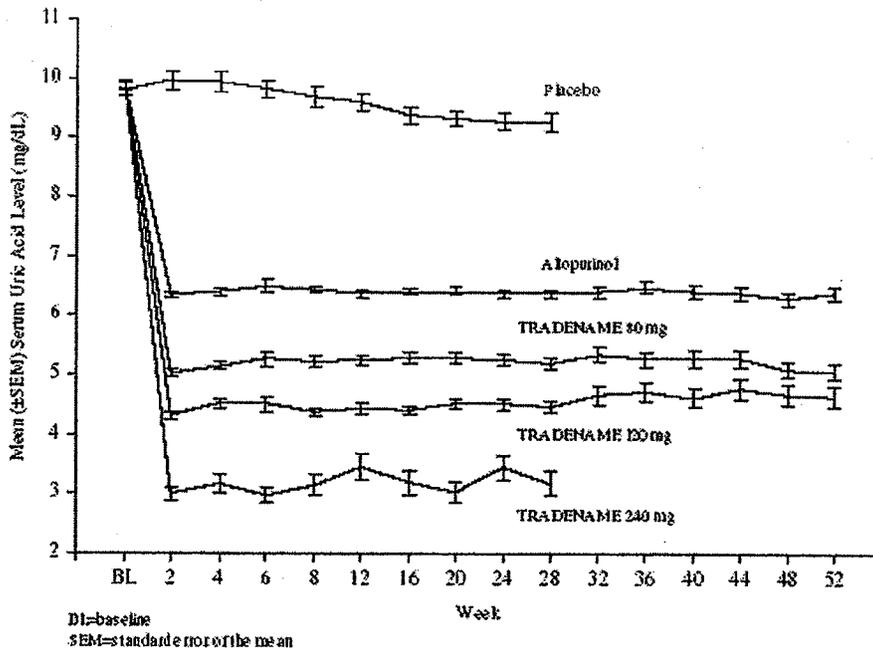


Figure 3. Time course of serum uric acid (Mean±SEM) in the pivotal trials (Shown are Placebo, Allopurinol, Febuxostat)

If there were no cardiovascular safety events (Please refer to the review by Medical Officer), the 80, 120 mg dose groups offer substantial therapeutic benefit over the current treatment option-allopurinol. Based on PK/PD modeling and simulations, it appears that the lower dose of 40 mg would offer similar benefit to that of allopurinol as shown in Figure 4 below. However, it is not possible to characterize risk at this dose as there is no clear dose-response (risk) relationship. If the cardiovascular events that were observed in the trial are acceptable, in view of overall utility of the drug, then a 40 mg dose would be a useful alternative either to (a) initiate treatment and later adjust the dose

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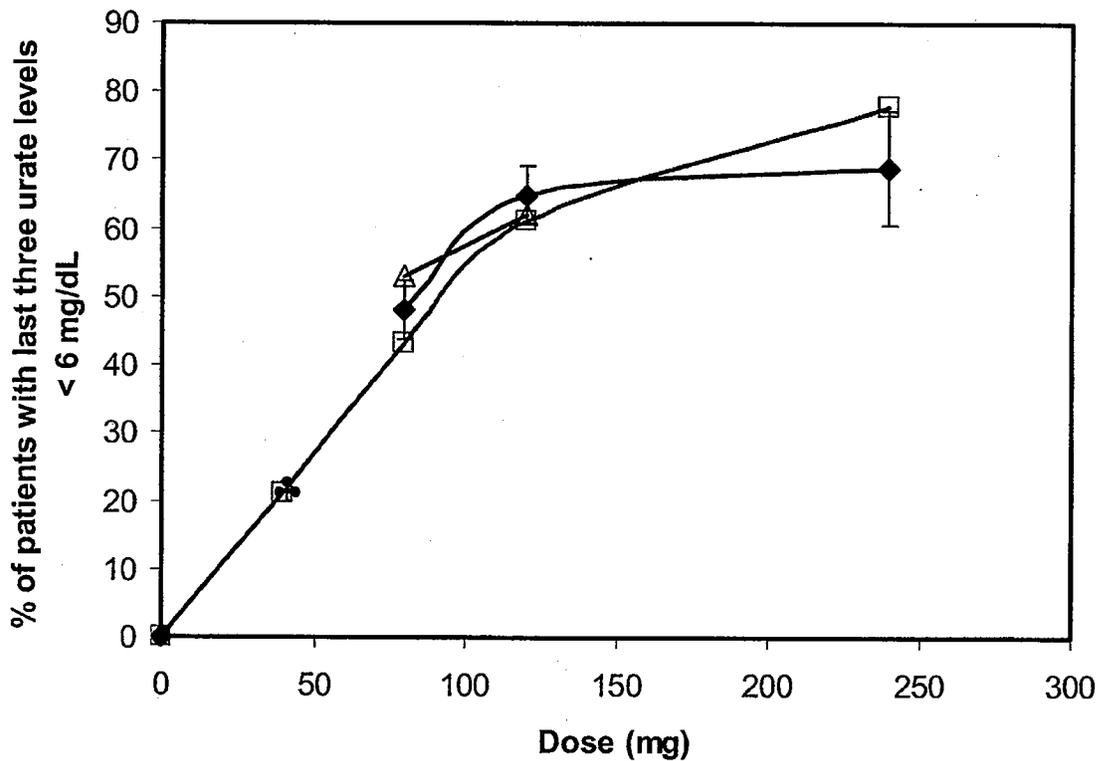


Figure 4. Relationship between primary endpoint vs dose of febxostat (♦- observed in C02-009; Δ- Observed in C02-010; □- Predicted; ♣- Observed for Allopurinol) (Shown are Mean±2S.E for Observed and Mean for Predicted).

Sponsor's Analysis

Effectiveness

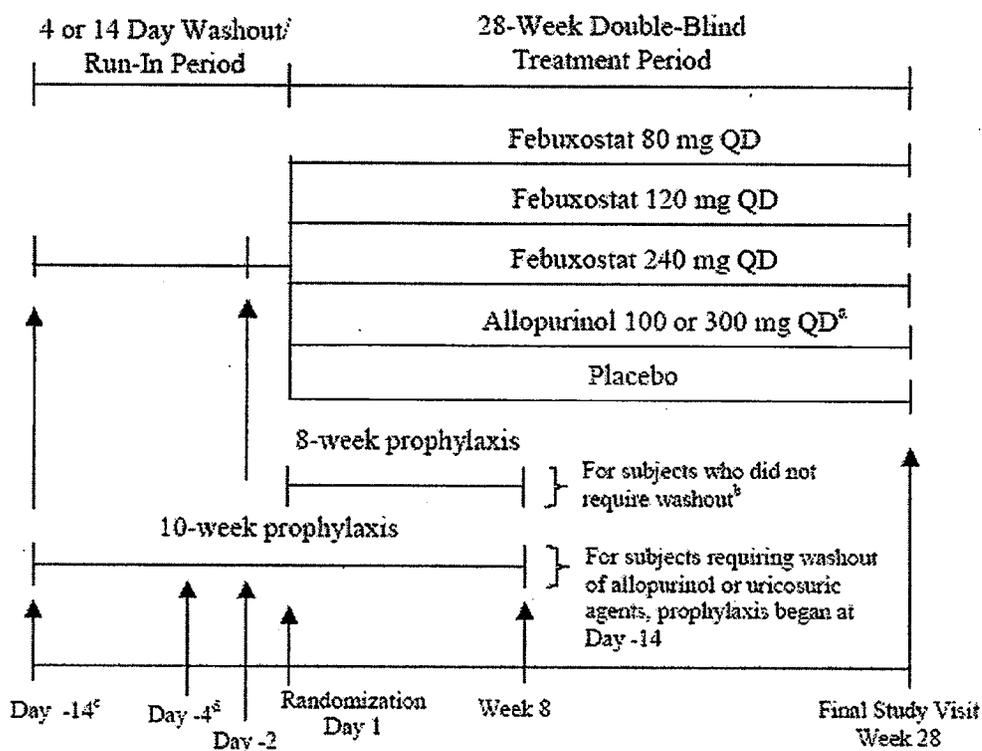
Data

The sponsor collected data on serum concentrations of febxostat and uric acid in one pivotal trial (Study C2-009) and dose finding study (Study TMX-00-004 and TMX-01-005).

