CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

12/18/08

CLINICAL PHARMACOLOGY REVIEW

NDA	21-856
Submission Date	7/17/2008 (Amendment 046)
Brand Name	ULORIC™
Generic Name	Febuxostat (TMX-67)
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia and Rheumatology Products (DAARP)
Sponsor	Tekeda Pharmaceuticals North America, Inc
Relevant IND	IND 58,229
Type of Submission	Resubmission #2: Complete Response to Deficiencies Identified in The Action Letter
Formulation; Strength(s)	Tablets; 40 and 80 mg
Proposed Dosing Regimen	• The recommended dose of ULORIC is 40 or 80 mg daily. [redacted] b(4) • No dose adjustment is necessary when administering ULORIC to patients with mild to moderate renal or hepatic impairment. • ULORIC can be administered without regard to food or antacid use.
Proposed Indication	For the treatment of hyperuricemia in patients with gout

Table of Content

1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding language in the package insert.

1.2 Phase 4 Commitment

As agreed upon in previous review cycles, the Sponsor will conduct the following study post-approval:

- A Double-Blind, Randomized, Two-Period Crossover Study to Evaluate the Effect of Multiple Oral Doses of Febuxostat on the Pharmacokinetics of a Single Oral Dose of Theophylline.

1.3 Summary of Clinical Pharmacology Findings in the Resubmission

The Sponsor submitted NDA 21-856 to seek an approval of ULORIC (febuxostat or TMX-67) for the treatment of hyperuricemia in patients with gout. During the first two review cycles, NDA 21-856 was deemed Approvable (Action Letters, October 14, 2005 and August 2, 2006). The Sponsor submitted a complete response in this submission to address the deficiencies identified in the Action Letters. The doses proposed for registration are 40 or 80 mg once daily (QD).

Refer to Clinical Pharmacology reviews dated August 29, 2005 and July 18, 2006 for more background information and Clinical Pharmacology conclusions.

The following items in the Action Letter of August 2, 2006 are related to Clinical Pharmacology:

> *A. "While not a deficiency impacting the approvability of Uloric, we request that you conduct a new warfarin-febuxostat interaction study. In the new study, the lead-in period for identifying a stable warfarin dose may need to be more than nine days and/or you should enroll more subjects such that a sufficient number of subjects are able to complete the trial. We would like data from this study to be submitted as a part of a resubmission. However, we would entertain a later submission of such data (including post-approval) if appropriate labeling were proposed*

b(4)

> *B. "In addition, we remind you of your February 17, 2006, commitment to perform the following studies. While we agreed to allow these studies to be performed in the post-approval period, in light of this approvable action,*

please consider beginning any of these studies that you have not already undertaken at the earliest possible time.

1. .....

2. A Double-Blind, Randomized, Two-Period Crossover Study to Evaluate the Effect of Multiple Oral Doses of Febuxostat on the Pharmacokinetics of a Single Oral Dose of Theophylline.

3. In Vitro Assessment of Induction Potential of Febuxostat in Primary Human Hepatocytes."

In this submission, the Sponsor submitted a study report (Study F-P107-162) on a new drug interaction study that evaluated the effect of febuxostat on PK and PD of warfarin to address Item A.

The new study results suggested that multiple oral doses of febuxostat (80 mg once-daily) had no effect on the PK or PD of warfarin at steady-state (Tables 1 and 2).

Table 1. C_{max} and AUC of R- and S-Warfarin on Day 14 Following Once-Daily Multiple Dosing With Warfarin and Febuxostat Relative to Warfarin and Placebo in Healthy Subjects.

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
R-Warfarin (N=27)		
C_{max}	0.9791	0.9407 - 1.0191
AUC_t	0.9923	0.9722 - 1.0128
AUC_τ	0.9898	0.9693 - 1.0107
S-Warfarin (N=27)		
C_{max}	0.9973	0.9534 - 1.0432
AUC_t	1.0103	0.9887 - 1.0323
AUC_τ	1.0049	0.9898 - 1.0202

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

Table 2. Mean Pharmacodynamic Parameter Estimates of INR and Factor-VII on Day 14 Following Once-Daily Multiple Dosing With Warfarin and Febuxostat or With Warfarin and Placebo in Healthy Subjects.

	INR_{max} [a]	$INR_{mean,24}$ [a]	$F\text{-}VII_{mean,24}$ [a] (%)
Regimen A: Warfarin and Febuxostat 80 mg (N=27)			
Mean	1.496	1.437	55.163
SD	0.172	0.142	11.014
Range	1.3-2.0	1.2-1.8	34.0-76.1
Regimen B: Warfarin and Placebo (N=27)			
Mean	1.504	1.448	52.925
SD	0.156	0.134	12.744
Range	1.2-1.8	1.2-1.7	27.0-77.5
P-value[b]	0.917	0.601	0.186

a Included only subjects with data from both crossover periods.

b p-values for comparing Regimens A versus B obtained from ANOVA analysis.

In this submission, the Sponsor also evaluated the induction potential of febuxostat on P450 isoforms in human hepatocytes and submitted the study report (Study 3210-0407-1800) to address Item B3.

The *in vitro* study results suggested that there was low potential for febuxostat to cause enzyme induction of CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4/5 compared to known inducers in human hepatocytes (Table 3) because % adjusted positive control response values for febuxostat-treated hepatocytes were <40%. The FDA draft drug interaction guidance recommends ≥40% of adjusted positive control response to suggest the compound has the induction potential that warrants further *in vivo* induction studies.

Table 3. Summary of Induction as a Percentage of Adjusted Positive Control Induction.

	Donor	Substrate	Positive Control	Fold-Change	Febuxostat % of Adjusted Positive Control Induction		
					3 μM	30 μM	300 μM
CYP1A/2	Hu362	Phenacetin (100 μM)	3-MC (2 μM)	3.9	-0.45	5.5	-31.4
	Hu369			7.0 [a]	1.9	-6.8	-7.5
	Hu373			4.7 [a]	-0.95	-10.1	-21.6
CYP2B6	Hu362	Bupropion (250 μM)	PB (1 mM)	9.6	4.0	4.2	-4.7
	Hu369			13.5	0.81	-0.41	0.02
	Hu373		RIF (10 μM)	6.1	0.68	-1.0	-6.4
CYP2C9	Hu362	Diclofenac (25 μM)	RIF (10 μM)	4.4	-0.67	6.7	0.83
	Hu369			2.3	-2.1	-22.3	2.5
	Hu373			2.1	-10.7	-44.8	-53.9
CYP2C19	Hu362	(S)-Mephenytoin (250 μM)	RIF (10 μM)	4.9	1.5	6.8	-5.0
	Hu369			3.5	13.1	2.7	8.6
	Hu373			4.2	3.1	-2.5	-6.2
CYP3A4/5	Hu362	Testosterone (200 μM)	RIF (10 μM)	48.0	0.03	3.3	-1.6 [b]
	Hu369			4.8	-3.5	-1.1	-4.9
	Hu373			5.7	10.9	-0.66	-7.2

[a] Estimated values; Above ULOQ; [b] Estimated values; Below the LLOQ

Reviewer's Notes: Negative data indicated a lower activity was observed in febuxostat-treated hepatocytes than vehicle-treated hepatocytes.

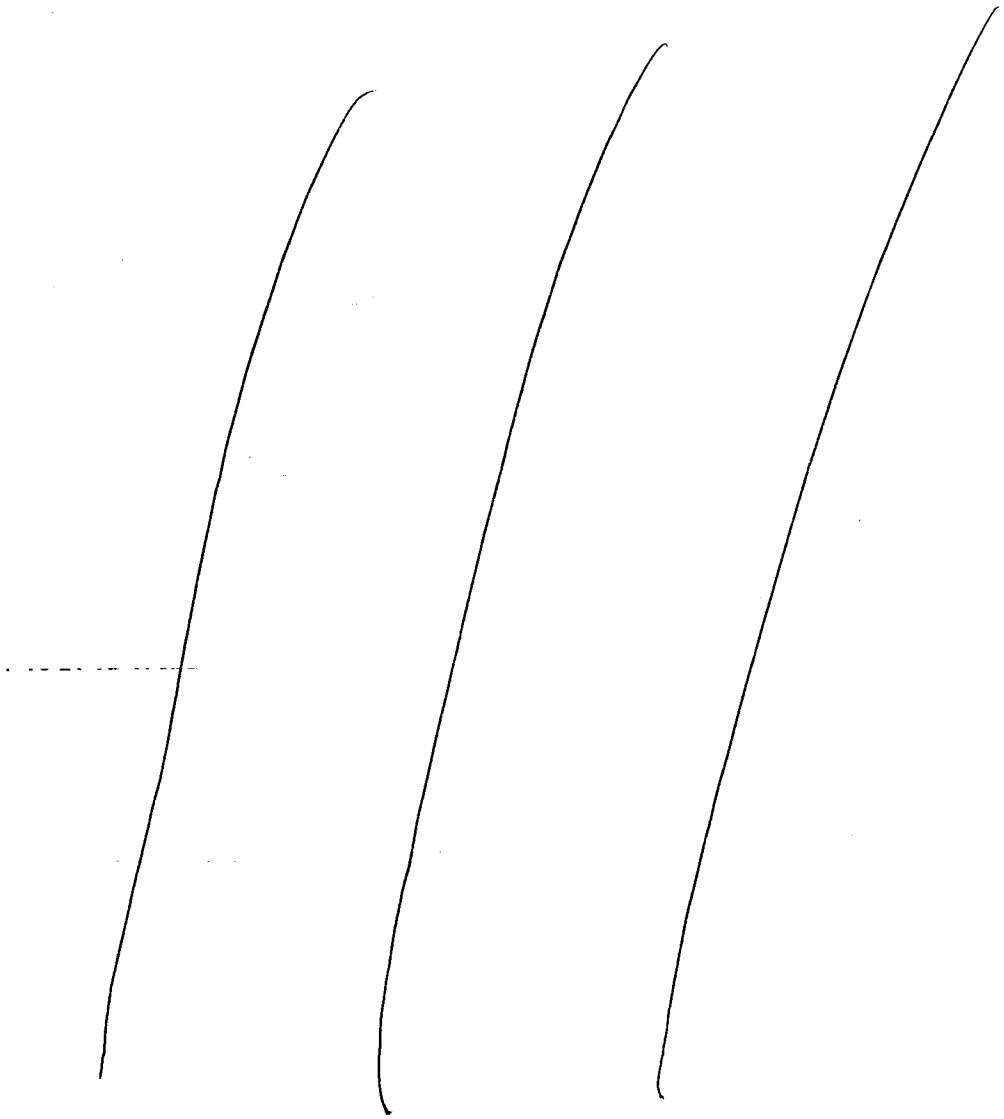
For Item B2, the Sponsor committed to conducting a drug-drug interaction study post-approval to evaluate the potential for interaction between febuxostat and theophylline [redacted] The protocol for such a study (F-P105-140) was submitted to IND 58,229 (SN 202). Protocol F-P105-140 was reviewed and comments were sent to the sponsor on 06/20/06.

b(4)

2 Labeling Recommendations

The following labeling recommendations were based on the new labeling proposal from the Sponsor (submitted on July 17, 2008). The labeling sections that are mostly related to Clinical Pharmacology are listed with tracked changes. Please refer to the final approval letter for final labeling recommendations.

b(4)



7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

3 Individual Study Reviews

3.1 CYP Induction Evaluation

Study 3210-0407-1800 – In Vitro Assessment of the Induction Potential of Febuxostat in Primary Human Hepatocytes

---

Objective: To utilize primary cultures of human hepatocytes to evaluate the potential of febuxostat to induce liver microsomal cytochrome P450 (CYP450) enzymes.