TMX-00-004/TMX-01-005: TMX-00-004 was a Phase 2, double-blind (40, 80 or 120 mg), placebo-controlled, multi-center study in subjects who have a history or presence of gout as defined by the American College of Rheumatology, with hyperuricemia defined as a serum urate level of ≥ 8.0 mg/dL at the Day -2 visit. Double-blind treatment visits occurred on Days 7, 14, 21 and 28. Subjects who completed the 4-week double-blind treatment period were given the option of enrolling into a 52-week open-label study of febuxostat. This study permitted increases or decreases in the dose of febuxostat at selected timepoints. Of 116 subjects enrolled in open label phase, 88 subjects had at least 1 non-trough population pharmacokinetic and pharmacodynamic sample available, and 86 of them were included in the population analyses. All subjects were to initially receive 80 mg of febuxostat once daily. Up to 3 dose adjustments were allowed at study visits that occurred between Weeks 4 and 24 upon review of a subjects serum urate concentrations and adverse events. Only febuxostat doses of 40 mg QD, 80 mg QD, and 120 mg QD were allowed.

Study C02-009: This was a phase 3, multicenter, randomized, allopurinol- and placebocontrolled, parallel-group design, five-arm study with a 28-week Double-Blind Treatment Period (Figure 5). One thousand and seventy-two subjects were randomly assigned in a 1:2:2:1:2 ratio to receive placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, or allopurinol (300 mg QD for subjects with serum creatinine ≤ 1.5 mg/dL at Day -2, and 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤ 2.0 mg/dL at Day -2).

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- Subjects randomly assigned to allopurinol who had serum creatinine ≤ 1.5 mg/dL at Day -2 received allopurinol 300 mg QD during the study; subjects randomly assigned to allopurinol who had serum creatinine > 1.5 mg/dL and ≤ 2.0 mg/dL at Day -2 received allopurinol 100 mg QD.
- Subjects who were not receiving allopurinol or uricosuric agents prior to study began treatment with naproxen or colchicine at the Day 1 Visit.
- Screening Visit for subjects requiring washout of allopurinol or uricosurics.
- Screening Visit for subjects not requiring washout of allopurinol or uricosurics; all other subjects had a Day -4 Visit.

Figure 5. Study design for C02-009

Of the 1072 subjects who were enrolled in the study, 138 subjects had at least one usable non-trough pharmacokinetic sample. Of these 138 subjects, 134 subjects had at least 2 samples with at least 1 being a non-BLQ (Below Limit of Quantitation) non-trough population pharmacokinetic measurement. Of the 134 subjects, 125 of them were included in the final population analyses after removing the outliers.

Methods

Data from the two studies on serum concentrations of febuxostat and uric acid were separately analyzed by the sponsor using indirect response PK/PD model as shown in Figure 6.

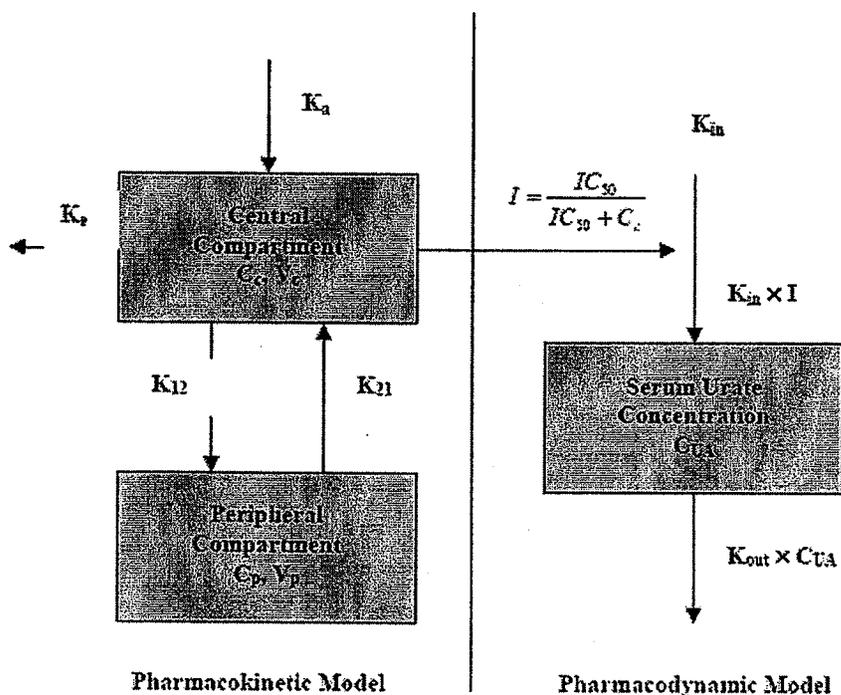


Figure 6. Indirect Response Pharmacokinetic-Pharmacodynamic Model

Population Pharmacokinetic-Pharmacodynamic Analyses

Population PK/PD analysis was performed using NONMEM (Version 5, Globomax LLC, Hanover, MD). The pharmacokinetic parameters (log-normal distribution) included Cl , the apparent clearance, V_c , the apparent volume of distribution for the central compartment, Q , the distribution clearance, V_p , the apparent volume of distribution for the peripheral compartment, K_a , the absorption rate constant, and t_{lag} , the absorption lag time. The residual variability model for PK was a combination of additive and proportional components. For PD the residual error model had only additive component. Outliers were defined by absolute weighted residual ($|WRES|$) >5 , were screened after fitting the initial model (no covariates) to the data. Covariate model building was performed using Generalized Additive Model (GAM) analyses through Xpose 3.102 (Uppsala University, Sweden) and S-PLUS Ver 6.2 Professional (Insightful Corporation, US). Following the GAM analyses, a Forward Selection procedure was applied using NONMEM to select the covariates which have a significant effect on the PK and PD parameters. A full model was achieved by including all the covariates that caused a statistically significant ($\alpha=0.01$) decrease in the objective function of greater than 6.83. After the full model was built, a Backward Elimination procedure was applied. All the covariates that their removal caused a statistically significant ($\alpha=0.001$) increase in the objective function of greater than 10.83 were kept in the model and others were removed from the model one by one, starting with the least significant. Following completion of the Backward Elimination procedure, the final model was obtained. The final model was re-run using FOCE method.

Findings

Figure 7 and 8 show the observed data (A-Febuxostat, B-Serum Urate) and predictions based on the PK/PD model at various dose levels. The summary of the pharmacokinetic parameters obtained from analyzing the data from Study TMX 01-005 and C02-009 are shown in Table 1, 2 below:

Table 1. Summary of PK parameters from TMX-01-005 study

Parameter	θ (95% CI) ^a	CV (95% CI) ^b
Cl (L/h)	6.35 (4.70-8.00)	16.2 (11.7-19.8)
V _c (L)	25.9 (22.1-29.7)	NE ^c
Q (L/h)	5.45 (3.27-7.63)	69.1 (43.4-87.6)
V _p (L)	28.2 (23.7-32.7)	26.6 (6.60-37.0)
K _a (h ⁻¹)	19.0 (9.93-28.1)	208 (132-262)
t _{1/2g} (h)	0.473(0.440-0.506)	NE ^c
Residual ^d (µg/mL)	0.0103(0.00542-0.0136)	48.2 (42.7-53.1)
θ_{C_1/C_3} (95% CI) ^e	0.0395 (0.0201 -0.0589)	
θ_{S_{MK}/C_1} (95% CI) ^f	-1.05 (-2.00 to -0.0955)	

a Population mean (its 95% confidence interval).

b Inter-individual variability (its 95% confidence interval).

c Not estimated; η 's for V_c and t_{1/2g} were not included in the model so the inter-individual variability for V_c and t_{1/2g} were not estimated.

Table 2. Summary of PK parameters from C02-009 study

Parameter (Unit)	θ (95% CI) ^a	CV (95% CI) ^b
Cl (L/h)	4.78 (2.84-6.72)	17.6 (11.1-22.3)
V _c (L)	32.2 (26.7-37.7)	NE ^c
Q (L/h)	5.75 (3.22-8.28)	NE ^c
V _p (L)	22.4 (17.6-27.2)	NE ^c
K _a (h ⁻¹)	13.7 (2.94-24.5)	175 (132-210)
t _{1/2g} (h)	0.234 (0.218-0.250)	NE ^c
Residual ^d	NE ^c	71.6 (65.0-77.5)
θ_{C_1/C_3} (95% CI) ^e	0.0138 (0.00343-0.0242)	
θ_{FIB/C_1} (95% CI) ^f	-1.21 (-2.01 to -0.412)	
θ_{WT/C_1} (95% CI) ^f	0.0174 (-0.000632 to 0.0354)	

a Population mean (its 95% confidence interval).

b Inter-individual variability (its 95% confidence interval).

c Not estimated; η 's for V_c, Q, V_p, and t_{1/2g} were not included in the model so the inter-individual variability for V_c, Q, V_p, and t_{1/2g} were not estimated.

The summary of the pharmacokinetic and pharmacodynamic parameters are shown in Table 3 and 4 below:

Table 3. Summary of PK and PD parameters from Study TMX-01-005

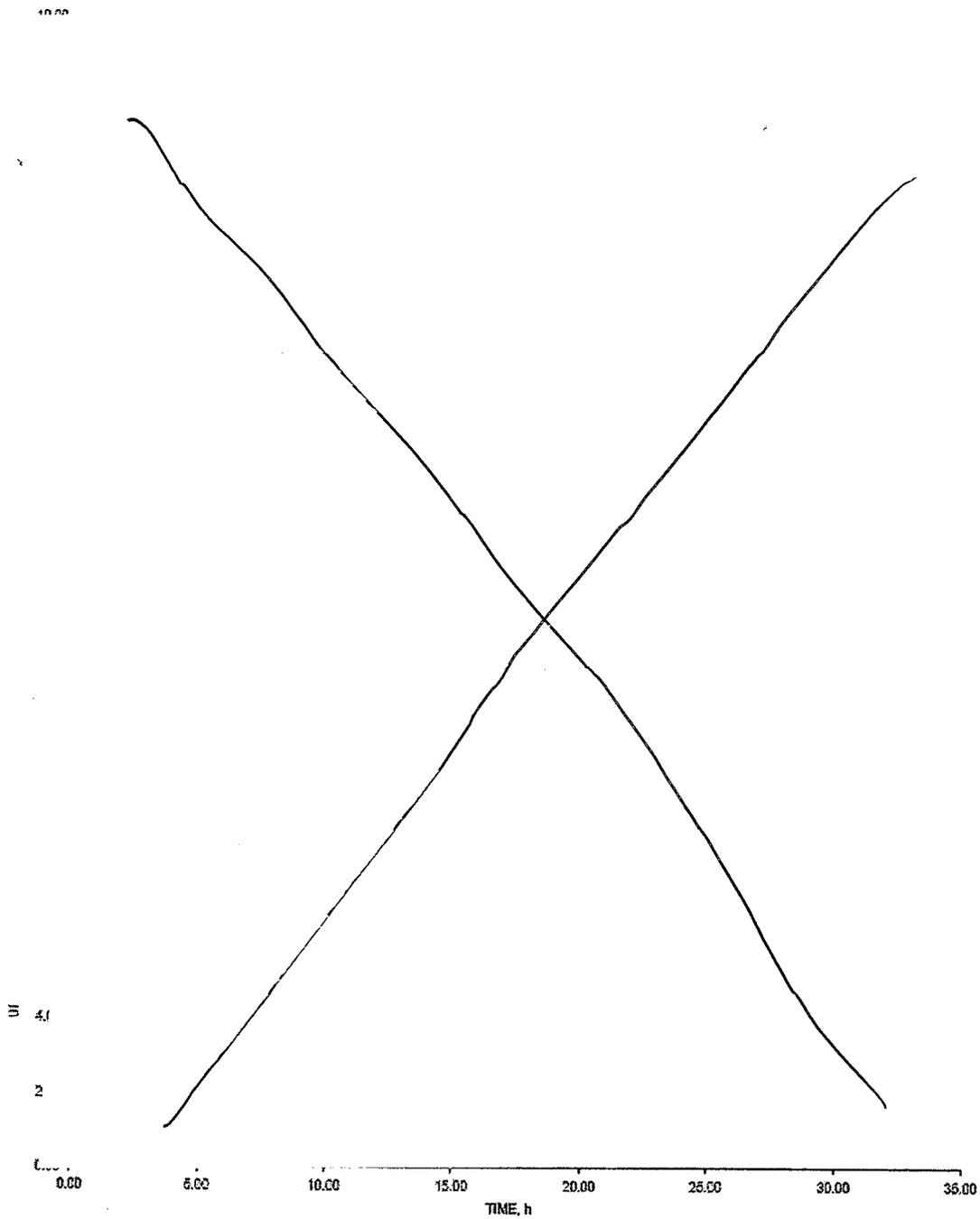
Type	Parameter	θ (95% CI) ^a	CV (95% CI) ^b
Pharmacokinetic	Cl (L/h)	6.80(5.27-8.33)	15.0(9.81-18.9)
	V _c (L)	28.4(23.3-33.5)	NE ^c
	Q (L/h)	5.56(2.64-8.48)	85.2(0-132)
	V _p (L)	28.7(23.9-33.5)	26.9(0-41.2)
	K _a (h ⁻¹)	7.19(2.68-11.7)	210(0-297)
	t _{lag} (h)	0.388(0.127-0.649)	NE ^c
	Residual ^d (µg/mL)	0.00904(0.00319-0.0124)	46.4(37.3-57.4)
	$\theta_{Cl/Cl}$ (95% CI) ^e	0.0327(0.0157-0.0497)	
Pharmacodynamic	$\theta_{SM/Cl}$ (95% CI) ^f	-1.07(-2.02 to -0.123)	
	K _{in} (mg/dL/h)	0.262(0.195-0.329)	NE ^c
	IC ₅₀ (µg/mL)	0.209(0.176-0.242)	48.4(37.3-57.4)
	K _{out} (h ⁻¹)	0.0510(0.0376-0.0644)	NE ^c
	Residual ^d (mg/dL)	0.620(0.550-0.683)	NE ^g
	$\theta_{BUA/K_{out}}$ (95% CI) ^h	-0.00235(-0.00303 to -0.00167)	

- a Population mean (its 95% confidence interval).
- b Inter-individual variability (its 95% confidence interval).
- c Not estimated; η 's for V_c, t_{lag}, K_{in}, and K_{out} were not included in the model so the inter-individual variability for V_c, t_{lag}, K_{in}, and K_{out} were not estimated.