Method: Febuxostat (3, 30 and 300 μM) and known CYP450 inducers 3-methylcholanthrene (3-MC, a prototypical CYP1A1/2 enzyme inducer), phenobarbital (PB, a prototypical CYP2B6 enzyme inducer) and rifampicin (RIF, a prototypical CYP2C9, CYP2C19 and CYP3A4/5 enzyme inducer) were incubated in cultures of human hepatocytes from three separate donors (Hu362, Hu369, and Hu373) (Table 1) for three consecutive days. Microsomes were isolated and the activities of CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 were determined using selective metabolite markers. Protein levels for each CYP450 were analyzed by Western immunoblotting.

Table 1. Primary Human Hepatocyte Donor Information.

Donor	Sex	Age (Years)	Race	Weight (lbs)	Height	HBV,HCV	Alcohol or Drug Use	Cell Viability (%)
Hu362	M	44	Caucasian	239	5' 9"	No Known	No	79
Hu369	M	69	Hispanic	156	5' 5"	No Known	No	81
Hu373	F	49	Caucasian	142	5' 2"	No Known	No	85

Febuxostat Lot No: 31649CB00; A fresh stock solution of febuxostat was prepared in dimethyl sulfoxide (DMSO) prior to or on the first day of dosing. The stock solution was diluted daily in modified Chee's medium such that the final DMSO concentration was 0.1% to achieve the final dosing concentrations of 3, 30 and 300 μM.

Reviewer's Notes: C_{max} of febuxostat at 80 mg (the highest proposed clinical dose) was approximately 11 μM. Therefore concentrations of 3 to 30 μM are of clinical relevance.

RIF (10 μM), PB (1 mM) and 3-MC (2 μM) were used as positive controls for induction of CYP isoforms in human hepatocytes. At these concentrations, the positive controls induce CYP450 activity without causing cytotoxicity. Negative control (vehicle) cultures were treated with vehicle (0.1% DMSO).

Enzyme Activity:
CYP450 enzyme activities were determined in microsomes prepared from hepatocytes pooled from the various treatment groups with marker substrates for determination enzyme activities of each isoform (see table below).

Reviewer's Note: Because the hepatocytes from each treatment were pooled, intra-well variability is not known. Induction signal maybe diluted if some wells had experimental error. However, positive treatment groups were done the same way and showed induction signal. The results for the test compound could be considered acceptable if assume no bias in carrying out the experiment.

CYP Isozyme	Substrate	Substrate Concentration (μM)	Marker Metabolite
1A1/2	Phenacetin	100	APAP
2B6	Bupropion	250	OHBP
2C9	Diclofenac	25	4OHDC
2C19	(S)-Mephenytoin	250	4HMPN
2D6	Dextromethorphan	15	DRR
2E1	Chlorzoxazone	50	6HCLZ
3A4/5	Testosterone	200	6ßT

$$\text{: Fold Induction} = \frac{\mu(sample)}{\mu(DMSO\ control)}$$

$$\text{Percent of Adjusted Positive Control} = \frac{\mu(sample) - \mu(DMSO)}{\mu(positive\ control) - \mu(DMSO)} \times 100$$

μ denotes mean of replicates for each group.

Protein Expression:
Induction of immunoreactive CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 proteins were confirmed by Western immunoblotting using microsomes.

Results:
CYP1A1/2: The positive control (2 μM 3-MC) showed 3.9- to 7-fold induction compared to the vehicle control (Table 2). Percent increases in enzyme activity in febuxostat-treated hepatocyte were <6% of the adjusted positive control response. A decrease in activity and corresponding

protein levels for CYP1A1/2 isoforms at the high febuxostat concentrations may indicate a suppression of CYP protein expression. The report stated that "No change in cell morphology or attachment was observed upon febuxostat incubation with hepatocytes indicating that this protein suppression is not likely due to cytotoxicity."

Reviewer's Note: If the study included cell viability test, the data will be more convincing.

CYP2B6: PB was used as positive control for Hu362 and Hu369 while RIF was used as a positive control for Hu373 due to loss of PB-treated cultures during dosing. The positive control (1 mM PB) showed 9.6- and 13.5-fold induction compared to the vehicle control, and 10 μM RF showed 6.1-fold induction compared to the vehicle control. Percent increases in enzyme activity in febuxostat-treated hepatocyte were <5% of the adjusted positive control response.

CYP2C9: The positive control (10 μM 3-RIF) showed 2.1- to 4.4-fold induction compared to the vehicle control. Percent increases in enzyme activity in febuxostat-treated hepatocyte were <7% of the adjusted positive control response.

CYP2C19: The positive control (10 μM 3-RIF) showed 3.5- to 4.9-fold induction compared to the vehicle control. Percent increases in enzyme activity in febuxostat-treated hepatocyte were <14% of the adjusted positive control response.

CYP3A4/5: The positive control (10 μM 3-RIF) showed 4.8- to 48-fold induction compared to the vehicle control. Percent increases in enzyme activity in febuxostat-treated hepatocyte were <11% of the adjusted positive control response.

CYP2D6: CYP2D6 is not known to be an inducible CYP450.

CYP2E1: No suitable inducers for CYP2E1 activity have been identified. In this study, CYP2E1 activity was modestly increased by RIF in all three human preparations. However, fold increases were low (1.4 - to 2.1-fold over vehicle controls). Due to lack of positive controls, results for induction potential of febuxostat for CYP2E1 were inconclusive.

Table 2. Summary of Induction as a Percentage of Adjusted Positive Control Induction.

	Donor	Substrate	Positive Control	Fold-Change	Febuxostat % of Adjusted Positive Control Induction		
					3 μM	30 μM	300 μM
CYP1A/2	Hu362	Phenacetin (100 μM)	3-MC (2 μM)	3.9	-0.45	5.5	-31.4
	Hu369			7.0 [a]	1.9	-6.8	-7.5
	Hu373			4.7 [a]	-0.95	-10.1	-21.6
CYP2B6	Hu362	Bupropion (250 μM)	PB (1 mM)	9.6	4.0	4.2	-4.7
	Hu369			13.5	0.81	-0.41	0.02
	Hu373		RIF (10 μM)	6.1	0.68	-1.0	-6.4
CYP2C9	Hu362	Diclofenac (25 μM)	RIF (10 μM)	4.4	-0.67	6.7	0.83
	Hu369			2.3	-2.1	-22.3	2.5
	Hu373			2.1	-10.7	-44.8	-53.9
CYP2C19	Hu362	(S)-Mephenytoin (250 μM)	RIF (10 μM)	4.9	1.5	6.8	-5.0
	Hu369			3.5	13.1	2.7	8.6
	Hu373			4.2	3.1	-2.5	-6.2
CYP3A4/5	Hu362	Testosterone (200 μM)	RIF (10 μM)	48.0	0.03	3.3	-1.6 [b]
	Hu369			4.8	-3.5	-1.1	-4.9
	Hu373			5.7	10.9	-0.66	-7.2

[a] Estimated values; Above ULOQ
[b] Estimated values; Below the LLOQ

Reviewer's Notes: Negative data indicated a lower activity was observed in febuxostat-treated hepatocytes than vehicle-treated hepatocytes.

Conclusion:

The FDA draft drug interaction guidance recommends ≥40% of adjusted positive control response to suggest the compound has the induction potential that warrants further *in vivo* induction studies. The results from this study suggest that there is low potential for febuxostat to cause enzyme induction of CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4/5 compared to known inducers in human hepatocytes.

3.2 Drug Interaction Study with Warfarin

Study F-P107-162: A Phase 1, 2-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

---

Study Period:	June 21, 2007 to August 11, 2007
Principal Investigator:	[redacted] MD
Clinical Site:	[redacted]
Sample Analysis Periods:	Warfarin: August 9 to August 31, 2007 Febuxostat: August 24 and 25, 2007
Analytical Sites:	Warfarin: [redacted] Febuxostat: [redacted]

b(4)

Rationale for the study: Although the *in vitro* metabolism study did not show that febuxostat had significant effect on the activity of CYP2C9 (the main human liver CYP450 isoform involved in the biotransformation of warfarin), due to the narrow therapeutic index of warfarin and likely co-administration of febuxostat and warfarin in patients with gout, the sponsor conducted an *in vivo* drug interaction study (Study C03-057) previously to evaluate the effect of multiple dose febuxostat (120 mg QD) on PK and PD of warfarin. In that study, although data from 13 subjects who completed the trial indicated a lack of interaction between febuxostat and warfarin, overall, one cannot conclusively rule out an interaction based on this study as one third of the subjects discontinued the trial with an increase in INR. The possible reason for discontinuations could be due to the difficulty in stabilizing INR in these patients. Because of inconclusive conclusion from the previous warfarin interaction study and there are reports of increased INR values in the clinical database in subjects on febuxostat, the FDA recommended the Sponsor to conduct a new warfarin interaction study with sufficient subjects to complete the trial for a conclusive determination. The Sponsor conducted this study to further evaluate the effect of febuxostat (80 mg QD) on the PK and PD of warfarin by increasing the number of subjects, increasing the duration of the warfarin lead-in period, and requiring a stable INR of $\geq$1.5 to $\leq$2.0 for 3 days prior to subject randomization.