Table 4. Summary of PK and PD parameters from Study C02-009

Type	Parameter (Unit)	θ (95% CI) ^a	CV (95% CI) ^b
Pharmacokinetic	Cl (L/h)	4.93(3.01-6.85)	18.3 (12.2-22.8)
	V _c (L)	32.2(26.7-37.7)	NE ^c
	Q (L/h)	5.57(3.06-8.08)	NE ^c
	V _p (L)	22.2(17.4-27.0)	NE ^c
	K _a (h ⁻¹)	13.7(2.27-25.1)	176(132-211)
	t _{lag} (h)	0.234(0.217-0.251)	NE ^c
	Residual ^d	NE ^c	71.2(64.7-77.2)
	$\theta_{Cl/Cl}$ (95% CI) ^e	0.0142(0.00440-0.0240)	
	$\theta_{WT/Cl}$ (95% CI) ^f	0.0155 (-0.00257 to 0.0336)	
	$\theta_{FIB/Cl}$ (95% CI) ^g	-1.23 (-2.02 to -0.444)	
Pharmacodynamic	K _{in} (mg/dL/h)	0.0462 (0.0252-0.0672)	NE ^c
	IC ₅₀ (µg/mL)	0.239 (0.193-0.285)	66.7 (53.4-77.8)
	K _{out} (h ⁻¹)	0.0255 (0.0176-0.0334)	NE ^c
	Residual ^d	0.863 (0.761-0.953)	NE ^h
	$\theta_{BUA/K_{in}}$ (95% CI) ⁱ	0.0211 (0.0144-0.0278)	

- a Population mean (its 95% confidence interval).
- b Inter-individual variability (its 95% confidence interval).
- c Not estimated; η 's for V_c, V_p, Q, t_{lag}, K_{in}, and K_{out} were not included in the model so the inter-individual variability for V_c, V_p, Q, t_{lag}, K_{in}, and K_{out} were not estimated.



b(4)

Figure 7. Time course of serum (A) Febuxostat (B) Urate concentrations after 80, 120 and 240 mg dose in TMX-01-005 (Note: Samples are collected at various time intervals on different occasions. The time scale does not refer to sampling done on a single day)

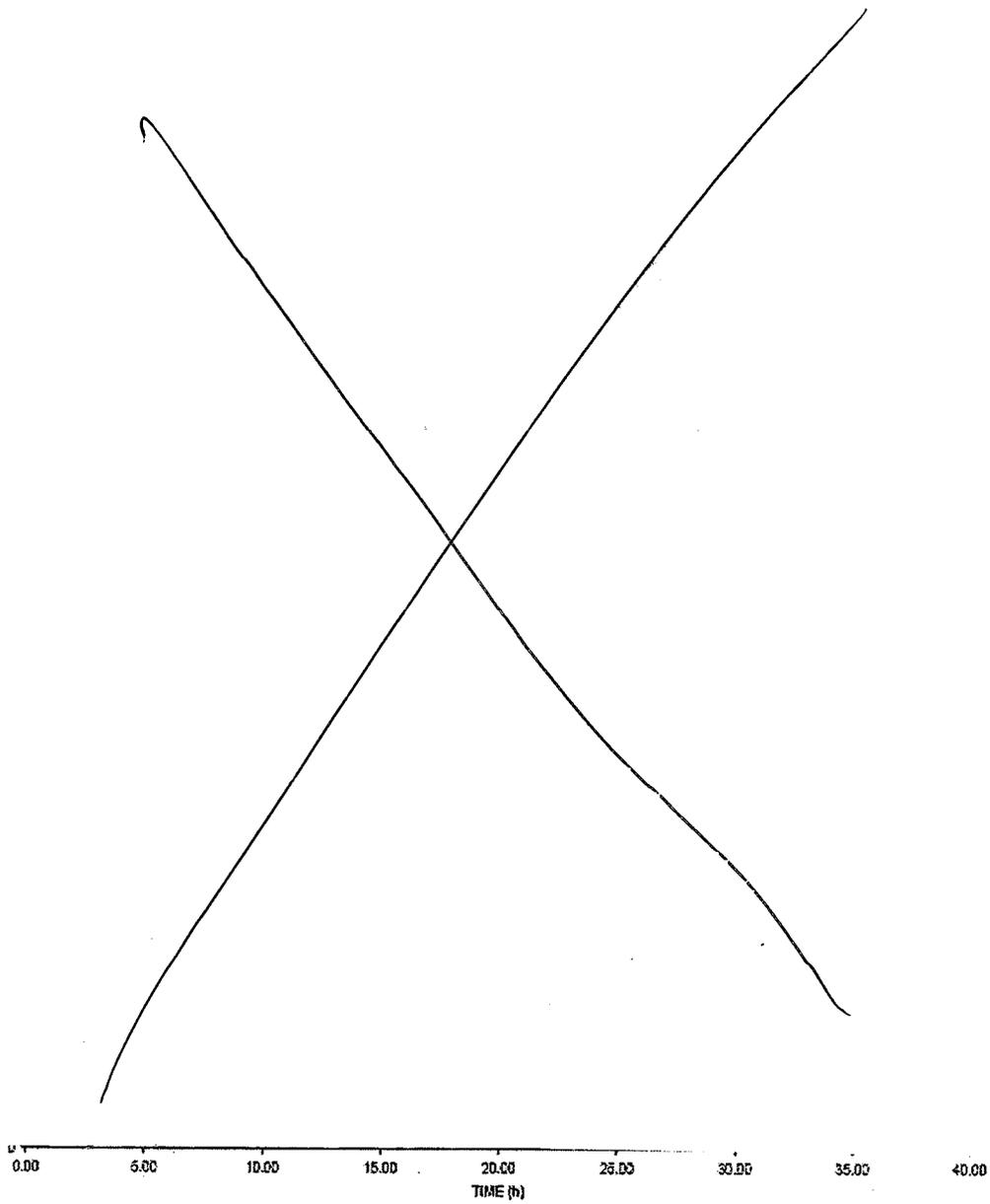


Figure 8. Time course of serum (A) Febuxostat (B) Urate concentrations after 80, 120 and 240 mg dose in C-02-009 (Note: Samples are collected at various time intervals on different occasions. The time scale does not refer to sampling done on a single day).

Safety

The sponsor examined relationship between dose-safety events in Phase I, II and III studies. Adverse events of special interest (cardiovascular, hypertension, gastrointestinal, renal, lipid metabolic; thyroid, rash, hepatic, neurological, and hematological adverse events) were summarized for the Phase 3 controlled and Phase 2/3 studies. These organ systems were selected because of the known high prevalence of certain comorbidities in the gout population (cardiovascular disease, hypertension, renal and lipid disorders) or because of known side effects (cutaneous rash, hepatotoxicity, bone marrow toxicity) of the only other available XO inhibitor, allopurinol. Finally, additional organ systems were added because of findings in the febuxostat preclinical (thyroid effects) or clinical (diarrhoea, nausea, and 1 event of Guillain-Barré syndrome) program. Data from all subjects in a grouping who received at least 1 dose of febuxostat were included in the safety analyses. Since the placebo and febuxostat 240 mg QD treatment groups were only included in Study C02-009, statistical comparisons were performed only between and/or within the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups for the analyses of the Phase 3 controlled studies.

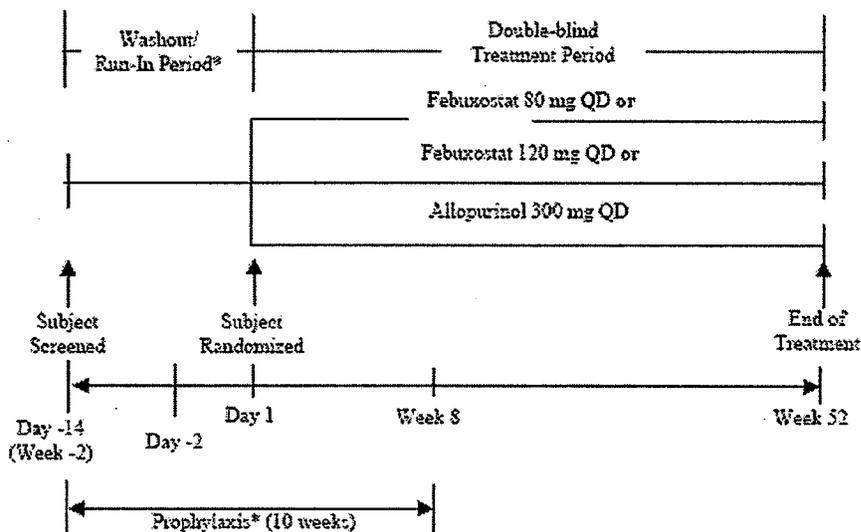
The overall incidence of treatment-related adverse events in the Phase 3 controlled studies was 23%, 21%, and 19% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups, respectively, and 29% and 23% in the febuxostat 240 mg QD and placebo groups, respectively. None of the differences between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups in HLTs (High Level Terms) were statistically significant. The incidence of specific treatment-related adverse events was low. The incidence of treatment-related nausea was numerically higher in the febuxostat 240 mg QD group (4%) compared to all other treatment groups (<1-2%). Additionally, the incidence of treatment-related diarrhoea was numerically higher in the febuxostat 240 mg QD group (7%) compared to all other treatment groups (2-4%). The incidence of all other specific treatment-related events was similar across treatment groups.