Objective: To evaluate the effect of multiple once-daily doses of febuxostat 80 mg on the pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin after multiple oral doses of warfarin.

Study Design: This was a Phase 1, single-center, double-blind, placebo-controlled, randomized, 2-way crossover study of febuxostat or placebo for febuxostat (hereinafter referred to as placebo) with open-label warfarin. As detailed in the table and Figure 1 below, the study consisted of the Screening Period, Warfarin Lead-in Period, Crossover Period, and Follow-up Period. The Screening Period was defined as a maximum of 28 days prior to Day 1 of the Warfarin Lead-in Period. The Warfarin Lead-in Period included Days 1 to 12, and the Crossover Period consisted

of two 14-day double-blind dosing periods. There was no washout interval between Crossover Periods 1 and 2 to limit the extent of each subject's exposure to warfarin and minimize the potential for INR instability. The Follow-up Period included Day 15 of Crossover Period 2 through 30 days postdosing.

Warfarin Lead-in Period (Days)	Crossover Period		Sequence
	Period 1 (Days)	Period 2 (Days)	
Warfarin QD (1-12)	Regimen A Warfarin QD (1-14) Febuxostat 80 mg QD (1-14)	Regimen B Warfarin QD (1-14) Placebo QD (1-14)	1
	Regimen B Warfarin QD (1-14) Placebo QD (1-14)	Regimen A Warfarin QD (1-14) Febuxostat 80 mg QD (1-14)	2

During the Warfarin Lead-in Period, subjects received once-daily doses of 5 mg warfarin on Days 1 and 2. During Days 3 through 9, the dose of warfarin was titrated, at the discretion of the investigator, to achieve and maintain a target INR (≥1.5 to ≤2.0). The titrated stable dose of warfarin dose maintained INR within this targeted range for the next 3 consecutive days (Days 10, 11, and 12) of the Warfarin Lead-in Period, in order for a subject to have entered the Crossover Period. Subjects continued to receive the titrated stable dose of warfarin once daily on Days 1 through 14 in each Crossover Period concomitantly with either 80 mg febuxostat or placebo, based on the assigned sequence groups.

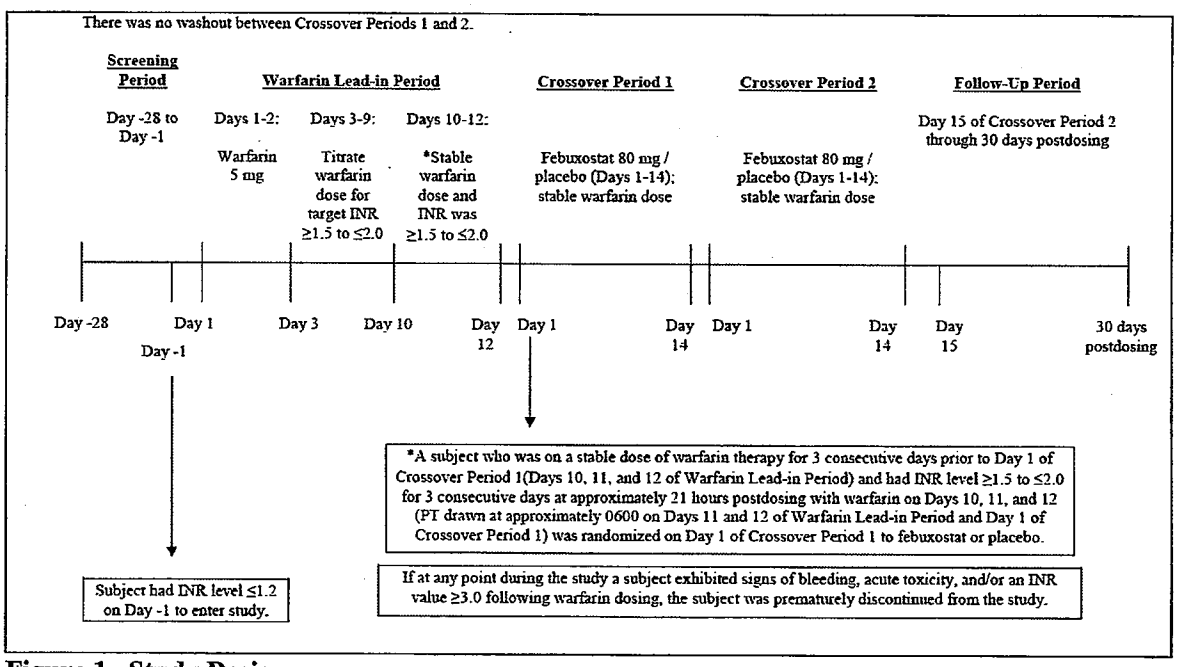


Figure 1. Study Design.

Sampling:

Blood samples for INR:

Warfarin Lead-in Period: Approximately 21-hour postdosing with warfarin on Days 1 through 11 before warfarin dosing the next day.
Crossover Periods 1 and 2: Predose only on Days 3, 5, 7, 9, 11, 12, and 13, and predose (0 hr), and approximately 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose on Day 14.

Blood samples for Factor VII:
Warfarin Lead-in Period: Day 1 predose.
Crossover Periods 1 and 2: Predose only on Days 12 and 13. Day 14 predose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and approximately 24 hours postdose.

Blood samples for warfarin PK: Predose only on Days 12 and 13, and predose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose on Day 14.

Blood samples for febuxostat exposure: Predose and 24 hours postdose on Day 14

Test Product:

Test Product, Dose and Mode of Administration, and Lot Number:						
Test Product	**Product Dosage Strength**	**Study Dose**	**Mode of Administration**	**Manufacturer**	**Drug Product Lot Number**	**Over-encapsulation Lot Number**
Febuxostat	40 mg Capsule[a]	80 mg	Oral	Abbott Laboratories (Abbott Park, Illinois)	06-009096[b]	18371.3
Warfarin Sodium	1 mg Tablet	Variable	Oral		302931	NA
Warfarin Sodium	2 mg Tablet	Variable	Oral		302601	NA
Warfarin Sodium	2.5 mg Tablet	Variable	Oral		302965	NA
Warfarin Sodium	3 mg Tablet	Variable	Oral		303072	NA
Warfarin Sodium	4 mg Tablet	Variable	Oral		302872	NA
Warfarin Sodium	5 mg Tablet	Variable	Oral		303139	NA
Reference Therapy, Dose and Mode of Administration, and Lot Number:						
Test Product	**Product Dosage Strength**	**Study Dose**	**Mode of Administration**	**Manufacturer**	**Drug Product Lot Number**	**Over-encapsulation Lot Number**
Placebo for Febuxostat	Capsule	NA	Oral		NA	070031

b(4)

b(4)

[a] Febuxostat 20 mg tablets were manufactured by Abbott Laboratories; overencapsulation of the febuxostat tablets into 40 mg capsules was performed by

b(4)

[b] Lot number for the 20 mg tablets used to manufacture the overencapsulated 40 mg capsule.

Febuxostat was overencapsulated to ensure blinding of study drug. Two febuxostat 20 mg tablets were placed in an iron gray opaque (No. 00) gelatin capsule to create a 40 mg capsule dosage form. Two such capsules were given to subjects to achieve a total 80 mg dose of febuxostat. Matching placebo capsules were identical in size, shape, weight, and color to the febuxostat capsules. Two capsules were given to subjects. Dissolution profiles for the over-encapsulated (blinded) products were compared to those of the unblinded product to confirm similarity of the respective drug release profiles (Investigator's Brochure).

Sample Analysis:
Warfarin: Plasma concentrations of R- and S-warfarin were determined using a validated LC-MS/MS assay at [redacted] Briefly, a 100 µL aliquot of plasma was spiked with the internal standard [redacted] and an aliquot analyzed by LC-MS/MS. The lower limit of quantitation (LLOQ) for R- and S-warfarin was 10.0 ng/mL using a plasma sample volume of 100 µL. Concentrations below the LLOQ were reported as zero.

b(4)

Febuxostat: Plasma febuxostat concentrations were determined using a validated liquid chromatography assay with fluorescence detection at [redacted]. Briefly, a 0.5 mL aliquot of plasma was spiked with the internal standard [redacted] and an aliquot analyzed by high performance liquid chromatography (HPLC). The LLOQ for febuxostat was 0.0100 µg/mL using a plasma sample volume of 0.5 mL. Concentrations below the LLOQ were reported as zero.

b(4)

Subjects: 134 subjects (male or female healthy subjects 18-55 years) were screened and 32 subjects (31 males and 1 female) actually entered the Warfarin Lead-in Period, having met all inclusion criteria and having met none of the exclusion criteria (Table 1 and Figure 2). The mean age was 32.9 years, the mean weight was 78.5 kg, the mean height was 175.4 cm, and the mean BMI was 25.6 kg/m^2. Female subjects were to have been of nonchildbearing potential. Twenty-eight eligible subjects from the Warfarin Lead-in Period were randomized to the Crossover Period.

Table 1. Baseline Demographic Characteristics.

Variable	All Warfarin Lead-in Subjects (N=32)	All Randomized Subjects (N=28)	All Nonrandomized Subjects (N=4)
Gender n (%)			
Male	31 (96.9)	28 (100.0)	3 (75.0)
Female	1 (3.1)	0	1 (25)
Ethnicity n (%)			
Hispanic or Latino	8 (25.0)	7 (25.0)	1 (25.0)
Not Hispanic or Latino	24 (75.0)	21 (75.0)	3 (75.0)
Race n (%)			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Black or African American	7 (21.9)	7 (25.0)	0
Native Hawaiian or other Pacific Islander	0	0	0
White	25 (78.1)	21 (75.0)	4 (100.0)

Four subjects were prematurely discontinued from the study prior to randomization. Twenty-eight eligible subjects from the Warfarin Lead-in Period were randomized to the Crossover Period, having met all inclusion criteria on Day 1 of Crossover Period 1. Twenty-seven subjects completed both Crossover Periods; one subject (Subject 114) was prematurely discontinued

during Period 2 of the Crossover Period due to a protocol violation (investigator decision: unacceptable conduct), as summarized in Table 2. This subject was not included in the PK/PD analysis as he did not have complete data for both regimens of the Crossover Period.

As of note, the protocol excludes subjects who have impaired renal function (CLcr<80 mL/min), who are strict vegetarian, who are CYP2C9 poor metabolizers and who have high warfarin sensitivity based on VKORC1 genotyping results (i.e., G-1639A genotype of AA).

The patient drop-out rate decreased by allowing time for INR stabilization prior to crossover period.

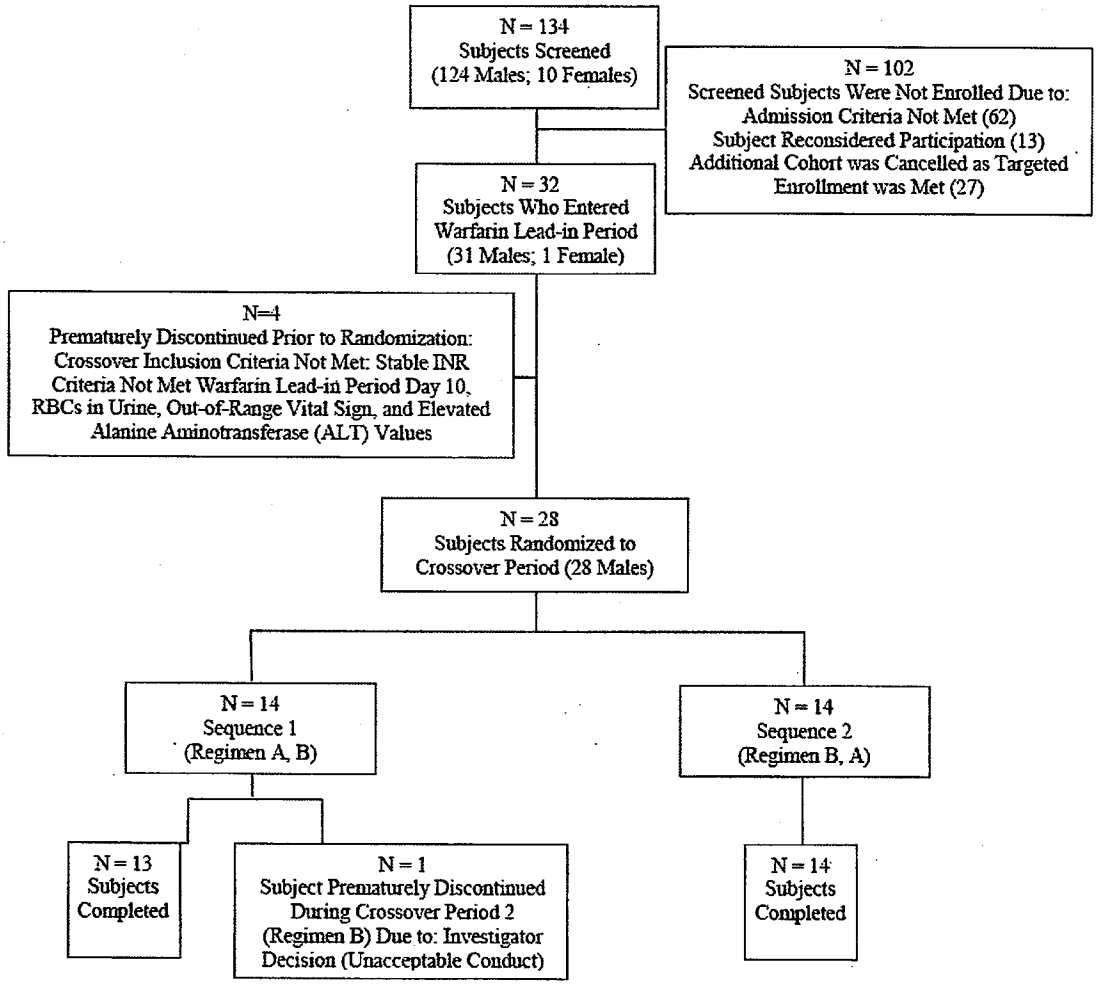


Figure 2. Flowchart Summarizing Subject Disposition.

Table 2. Subjects who Prematurely Discontinued From the Study.

Subject Number	Sequence Group /Period	Duration of Treatment (Days)	Reason for Discontinuation	Comment
349171085	Warfarin Lead-in Period	10	Crossover Period Inclusion Criterion 2 Not Met	Subject did not meet Stable INR Crossover Period Inclusion Criterion: INR Level was not within the protocol specified range (≥1.5 to ≤2.0) on Day 10 of the Warfarin Lead-in Period.
349171009	Prior to Randomization (Completed Warfarin Lead-in)	12	Crossover Period Inclusion Criterion 4 Not Met	Investigator's decision based on out-of-range vital signs.
349171008		12	Crossover Period Inclusion Criterion 5 Not Met	Investigator's decision based on an out-of-range Warfarin Lead-in Period Day 12 safety laboratory value (ALT elevated).
349171054		12		Investigator's decision based on an out-of-range Warfarin Lead-in Period Day 12 safety laboratory value (RBCs in urine).
114	Sequence 1, Crossover Period 2	23	Investigator Decision	Subject's conduct was unacceptable. Subject received all 14 doses of febuxostat in Period 1, but was prematurely discontinued after receiving 9 doses of placebo in Period 2.

Results:

Warfarin Dose: The distribution of stable warfarin doses (given during the Crossover Period) is presented in Table 3.

Table 3. Distribution of Stable Warfarin Dose for Subjects Included in the Crossover Period and PK/PD Analysis.

	Crossover Period Subjects (N=28)	PK/PD Analysis Subjects (N=27)
Warfarin Dose (mg)	Number of Subjects	Number of Subjects
3.0	4	4
3.5	3	3
4.0	4	4
4.5	5	4[a]
5.0	3	3
5.5	1	1
6.0	1	1
6.5	2	2
7.0	2	2
7.5	3	3

a One subject (Subject 114) did not complete both regimens as he was prematurely discontinued from the study due to protocol violation. His data was therefore excluded from the PK/PD analysis.

Vitamin K dosing: All 4 nonrandomized subjects (Subjects 349171008, 349171009, 349171054, and 349171085), and one randomized subject (Subject 104), received a single subcutaneous administration of Vitamin K (Phytomenadione) to assist with lowering the subject's INR values.

Subject 104 was administered Vitamin K (one 2 mg subcutaneous injection) prior to discharge after completing Crossover Period 2 (Regimen A, febuxostat arm). This treatment was given only after all PD blood samples had been drawn and did not impact the PD analysis of this study. *(Reviewer's Note: Although the report indicated that this subject received Vitamin K due to increased INR, based on the INR_{max} value of 1.7, it does not seem that this patient needed Vitamin K treatment.)*

Pharmacokinetic Results:
Following multiple oral doses of warfarin with 80 mg febuxostat (Regimen A) or warfarin with placebo (Regimen B), R- and S-warfarin and/or febuxostat levels appeared to be at steady-state on Day 14 based on trough concentrations.

For subjects in the febuxostat regimen, individual trough plasma concentrations of febuxostat were within the expected range (nonzero range = 0.01080 to 0.07930 µg/mL) but close to the LLOQ of 0.0100 µg/mL. However, four febuxostat predose or 24-hour postdose values were below the LLOQ, with two of these coming from one subject (Subject 116) who did not have measurable predose and 24-hour postdose febuxostat levels. Laboratory results for uric acid obtained on Day 7 of Period 2 and the day after the last febuxostat dose confirmed reduced uric acid levels which suggest the subject was compliant with febuxostat dosing. Furthermore, this subject's individual ratio for warfarin C_{max} and AUCs, and the point estimates for these values were close to unity. Therefore, omitting this subject from the statistical analysis would not be expected to change the overall PK results or conclusions.

PK parameters for R- and S-warfarin are listed in Table 4. The 90% confidence intervals for the ratios of the central values when warfarin was administered with febuxostat (Regimen A) relative to warfarin with placebo (Regimen B) on Day 14, were within the no effect limit of 0.80 to 1.25 for R- and S-warfarin C_{max}, AUC_t, and AUC_τ values (Table 5).

Table 4. Mean Plasma Pharmacokinetic Parameter Estimates of R- and S-Warfarin on Day 14 Following Once-Daily Multiple Dosing With Warfarin and Febuxostat or With Warfarin and Placebo in Healthy Subjects.

	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_τ (ng·h/mL)	V_{ss}/F (L)	CL_{ss}/F (L/h)	$t_{1/2z}$[a] (h)
R-Warfarin (Regimen A)							
N	27	27	27	17	14	17	14
Mean	0.983	914	16411	16682	29.0	0.313	63.3 (56.6)
SD	0.726	257	4239	4500	11.5	0.058	21.8
CV%	74	28	26	27	40	19	34
R-Warfarin (Regimen B)							
N	27	27	27	17	14	17	14
Mean	1.67	933	16614	16897	25.3	0.310	55.0 (48.8)
SD	2.06	253	4636	4849	11.2	0.056	19.5
CV%	123	27	28	29	44	18	35
S-Warfarin (Regimen A)							
N	27	27	27	21	21	21	21
Mean	0.964	765	12153	12770	28.5	0.429	49.8 (40.2)
SD	0.732	190	2759	2717	19.1	0.134	32.6
CV%	76	25	23	21	67	31	65
S-Warfarin (Regimen B)							
N	27	27	27	21	21	21	21
Mean	1.11	769	12073	12706	24.1	0.428	41.2 (34.3)
SD	0.923	191	2850	2593	10.3	0.125	19.4
CV%	83	25	24	20	43	29	47

Note: Regimen A = Warfarin and Febuxostat 80 mg.
Note: Regimen B = Warfarin and Placebo.
a Arithmetic mean (harmonic mean).

Table 5. C_{max} and AUC of R- and S-Warfarin on Day 14 Following Once-Daily Multiple Dosing With Warfarin and Febuxostat Relative to Warfarin and Placebo in Healthy Subjects.

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
R-Warfarin (N=27)		
C_{max}	0.9791	0.9407 - 1.0191
AUC_t	0.9923	0.9722 - 1.0128
AUC_τ	0.9898	0.9693 - 1.0107
S-Warfarin (N=27)		
C_{max}	0.9973	0.9534 - 1.0432
AUC_t	1.0103	0.9887 - 1.0323
AUC_τ	1.0049	0.9898 - 1.0202

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

Pharmacodynamic Results:

Prothrombin time (PT) in this study was measured and reported as the INR level for PD assessment. Following administration of warfarin with febuxostat (Regimen A), mean PD parameter estimates ([the maximum INR value observed post Day 14 warfarin dose (INR_{max}), the

24-hour mean international normalized ratio ($INR_{mean,24}$), and the 24-hour mean Factor VII ($F\text{-}VII_{mean,24}$)] were almost identical to those values when warfarin was administered with placebo (Regimen B) (ANOVA p-values of p=0.917, p=0.601, p=0.186, respectively) indicating that multiple oral doses of febuxostat had no effect on warfarin PD parameters (Table 6).