Conclusions/Reviewer's Comments

The sponsor analyzed the time course of febuxostat and serum uric acid concentrations using an indirect response PK/PD model which is the right model. There are no significant covariates that would necessitate dosage adjustments. However, the modeling approach has the following shortcomings:

1. Analyzing the data from two studies separately which for example shows two different covariate effects on PK although they are not clinically relevant. It is always a good practice to integrate all the available information into one model.
2. The sponsor used baseline serum uric acid as a covariate in the PK/PD model which is not correct. The indirect response model allows the effects to be proportional to the baseline. The sponsor included the baseline twice in the model which lead to a dramatic drop in %CV of k_{in} or k_{out} from 11% to 0.01%. Also as mentioned above, the sponsor should have integrated both these studies into one single analysis.
3. Although this is of minor concern, as a good modeling practice prior information should be borrowed from studies where sampling was done extensively. For example, in the PK analysis, the sponsor tried to estimate K_a when there were hardly any data (1-2 points) in the absorption phase. The average values of K_a in various analysis ranges from 7-19 hr^{-1} .

estimates were obtained using FOCE method. The sequential model was fit using FO and FOCE method.



* Subjects who were not receiving allopurinol or uricosuric agents prior to the study began treatment with naproxen or colchicine at the Day 1 Visit. These subjects were not required to complete a 14-day Washout/Run-in Period prior to randomization; however, they were required to complete all Screening and Day -2 procedures. For subjects who did not require a Washout Period, the Screening Visit could have occurred anytime between Day -14 and Day -3.

Figure 9. Study design for C02-010

Safety

The information submitted in the ISS (Integrated Summary of Safety) report was reviewed. For non-cardiovascular safety events, there is no evidence of dose-response relationship. This could also be due to the narrower dose range studied (80 and 120 mg) studied. Numerically there are higher incidences of oedema, nausea and diarrhea at 240 mg dose group. The sponsor is not seeking approval for 240 mg dose group, but it was included in the study to understand the safety issues. There is concern about more cardiovascular safety issues (Not reviewed here) in febuxostat group in comparison to allopurinol. Please refer to Medical Officer's review on safety for greater discussion on this issue.

Findings

Healthy Subjects

A two compartment model could describe the PK of febuxostat satisfactorily. The PD data was also well characterized using the indirect response model. The goodness of fit plots are shown in Figure 10-11. The estimates of the parameters are shown in Table 5 below:

Table 5. PK/PD parameters in healthy subjects

Parameter	θ (% SE)	CV (% SE)
Ka (h ⁻¹)	6.38 (16.8)	56 (52)
CL (L/h)	10.3 (3.6)	30 (22)
Vc (L)	20.1 (6.4)	34 (22)
Q (L/h)	2.05 (11.5)	45 (44)
Vp (L)	18.4 (6.2)	40 (36)
Lag time (h)	0.22 (2.6)	18 (48)
Residual		
• Proportional	33% (15.4)	
• Additive	0.007 (25)	
Kin (mg/dL/h)	0.144 (3.3)	11 (41.5)
Kout (1/h)	0.0289 (3.8)	51 (19.4)
IC50 (ug/mL)	0.065 (5.4)	21 (15)
Residual	0.19 (12.2)	

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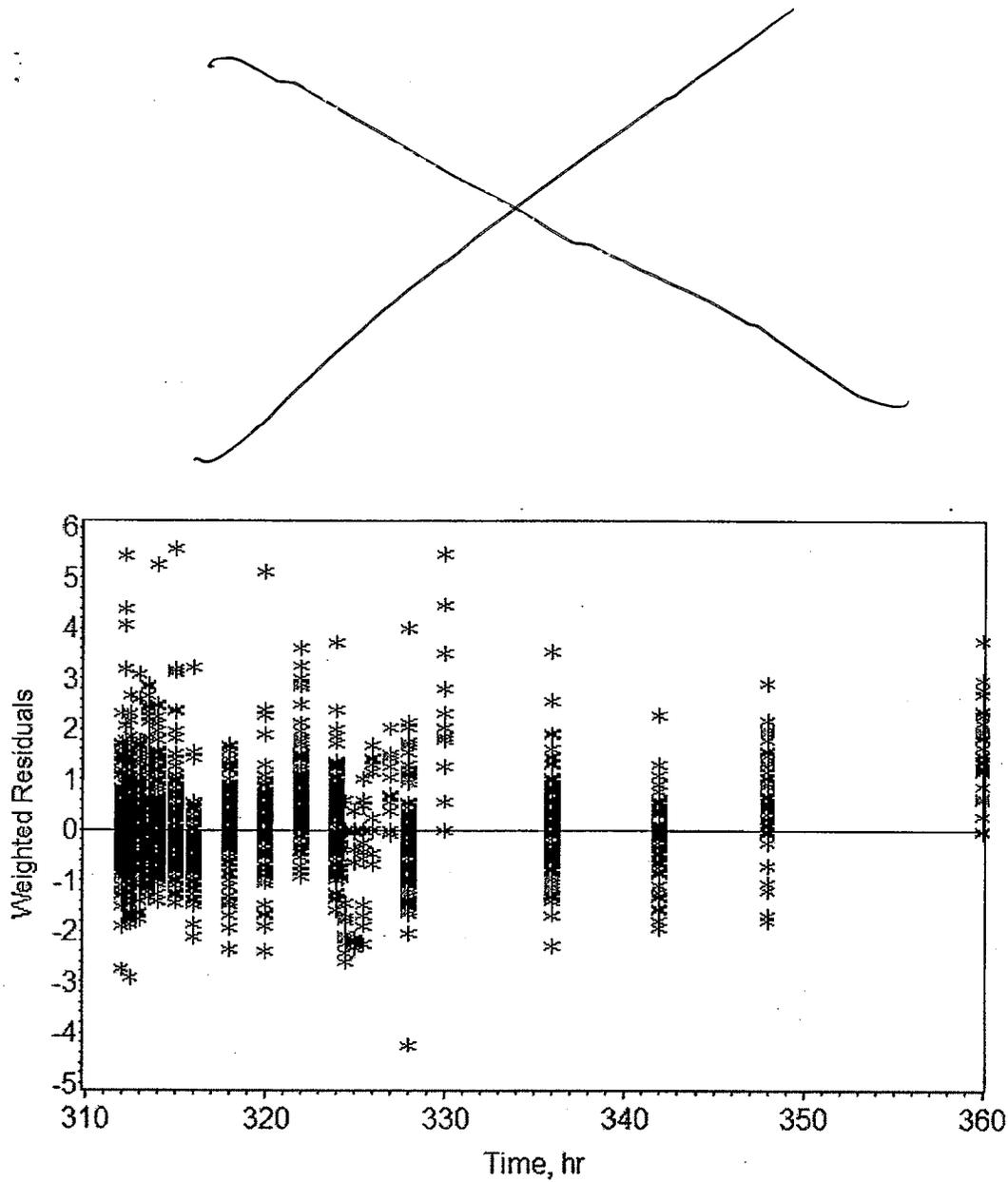


Figure 10. Goodness of fit plots for PK in healthy subjects (A) Observed vs Predicted (Population; PRED, Individual Predicted; IPRED) (B) WRES vs Time (Note the minor trend in WRES vs Time is not a concern here)