Table 6. Mean Pharmacodynamic Parameter Estimates of INR and Factor-VII on Day 14 Following Once-Daily Multiple Dosing With Warfarin and Febuxostat or With Warfarin and Placebo in Healthy Subjects.

	INR_{max}[a]	$INR_{mean,24}$[a]	$F\text{-}VII_{mean,24}$[a] (%)
Regimen A: Warfarin and Febuxostat 80 mg (N=27)			
Mean	1.496	1.437	55.163
SD	0.172	0.142	11.014
Range	1.3-2.0	1.2-1.8	34.0-76.1
Regimen B: Warfarin and Placebo (N=27)			
Mean	1.504	1.448	52.925
SD	0.156	0.134	12.744
Range	1.2-1.8	1.2-1.7	27.0-77.5
P-value[b]	0.917	0.601	0.186

a Included only subjects with data from both crossover periods.

b p-values for comparing Regimens A versus B obtained from ANOVA analysis.

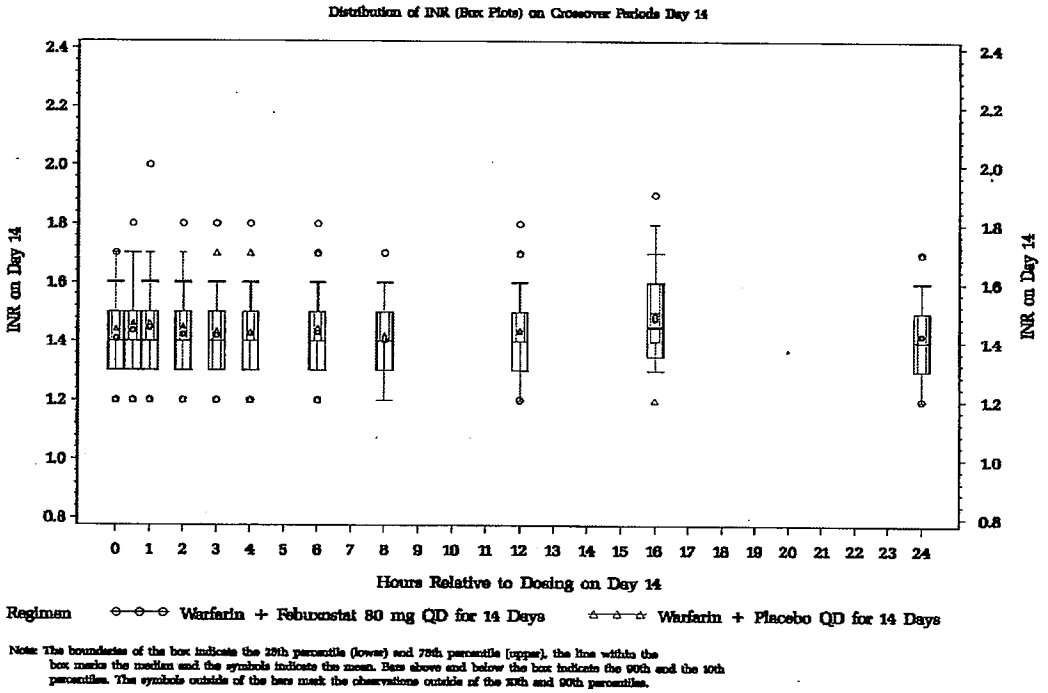


Figure 3. Distribution of INR on Crossover Periods Day 14.

Conclusion: Multiple once-daily oral doses of febuxostat 80 mg with warfarin had no effect on the PK or PD of warfarin at steady-state.

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

/s/

Lei K Zhang
12/17/2008 09:24:43 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
12/18/2008 04:42:51 AM
BIOPHARMACEUTICS

7/18/06

CLINICAL PHARMACOLOGY REVIEW

NDA	21-856
Submission Dates	2/17/2006 (Amendment 33)
Brand Name	Uloric™
Generic Name	Febuxostat (TMX-67)
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology 2 (DCP2)
OND Division	Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Sponsor	TAP Pharmaceuticals
Relevant IND	IND 58,229
Type of Submission	Resubmission: Complete Response to Deficiencies Identified in The Action Letter; Safety Update
Formulation; Strength(s)	Tablets; 80, and 120 mg
Dosing Regimen	Once Daily
Indication	Hyperuricemia in patients with gout

1.1 Executive Summary

NDA 21-856 is seeking approval of febuxostat (TMX-67) for the management of hyperuricemia in patients with gout. The doses proposed for registration are 80 mg and 120 mg once daily (QD). During the first review cycle, NDA 21-856 was deemed Approvable (Action Letter, October 14, 2005). The Sponsor submitted a complete response in this submission to address the deficiencies identified in the Action Letter.

The following items (Items 2, 3, 4 and 5) in the Action Letter are related to Clinical Pharmacology:

2. *Evaluate the potential for pharmacokinetic interactions with Uloric when coadministered with theophylline, azathioprine or mercaptopurine. Uloric should be studied at its maximum proposed clinical dose, and theophylline, azathioprine and mercaptopurine may be studied at sub-therapeutic doses in order to decrease the incidence of adverse effects, if indeed Uloric does increase the exposure to these compounds in which xanthine oxidase plays a role in their metabolism. The results of these studies will provide information on dose selection when these drugs are co-administered. Without these studies, co-*

administration of Uloric with theophylline, mecaptopurine or azathioprine will need to be contraindicated and risk minimization strategies may be needed to assure that no such concomitant use will occur in the actual use setting.

3. *Evaluate the potential for concomitant administration of warfarin and Uloric to result in hemorrhagic adverse events, and further address the potential for Uloric to cause hemorrhagic events without co-administration of an anticoagulant. A significant concern exists due to the finding that two subjects died as a result of retroperitoneal hemorrhages while being treated with Uloric, both of whom were receiving warfarin as well. Additional hemorrhagic events were also noted in the safety database. We do not agree with your conclusion that there were no drug-drug interaction with warfarin in the clinical pharmacology study, due to our conclusion that the drug-drug interaction study with warfarin was inadequate to allow for definitive conclusions. The removal of subjects with an increased INR from the final analysis in the warfarin drug-drug interaction trial was problematic. In addition, there were reports of increased INR values in the clinical database in subjects receiving concomitant treatment with Uloric and warfarin.*

4. *Evaluate the induction potential of Uloric on human CYP P450 enzymes. This study may be conducted in vitro or in vivo.*

5. *Test the dissolution of febuxostat 80-mg and 120-mg tablets using a USP Apparatus 2 (paddle) at 75 rpm with 900 mL of 0.05 M potassium phosphate buffer, at pH 6.8, and maintained at 37°C with the following acceptance criteria: Q= — at T=15 min. The current dissolution method and acceptance criterion will be revisited if lower dose-strength tablets will be developed for future clinical studies. Solubility permitting, a different pH medium (such as phosphate buffer pH 6.2) may be appropriate to slow down the drug release at early time points and provide a discriminating condition.* b(4)

For Item #2, the Sponsor agreed to a contraindication in the package insert for co-administration of theophylline with febuxostat. In addition, sponsor also committed to conducting a drug-drug interaction study as a post-marketing commitment to evaluate the potential for interaction between febuxostat and theophylline.

b(4)

The protocol for such a study (F-P105-140) was submitted to IND 58,229 (SN 202). Protocol F-P105-140 was reviewed on 06/01/06 and comments were sent to the sponsor on 06/20/06.

The Sponsor also agreed to a contraindication for co-administration of azathioprine and mercaptopurine with febuxostat. However, as the interaction with azathioprine and mercaptopurine would present a significant safety risk to clinical trial subjects, these interactions would not be studied. This approach was acceptable to the Agency (FDA meeting minutes dated December 21, 2005).

For Item #3, the Sponsor provided additional information to address agency's concerns. From a Clinical Pharmacology perspective, although data from 13 subjects who completed the trial indicated a lack of interaction between febuxostat and warfarin, overall, one cannot conclusively rule out an interaction based on this study as one third of the subjects discontinued the trial with an increase in INR. The possible reason for discontinuations could be due to the difficulty in stabilizing INR in these patients. A new warfarin interaction study with sufficient subjects to complete the trial is needed for a conclusive determination. In the new study, the lead-in period for identifying a stabilized warfarin dose may need to be more than 9 days and/or enroll more subjects (see Section 1.3 "Review of Additional Information for Study C03-057 (Warfarin Interaction Study)"). With the current data, b(4)

For Item #4, the Sponsor commits to conducting an *in vitro* human CYP induction study as a post-approval commitment. The design of this study will be consistent with the Agency's October 2004 Preliminary Concept Paper: *Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*. This approach is acceptable.

For Item #5, the Sponsor accepted Agency's recommendations for the final dissolution method and acceptance criteria for febuxostat 80 mg and 120 mg tablets.

Clinical Pharmacology related labeling comments are attached in Appendix 1.

1.2 Recommendations

From a Clinical Pharmacology and Biopharmaceutics point of view, the Sponsor has addressed the deficiencies discussed in the Approvable Letter. The application is acceptable.

1.3 Review of Additional Information for Study C03-057 (Warfarin Interaction Study)

Study C03-057 is a randomized, double-blind, placebo-controlled, two-way, crossover study to evaluate the effect of febuxostat on the pharmacokinetics and pharmacodynamics of warfarin in normal healthy volunteers. The study included a Warfarin Lead-in Period followed by 2 Crossover Periods (without washout) where the subjects received either placebo or febuxostat 120 mg in addition to warfarin for 14 days. The Warfarin Lead-in Period was 9 days in duration. During the first 6 days, the subjects received titrated doses of warfarin to achieve an INR between 1.2 and 1.8. This was followed by a stable dose of warfarin for the last 3 days. Subjects continued on their stable dose of warfarin and the dose was not adjusted during the Crossover Periods. There were 22 subjects enrolled at the beginning of the study. Twenty-one subjects were randomized to either febuxostat or warfarin regimen after warfarin lead-in periods, and 13 subjects completed both crossover periods.

Data from these 13 subjects indicated no quantifiable interaction of febuxostat on warfarin (either PK or INR, Factor VII activity values). However, during the first review cycle, a concern

was raised about the validity of the conclusion that there is a lack of interaction of warfarin and febuxostat because eight out of nine subjects who discontinued from the study were due to increases in INR. The criteria (INR values) to withdraw these subjects from the study were not clear. No PK information was collected for subjects who discontinued from the study to determine whether the cause of increases in INR was due to a PK or PD alone interaction. Because increases in INR is the side effect one would expect if an interaction occurs, the conclusion of a lack of interaction of warfarin and febuxostat could not be accepted. In addition, there were reports of increased INR values in the clinical database in subjects receiving concomitant treatment with Uloric and warfarin. The Sponsor was asked to evaluate interaction potential between febuxostat and warfarin. In addition, sponsor was also asked to conduct a new interaction study with sufficient subjects to complete the trial to have a conclusive determination. In the 12/21/05 meeting, sponsor proposed to address this issue in the resubmission with additional data analyses and rationale and the Agency agreed to this proposal.

Sponsor's Clarification for Study C03-057:

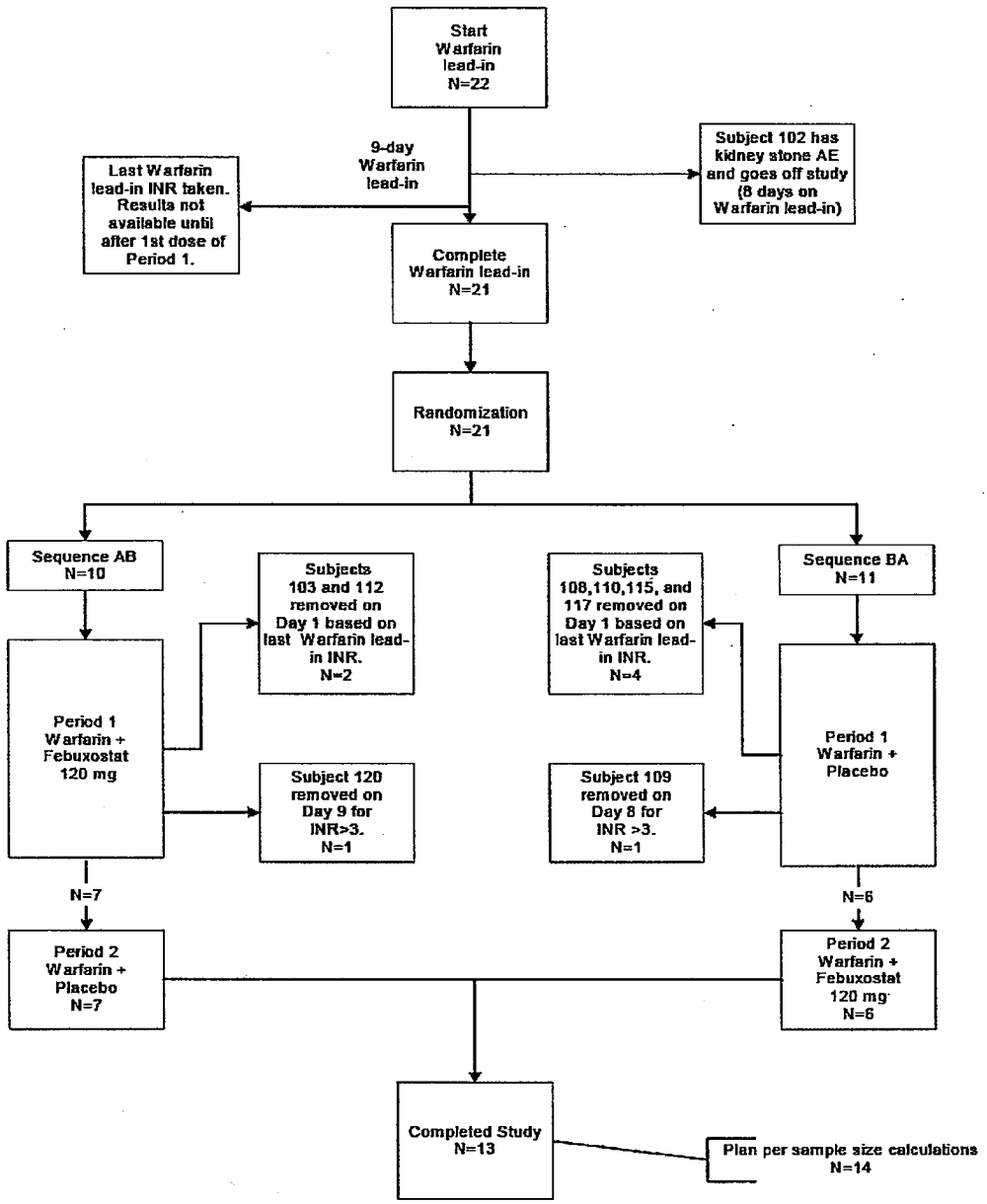
In this submission, the Sponsor provided clarifications on why subjects were withdrawn. All 8 subjects were withdrawn during the first crossover period. Six subjects were withdrawn on Day 1 after receiving the first dose of febuxostat (Subject 103 and 112) or placebo (Subjects 108, 110, 115 and 117) due to high and/or unstable pre-dose INR values (Figure 1 and Table 1). Because the lead-in INR values were not available at the randomization, those subjects were withdrawn after randomization on Day 1. Of note, Subject 117 was withdrawn due to Lead-in Period INRs that were both high and not stable (INRs Day 7: 1.99; Day 8: 2.21; Day 9: 2.66; Crossover Day 1 predose: 1.84; retest postdose Day 1: 2.58).

Table 1. Subjects Removed from the First Crossover Period Based on Predose INR

Subject Number	Lead-in INR (Day 9)	First Crossover Predose INR (Day 1)
108	2.26	2.47
110	2.26	2.22
115	2.05	2.17
112	2.34	2.34
103	2.21	2.16
117	2.66	1.84

Note: Subjects were withdrawn in a blinded manner.
Cross-reference: C03-057 Clinical Study Report

Figure 1. Disposition of Subjects in Study C03-057



The remaining 2 subjects were withdrawn during the first crossover period, for safety reasons due to high INR (>3.0) (Figure 1 and Table 2). One of these subjects (Subject 120) was on febuxostat and warfarin, while the other (Subject 109) was on warfarin and placebo. Also noted

that one subject (Subject 119) had 1 INR >3 in each of the Crossover Periods, neither of which was verified on repeat testing, and therefore this subject continued in the study.

Table 2. Subjects with Maximum INR >3 During Double-Blind Treatment

Subject Number	Predose INR	Maximum INR	Comments
119	1.92	3.09	Subject experienced an INR of 3.02 during the warfarin/placebo regimen and 3.09 during the warfarin/febuxostat regimen, but neither of these 2 elevations was confirmed upon retesting (retest INR of 2.8). Subject continued in study.
109	2.08	3.76	Subject was withdrawn[a] during treatment with the warfarin/placebo regimen because the increased INR was confirmed upon re-testing (retest INR of 3.25).
120	2.05	3.23	Subject was withdrawn[a] during the warfarin/febuxostat regimen because the increased INR was confirmed upon re-testing (retest INR of 3.23).

a Subjects were withdrawn in a blinded manner.
Cross-reference: C03-057 Clinical Study Report

Reviewer's Assessments:

Although the protocol specified a stabilized INR of 1.5-1.8 as an inclusion criterion, it was "soft" on the INR "cut-off" to withdraw patients from the trial. It all depended on investigator's judgment. It seems that an INR of 2 was used for withdrawal after the warfarin lead-in period and that repeated INR values of >3 was used for withdrawal during the crossover period. However, there is inconsistency in withdrawing subjects. For example, some subjects (Subjects 105, 109, and 120) who qualified for "discontinuation" due to high (>1.8) and unstable pre-dose INR continued in the trial (Table 3). Subjects 109 and 120 were withdrawn later due to high INR (>3) suggesting that their INR values were not stable at the randomization.

The INR data suggest that high drop out rate was likely due to difficulty in stabilizing INR in subjects who enrolled in the study. The design of the study was not optimal, and a lead-in period of 9 days may not be long enough for a stabilized INR in these subjects who were withdrawn from the study. Even for subjects who completed the trial, unstablized INR values were noticed during the first few days of the Crossover period 1. For example, Subjects 111 and 119 showed increased INR for the initial few days in the Crossover period 1 and INR values were stabilized for the remaining study period (Table 4). For Subject 111 the first crossover period was the febuxostat arm and for Subject 119, it was the placebo arm.

Table 3. Subjects Included in the Crossover Period.

Subject Number	Lead-in INR (Day 9)	Predose INR (Day 1)
101	1.84	1.81
105	2.15	2.05
106	1.63	1.72
109	2.00	2.08
111	1.49	1.48
114	1.48	1.53
118	1.79	2.68
119	1.88	1.92
120	2.05	2.05
151	1.58	1.63
152	1.28	1.42
153	1.39	1.57
154	1.47	1.68
155	1.49	1.45
156	1.34	1.70

Cross-reference: C03-057 Clinical Study Report

Note: Subject 118 continued in the study since Lead-in Period INRs were low and stable (INRs Day 7: 1.55; Day 8: 1.61; Day 9: 1.79; Crossover Day 1 predose 2.68; retest postdose Day 1: 1.89).

Table 4. Predose-INR Values for Subjects 111 and 119.

	Subject 111	Subject 119
Crossover Period 1	Febuxostat and Warfarin	Placebo and Warfarin
Day 1	1.48	1.92
3	1.61	1.97
5	1.73	2.17
7	2.07	2.75
9	2.24	2.58
11	2.43	2.72
12	2.73	2.69
13	2.63	2.77
14	2.6	2.79
Crossover Period 2	Placebo and Warfarin	Febuxostat and Warfarin
Day 19	2.61	2.89
21	2.83	3.09
23	2.75	2.95
25	2.50	2.89
27	2.15	2.54
29	2.26	2.26
30	2.10	2.25
31	2.18	2.26
32	2.23	2.30

Based on the information above, the link between increases in INR and febuxostat seems weak; however, an interaction between warfarin and febuxostat cannot be conclusively ruled out based on the available data. A new warfarin interaction study with sufficient subjects to complete the trial is needed for a conclusive determination. In the new study, the lead-in period for identifying a stable warfarin dose may need to be more than 9 days and/or enroll more subjects. The current data would not warrant a contraindication between febuxostat and warfarin.

[redacted] In the absence of data from a new study, [redacted] into the package insert.

b(4)

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology II
Office of Clinical Pharmacology

Concurrence:

Suresh Doddapaneni, Ph.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology II
Office of Clinical Pharmacology

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Lei K Zhang
7/17/2006 03:37:14 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/18/2006 08:03:33 AM
BIOPHARMACEUTICS
Although not indicated by track changes, labeling in the Appendix contains tentative Clin Pharm related FDA changes to the sponsor proposed language.