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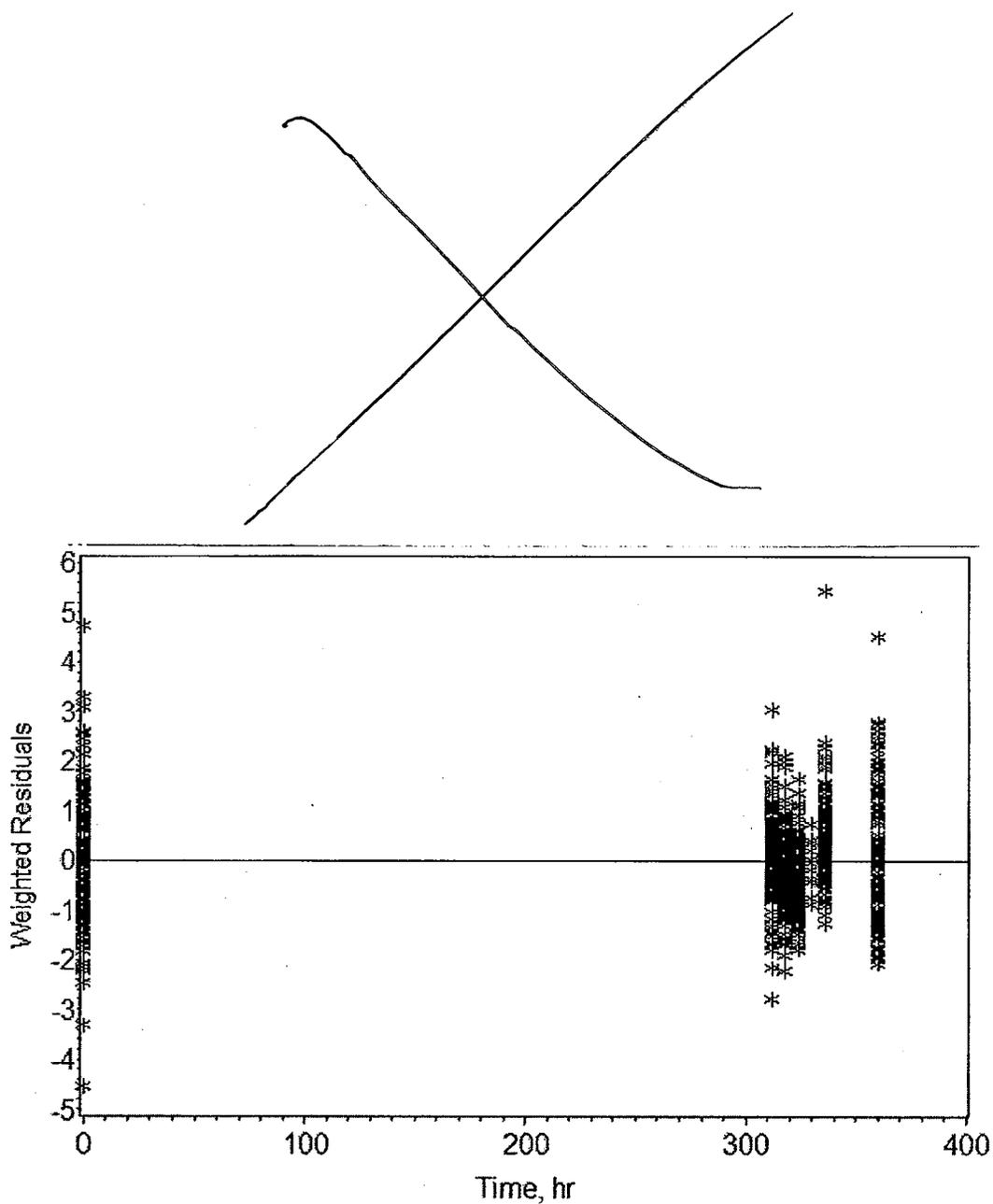


Figure 11. Goodness of fit plots for PD in healthy subjects (A) Observed vs Predicted (Population; PRED, Individual Predicted; IPRED) (B) WRES vs Time

Patients

For describing the data in patients, the absorption rate constant was fixed to 6.38 h^{-1} as obtained from healthy subjects. A two compartment model was adequate to describe the PK data in patients. The goodness of fit plots for PK and PD are shown in Figure 12, 13 respectively. The estimates of the parameters are shown in Table 6 below:

Table 6. Summary of PK/PD parameters in patients

Parameter	θ (% SE)	CV (% SE)
Ka (h^{-1})	6.38 (0)	206 (35.7)
CL (L/h)	8.38 (3.2)	22 (20.2)
Vc (L)	32.5 (6.4)	26 (79.2)
Q (L/h)	3.53 (12.8)	201 (45.2)
Vp (L)	23 (10.2)	36 (82)
Lag time (h)	0.22 (0)	11 (240)
Residual	57% (8.3)	
Kin (mg/dL*h)	0.254 (10.7)	10.48 (126)
Kout (h-1)	0.0261 (10.7)	7.7 (237)
IC50 (mg/dL)	0.207 (5.6)	70.35 (13.7)
Residual (mg/dL)	0.77 (9.2)	11 (240)

The plot of observed vs predicted concentrations clearly shows a bias in the predictions in a few patients. The higher concentrations ($> 12 \text{ ug/mL}$) are mostly in the 240 mg dose group. There is no covariate that appears to explain the higher concentrations seen in this dose group. Similar model in healthy subjects at 240 mg dose group, the model did not exhibit a significant bias at the higher dose levels. It is possible that there are some patients who are outliers or have unknown reasons for the high concentrations. The reviewer looked at covariates such as renal function, age, body weight, concomitant medications for their inclusion in the model. However, the reviewer could not detect any covariate that would explain the high serum levels in this dose group. Various models were tried to explain the data (mixture models for Ka, F), but did not improve the performance of the model.

Covariate(s) such as renal function, age, bodyweight were tested for their influence on clearance and volume of distribution (Figure 14-16). There weren't any significant covariates that would have changed the proposed dose in various subgroups.

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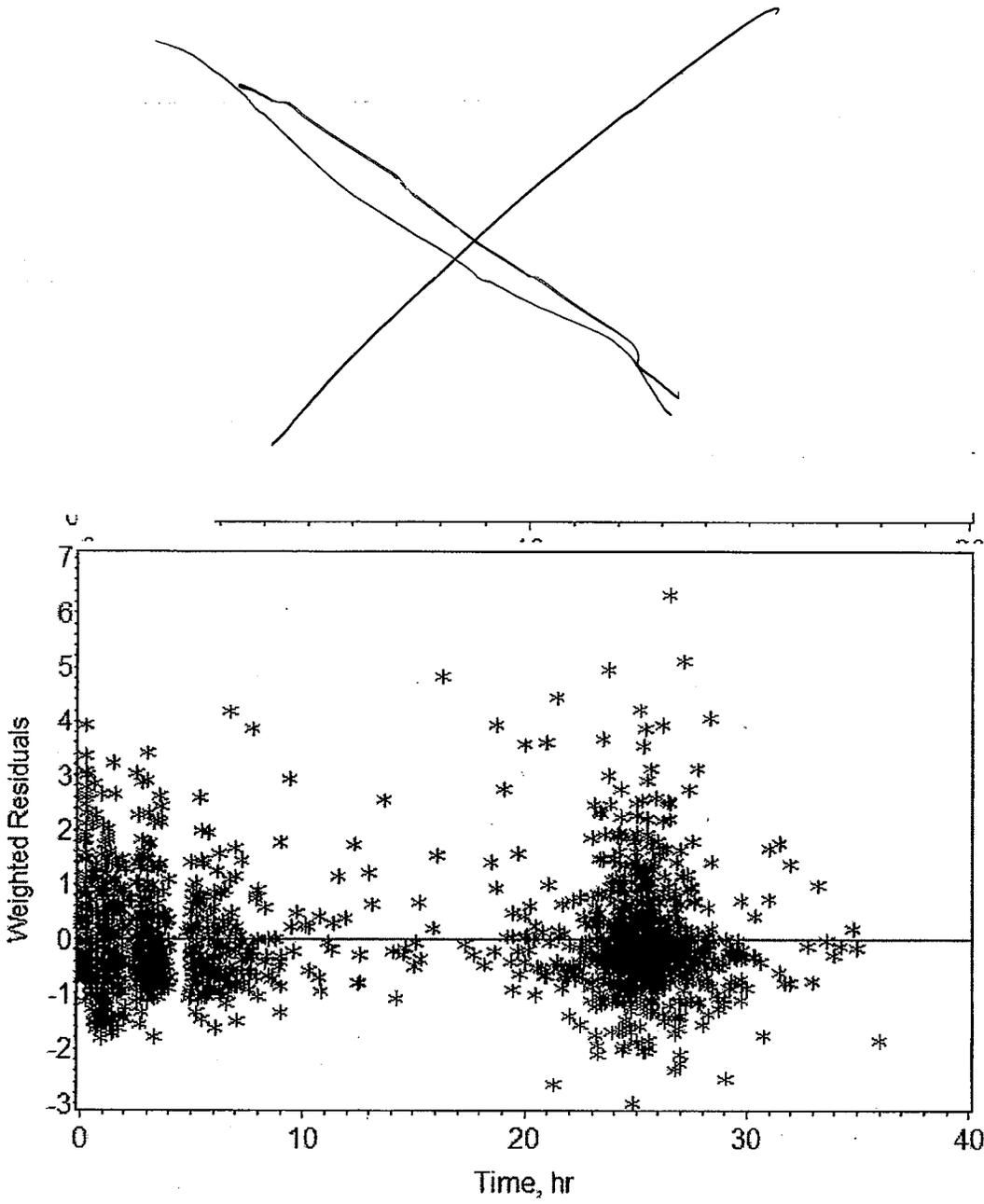