8/29/05

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-856
Submission Dates	12/14/2004, 2/15/2005, 4/1/2005, 5/5/2005, 6/2/2005, 7/13/2005, 7/19/2005
Brand Name	Urolic™
Generic Name	Febuxostat (TMX-67)
Reviewers	Lei Zhang, Ph.D. E. Dennis Bashaw, Pharm.D. (Drug Interaction Studies only)
PM Reviewer	V. Atul Bhattaram, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
PM Team Leader	Jogarao Gobburu, Ph.D.
OCPB Division	DPE III
OND Division	DAAODP (HFD-550)
Sponsor	TAP Pharmaceuticals
Relevant IND	IND 58,229
Type of Submission; Code	505 (b)(1); 1S
Formulation; Strength(s)	Tablets; 80 and 120 mg
Dosing Regimen	Once Daily
Indication	Hyperuricemia in patients with gout

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Febuxostat (TMX-67) is a new molecular entity that inhibits the synthesis of uric acid by inhibiting xanthine oxidase (XO), the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans.

This New Drug Application (NDA) proposes febuxostat for the management of hyperuricemia in patients with gout. The doses proposed for registration are 80 mg and 120 mg once daily (QD). Febuxostat is structurally different from allopurinol (a purine analog), the only XO inhibitor currently approved for the treatment of gout.

In the United States, there are about 2.5-4 million gout patients. Gout is a metabolic disorder in which tissue deposition of monosodium urate crystals from supersaturated body fluids results in acute attacks of inflammatory arthritis and the development of palpable crystalline aggregates (tophi), primarily in connective tissue, but potentially in virtually any organ. Tophaceous

deposits on tendons, bone, and joints can occur in any location. Gout typically progresses through four stages: asymptomatic hyperuricemia, acute gouty arthritis, intercertical gout (the variable interval between recurrent acute episodes), and chronic tophaceous gout. Gout is more common in males than females (9:1) and the predominant age range is 30-60 years.

Elevated serum uric acid (SUA) level is an important diagnostic measure in chronic gout and a clinical measure that can be monitored during the management of the disease and to guide therapy. Uric acid precipitates at approximately 7 mg/dL at 37°C. Therefore, serum urate level is a reliable predictor of gout. There is strong evidence of a correlation between reducing serum urate levels, and reduction in size of tophi, and decreasing frequency of gout flares over time. In a recent Arthritis Advisory Committee meeting (June 2, 2004), it was generally agreed that targeting SUA levels to < 6 mg/dL should be sought if SUA is used as a surrogate endpoint for chronic gout treatment.

Urate-lowering pharmacotherapy is the long-term treatment option for the management of patients with gout and frequent attacks of gouty arthritis, chronic gouty arthropathy, chronic tophaceous gout, gout-related renal impairment, or uric acid urolithiasis. The current choice of urate-lowering agents are the uricosuric drugs (eg, probenecid), which enhance renal uric acid excretion, and the XO inhibitor, allopurinol, which reduces uric acid production. Uricosuric drugs have limited efficacy and/or safety in patients with renal insufficiency or prior urolithiasis. About 2-4% patients who take allopurinol develop hypersensitivity and doses of allopurinol need to be decreased in patients with renal impairment.

To support this NDA application, the Sponsor conducted 29 clinical studies with febuxostat: 24 Phase 1 studies, 2 Phase 2 studies, and 3 Phase 3 studies. Two of these studies (Phase 3 Studies C02-009 and C02-010) are considered pivotal for the demonstration of the efficacy and safety of febuxostat in subjects with hyperuricemia and gout. Two open-label extension studies (Phase 2 Study TMX-01-005 and Phase 3 Study C02-021) are currently ongoing.

The Phase 3 pivotal trials C02-009 (a 28-week Phase 3 trial) and C02-010 (a 52-week Phase 3 trial) studied febuxostat doses of 80, 120 and 240 mg QD, 100 or 300 mg allopurinol and placebo. The primary efficacy endpoint is the proportion of subjects whose last three serum urate levels were below 6.0 mg/dL. The response rate for the febuxostat 80 mg QD treatment group was 51% and for 120 mg QD treatment groups was 63%, and both were more effective than the allopurinol 300/100 mg QD treatment group (response rate 22%). Response rates in the placebo and febuxostat 240 mg QD treatment groups were 0% and 69%, respectively. The urate-lowering effect of all active treatments was observed by Week 2 and was maintained throughout the course of treatment.

In terms of safety, the overall side effect profile of febuxostat is potentially worse than that of allopurinol. Cardiovascular adverse events have been identified during the review process as a significant concern. There were 6 cases of death in the U.S. development program (2 who received 80 mg febuxostat [retroperitoneal hemorrhage and respiratory failure], and 4 who were in the 120 mg febuxostat group [respiratory failure/anoxic encephalopathy, colon cancer metastasis, myocardial infarction, and acute myocardial infarction]). In the ongoing trials, there

were two additional death cases (one in 80 mg dose and one in 120 mg dose). In all cases the possible association with the drug could not be excluded with possible exception of the colon cancer metastasis case. Six out of eight cases occurred after 170 days of exposure to febuxostat. In addition to these reported deaths there were numberous reports of non-fatal cardiovascular events at a rate far in excess of the numbers in the allopurinol arm of the trial. Please refer to Dr. Joel Schiffenbaur's (efficacy) and Dr. Tatiana Oussova's (Safety) reviews for details of efficacy and safety review

The Clinical Pharmacology/Biopharmaceutics section of this NDA provides information on metabolism and PK/PD of febuxostat, dose-proportionality, food effect, extrinsic and intrinsic effects on PK/PD of febuxostat, and QTc evaluation in healthy subjects. Pop-PK/PD evaluation of febuxostat in gout patients was also conducted in Phase 2 and 3 studies.

Febuxostat is not marketed in any country at this time.

b(4)

1.1 Recommendations

From a Clinical Pharmacology and Biopharmaceutics point of view, the Sponsor has characterized the pharmacokinetic and pharmacodynamic performance of febuxostat. There are, however, some areas of concern that need to be addressed:

1. The *in vivo* drug interaction potential of febuxostat with drugs that are xanthine oxidase (XO) substrates needs to be evaluated:
   a. Theophylline: Febuxostat should be studied at its maximum proposed clinical dose and theophylline may be studied at a sub-therapeutic dose for decreasing side effects.
   b. Mecaptopurine or azathioprine: Febuxostat should be studied at its maximum proposed clinical dose and mecaptopurine or azathioprine may be studied at a sub-therapeutic dose for decreasing side-effects.

The results of these studies will provide information on dose selection when these drugs are co-administered. Without such studies, febuxostat needs to be contraindicated with theophylline, mecaptopurine and azathioprine.

2. The induction potential of febuxostat on human CYP-P450 needs to be evaluaed. Such study could be conducted either *in vitro* (human hepatocytes) or *in vivo*. Based on the results to date, the sponsor may study induction potential on CYP3A and CYP1A first. If there is no induction

on CYP3A, no further study to evaluate induction on CYP2C8 or CYP2C9 is needed. If there is induction on CYP3A, then they need to further study induction on CYP2C8 and CYP2C9.

3. We do not agree with the Sponsor's conclusions as they relate an absence of a drug-drug interaction with warfarin. The removal of subjects with an increased INR in the warfarin drug-drug interaction trial lowered the strength of the results. We also note that there are reports of increased INR values in the clinical database in subjects on febuxostat, taken in conjunction the concomitant use of warfarin and febuxostat should be contraindicated at this time.

4. A review of the data presented in the NDA suggests that lower doses should be used in certain populations to maintain, on average, similar plasma levels with normal volunteers. b(4)

Please convey the following comments to the Sponsor regarding "dissolution method and acceptance criterion" for febuxostat 80 and 120 mg tablets:

1. Please test the dissolution of febuxostat 80 mg and 120 mg tablets using USP Apparatus 2 (paddle) at 75 rpm with 900 mL of 0.05 *M* potassium phosphate buffer, pH 6.8, maintained at 37°C with the following acceptance criterion:

Time Point	**Specification**
15 minutes	Q =

b(4)

The current dissolution method and acceptance criterion will be revisited if lower dose strength tablets will be developed for future clinical studies. A different pH medium may be appropriate if solubility allows.

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

b(4)

1.2 Phase 4 Commitments

None (not applicable as the application is not "approvable" at this time).

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

A total of 27 *in vivo* pharmacokinetic and pharmacodynamic trials have been submitted in support of this NDA. In addition, there are more than 30 *in vitro* study reports included to characterize *in vitro* metabolism, transport, protein binding and dissolution profiles of febuxostat.

Absorption, Distribution, Metabolism and Elimination

In a radiolabeled study the absorption of febuxostat was estimated to be 49% (based on total radioactivity recovered in the urine). As unchanged febuxostat accounted for less than 16% of the dose in the feces, absorption could be as high as 84%. Maximum plasma concentrations of febuxostat occurred between 1.0 to 1.5 hours post-dose. The mean steady-state C_{max}, AUC_{24} for febuxostat at 120 mg (the maximum proposed clinical dose) was 5.3 ±1.7 μg/mL, and 12 ± 2 μg·h/mL, respectively. The apparent elimination half-life for febuxostat was about 5-10 hr. There was no appreciable accumulation of febuxostat following multiple dosing indicating that effective half-life for febuxostat was short.

C_{max} of febuxostat was dose-proportional from 10-300 mg (Studies TMX-99-001 and C02-023). However, AUC of febuxostat was dose proportional only up to 120 mg following single and multiple dose administration (Study TMX-99-001). A greater than dose-proportional increase in febuxostat AUC was observed for doses greater than 120 mg (Studies TMX-99-001 and C02-023). The cause of the change in PK at higher dose is unclear (possibly due to saturation of renal elimination which leads to an increase in the extent of enterohepatic recycling of febuxostat).

A high fat meal decreases the rate and the extent of absorption of febuxostat (C_{max} decreased 38%, AUC decreased 16%, and T_{max} delayed by 0.5 hr) (Study C03-054). Uric acid reduction in serum was slightly higher under fed conditions than fast conditions after multiple dosing (58% vs. 51%) (Study C02-036).