Figure 12. Goodness of fit plots for PK in patients (A) Observed vs Predicted (Population; PRED, Individual Predicted; IPRED) (B) WRES vs Time

b(4)

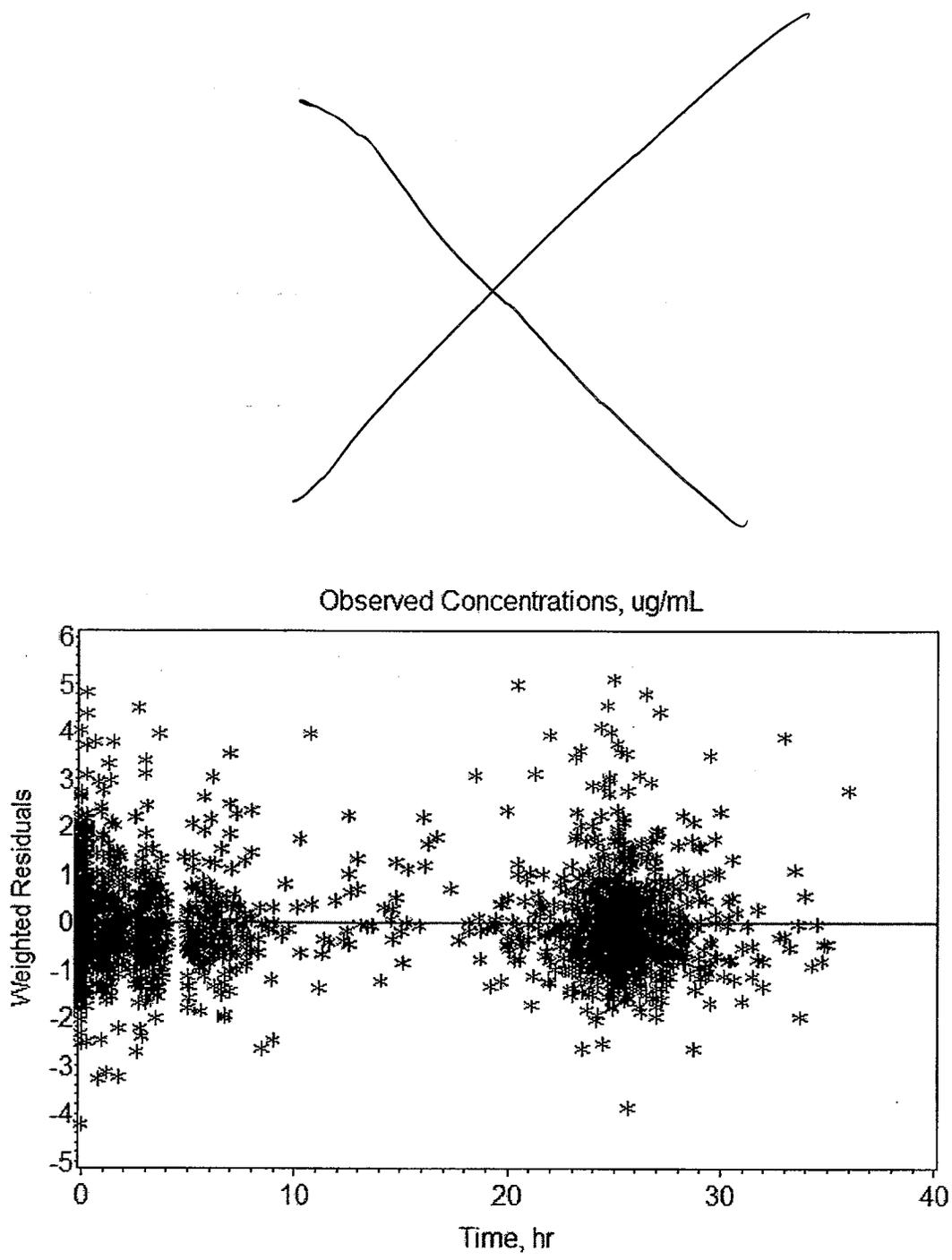


Figure 13. Goodness of fit plots for PD in patients (A) Observed vs Predicted (Population; PRED, Individual Predicted; IPRED) (B) WRES vs Time

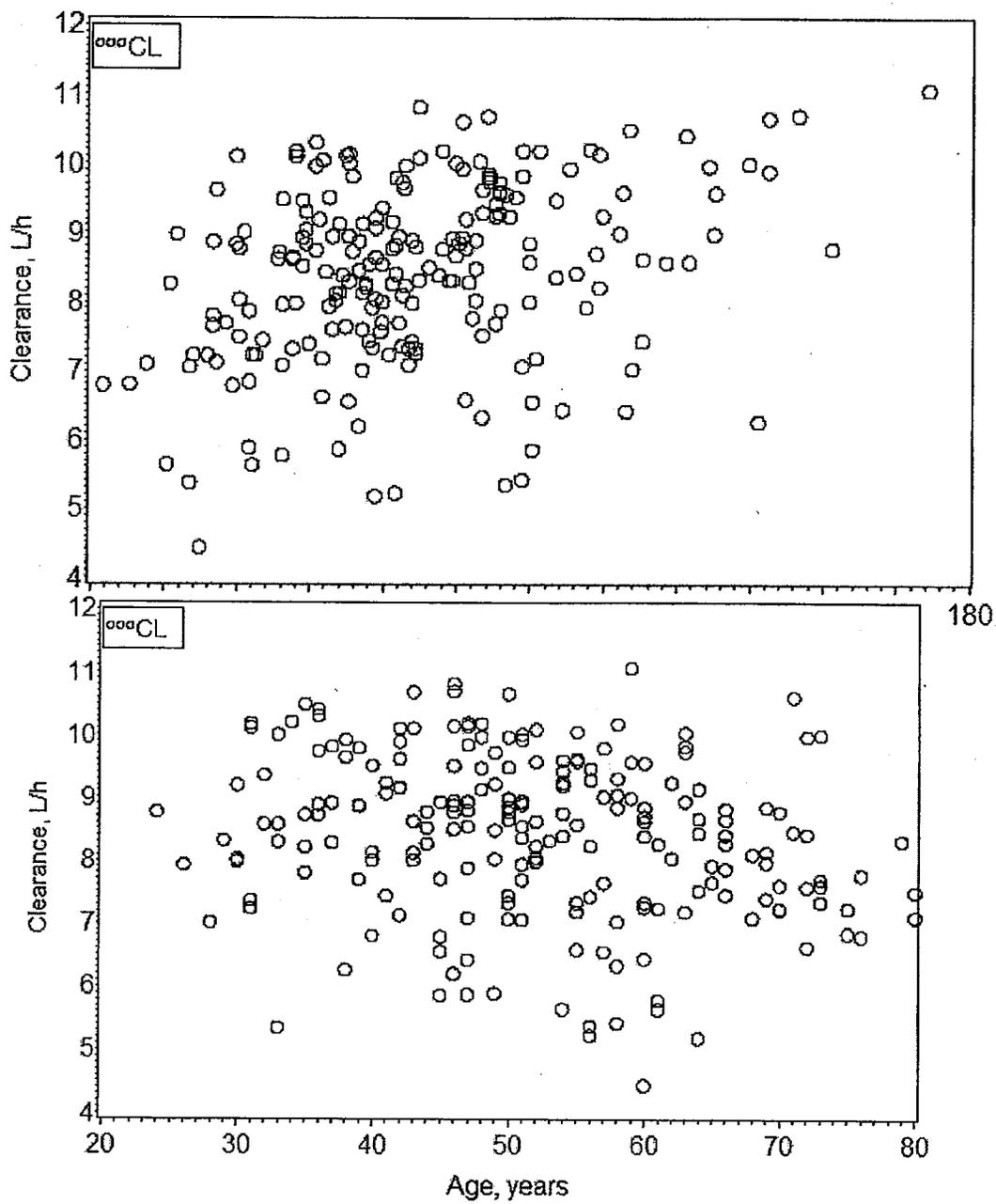


Figure 14 Relationship between clearance and total body weight (kg) and Age (Years)

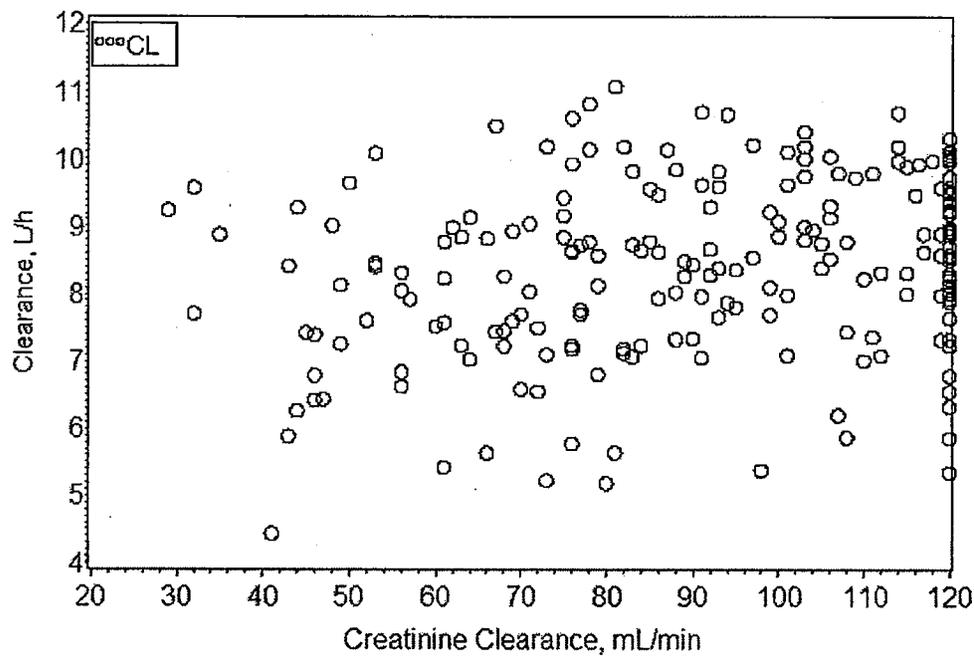


Figure 15. Relationship between clearance and Creatinine clearance (ml/min)

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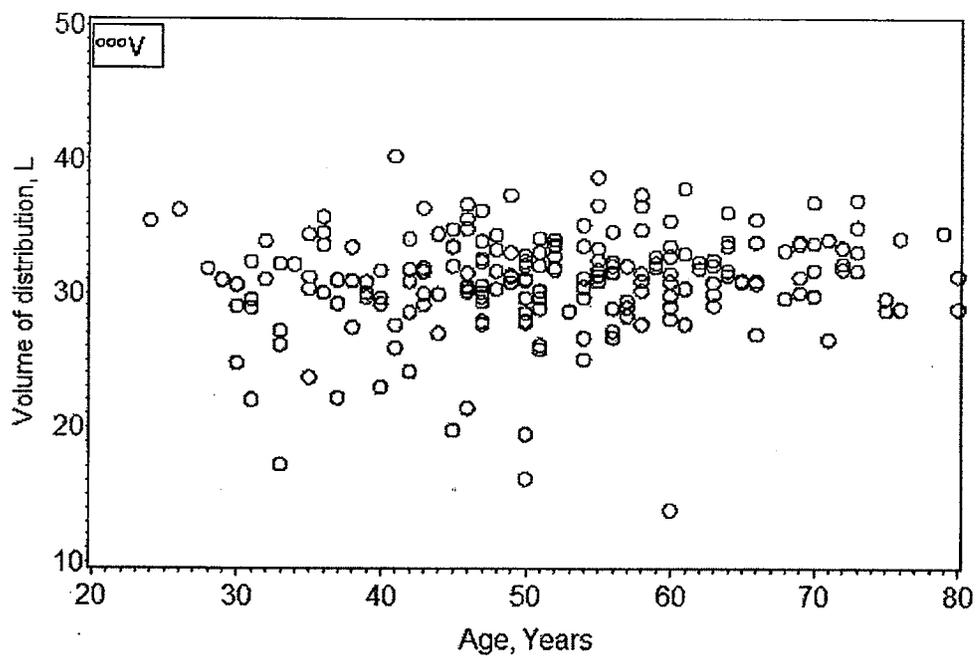
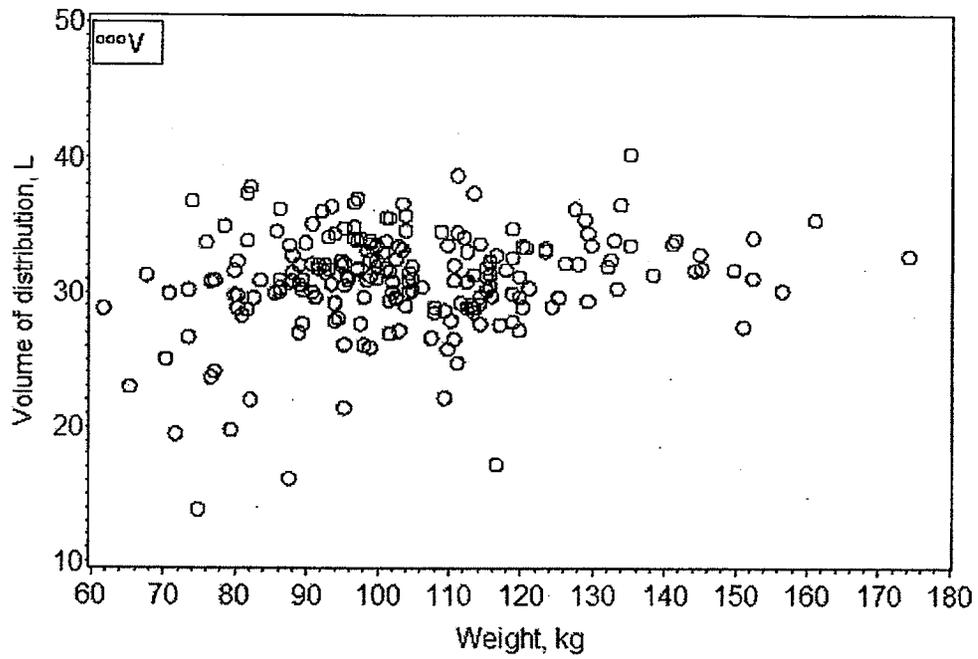


Figure 16 Relationship between volume of distribution and (A) Total body weight (B) Age, years.