Febuxostat is highly bound to plasma proteins (~99.3% bound), primarily to albumin. In subjects with renal impairment, a slight decrease in protein binding of febuxostat with increasing renal impairment was observed (98.8% in severe renally-impaired subjects vs 99.1% in subjects with normal renal function)(Study TMX-01-008). Febuxostat metabolites, 67M-1, 67M-2, and 67M-4 are less bound to plasma proteins than the parent drug (90.9%, 81.8%, and 91.2%, respectively). Mean apparent steady state volume of distribution (V_{ss}/F) in healthy subjects was around 50 L (CV ~40%) (pooled study data). It appeared that febuxostat V_{ss}/F increased slightly for subjects with moderate or severe renal impairment (Study TMX-01-008).

In vitro metabolism and *in vivo* ADME study (Study C03-040) indicated that febuxostat is metabolized both by conjugation and oxidative pathways. Acyl glucuronide metabolites of febuxostat (~35% of the dose) recovered in the urine, and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4 (a secondary metabolite from 67M-1, ~14% of the dose) recovered in the urine and feces appeared to be the major metabolites of febuxostat *in vivo*. 67M-1, 67M-2 and 67M-4 have been shown to be inhibitors of purified bovine milk[1]

[1] Xanthine oxidase is a component of the milk fat globule membrane and is the standard source in the literature for purified xanthine oxidase.

XO, and their potency was the same as or less than that of febuxostat. However, febuxostat was the major component in plasma with an AUC ratio of these metabolites to febuxostat at steady state of 0.03. Thus, even considering the protein binding differences between febuxostat and its metabolites, febuxostat would be responsible for the pharmacodynamic effect. Urinary excretion of unchanged febuxostat was typically accounted for less than 4% of the administered dose.

The relative contribution of P450 isoforms in the oxidative metabolism of febuxostat is not clear. It is likely that 67M-1 was mainly metabolized by non-P450 enzymes and the same maybe true for its metabolite, 67M-4. 67M-2 was mainly formed by CYP1A2, CYP2C8 and CYP2C9 in the liver. 67M-3, a major metabolite formed *in vitro*, was not detected in significant amount *in vivo*. 67M-3 was mainly metabolized by CYP1A1. Febuxostat is metabolized to its acyl glucuronide by several uridine diphosphate glucuronosyltransferase (UGT) isoforms (mainly UGT1A1, UGT1A3, UGT1A9, and UGT2B7).

Data from Caco-2 cells indicated that febuxostat had medium permeability at pH 7.4 and its permeability was enhanced by lowering pH. It is likely that febuxostat is a substrate of pH-dependent transporters. It was not clear whether P-gp was involved because of lack of positive control for P-gp activity in the assay.

Febuxostat was found to be a modest competitive inhibitor of CYP2D6 with a Ki of 40 μM (12.6 μg/mL). Febuxostat showed essentially no inhibitory activity against the other CYP isoform activities evaluated (i.e., CYP1A2, CYP2C9, CYP2C19, and CYP3A4), with Ki values greater than 100 μM. Inhibition potential of febuxostat on P-gp has not been studied.

The induction potential of febuxostat on human CYP enzymes has not been studied either *in vitro* (hepatocytes) or *in vivo*.

Special Populations

Hepatic Impairment (Study TMX-01-012): The plasma exposure to febuxostat was greater in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function following the administration of daily 80 mg oral doses of febuxostat for 7 days. An average of 20-30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatically impaired groups.

Greater exposure of febuxostat in hepatically-impaired groups did not translate to greater reduction in serum uric acid levels on Day 7. Percent reduction in both mild (49%) and moderate (48%) hepatic impairment groups were 13 and 14% less than the reduction observed in healthy group (62%). The mean percent decrease in serum urate for healthy subjects in other special population studies ranged from 52% to 58% (Study TMX-01-008 and Study 01-016). Therefore, 48-49% reduction of uric acid level observed in this study appeared to be comparable to healthy groups.

Dose adjustments for febuxostat in subjects with mild or moderate hepatic impairment, based on exposure results and serum uric acid reduction activity mentioned above, are not necessary. PK

or PD of febuxostat in subjects with severe hepatic impairment has not been studied. A dose recommendation could not be made for severe hepatic impairment patients.[2]

Renal Impairment (Study TMX-01-008): Following the administration of 80 mg oral doses of febuxostat daily for 7 days, AUC and $T_{1/2}$ of febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among all three renal impairment groups. Unbound AUC_{24} ($AUC_{24,u}$) of febuxostat increased about 60% from normal in mild, moderate and severe renal impairment. The percent decrease in serum urate on Day 7 appeared to be similar regardless of the renal function.

One potential concern in the administration of xanthine oxidase inhibitors is the development of xanthine stones in the kidneys, secondary to the build up of uric acid precursors. Serum xanthine concentrations on Day 7 for subjects with severe renal impairment were about 3-fold higher than those for subjects with normal renal function. However, the 24-hour mean serum xanthine concentrations (0.55 ± 0.24 mg/dL) in patients with severe renal impairment were substantially lower than the solubility limit of xanthine in pH 7.4 serum (10 mg/dL), indicating the low likelihood of xanthine stone formation.

Based on the results of this study (60% increase in AUC in renal impairment patients), patients with renal impairment should

— PK or PD of febuxostat in end-stage renal impairment patients who are on dialysis has not been studied. However, febuxostat is not expected to be routinely used in end-stage renal impairment patients who are on dialysis because dialysis would effectively remove uric acid. b(4)

Gender (Study TMX-01-016): The plasma exposure to febuxostat was greater in female subjects compared to male subjects following the administration of daily 80 mg oral doses of febuxostat for 7 days. An average of 35% and 15% increase was observed for C_{max} and AUC_{24}, respectively, 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.

Race: According to the literature, there is a racial difference in terms of gout incidence. The incidence of gout is higher in African Americans compared to Caucasians in the U.S. (3.11 per 1,000 person-years vs. 1.82 per 1,000 person-years). No specific pharmacokinetic study was conducted to investigate the effects of race.

Subgroup analysis (via a multivariate logistic regression model) of the pivotal Phase 3 efficacy data indicated that Caucasian subjects had a higher chance of achieving the primary efficacy

[2] Xanthine oxidase is widely distributed throughout mammalian tissues.

endpoint compared to non-Caucasian subjects (estimated adjusted odd ratio 1.605 (95%CI (1.192, 2.162)).

Age (Study TMX-01-016): The plasma exposure to febuxostat was similar between healthy subjects 18-40 years and subjects ≥ 65 years following the administration of daily 80 mg oral doses of febuxostat 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 febuxostat did not appear to be substantially affected by age. As a result, no dose adjustment would be recommended based on differences in age.

Pediatric Patients: The pharmacokinetic profile of febuxostat in pediatric patients has not been established. The Sponsor requests a full waiver from the pediatric assessment requirements on the basis that necessary studies are impossible or highly impractical because the number of patients is very small.

Gout Patients: Population PK analysis suggests that PK of febuxostat is similar in healthy subjects and gout patients. The mean apparent clearance is 8.4 L/hr for gout patients and 10.3 L/hr for healthy subjects. The estimated half-life ($t_{1/2,\beta}$) is 7.7 h in healthy subjects and 7.5 h in patients.

QTc Prolongation Potential

QT prolongation potential of febuxostat (80 and 300 mg QD for 4 days) was evaluated in Study C02-023. ——→ (moxifloxacin 400 mg) and placebo were included in the study. 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 data demonstrated that there were no QT or QTFc (corrected using the Fridericia's formula) interval prolongations for the febuxostat regimens (80 and 300 mg QD), whereas ——→ (moxifloxacin) 400 mg QD significantly prolonged QT and QTFc intervals. b(4)

Besides the formal QT study (C02-023), standard 12-lead resting ECGs were monitored in all Phase 2 and 3 studies. According to the safety medical officer, there was no indication of QT prolongation with the drug. The ECG analysis did not show any subjects with prolonged QT as an adverse event (AE). Most of cardiovascular AEs were of ischemic/thrombotic nature or chronic heart failure (CHF) exacerbation and not conduction/rhythm disturbances.

Drug interactions (Reviewed by Dennis Bashaw, Pharm.D.)

The potential for drug interactions was evaluated in eight *in vivo* clinical pharmacology studies in the United States which incorporated an evaluation of the effect of antacid, the relevant *in vitro* DDI results, drugs that can be expected to be coadministered with febuxostat, and warfarin.

Potential for febuxostat to affect other drugs	Potential for other drugs to affect febuxostat
Desipramine, Colchicine, Indomethacin, Naproxen, and Warfarin	Antacid, Colchicine, Indomethacin, Naproxen, and Hydrochlorothiazide

While the *in vitro* metabolism studies did not suggest a high likelihood of a CYP-P450 mediated DDI, a study was done to evaluate the effect of febuxostat on the pharmacokinetics of desipramine (a known 2D6 substrate) as a "possible" effect was seen *in vitro*.

From a therapeutic point of view, additional DDI studies were conducted to evaluate the effect of febuxostat coadministration with agents commonly used in the treatment of acute gouty attacks; colchicine, indomethacin, and naproxen. As hydrochlorothiazide is known to inhibit the renal secretion of uric acid (thus exacerbating serum uric acid levels), a DDI study incorporating both PK and PD measurements (serum uric acid) was also completed.

While minor changes in pharmacokinetics were seen in most of these studies, the changes do not reach the level where dosage adjustment would be necessary with the exception of naproxen's effect on febuxostat. Following co-administration of naproxen (at an anti-rheumatic dose of 500mg BID) with febuxostat, the C_{max} and AUC_{24} of febuxostat increased by approximately 28% and 40%, respectively, as compared to values following febuxostat administered alone. This increase in febuxostat levels may be related to an effect on the glucuronidation of febuxostat which is manifested by an approximately 40% drop in clearance. b(4)

Coadministration with an antacid did result in a delay in achieving febuxostat peak levels by 1 hour and a 31% decrease in peak levels and no effect on AUC. As the effect of febuxostat is felt to be more associated with exposure rather than peak level, these changes are not sufficient enough to result in a dosage adjustment recommendation.

As for effect of febuxostat on warfarin, the study incorporated multiple dosing (120 mg febuxostat for 14 days), a chiral assay, and assessments of coagulation (both INR and Factor-VII(F-VII) assay). In terms of the pharmacokinetics and pharmacodynamics of warfarin, the sponsor noted no significant difference in either the PK or PD of warfarin. This conclusion is, however, based on data from only 13 of the 22 subject who were randomized to the treatment phase of the study. An additional 8 subjects were dropped from the dataset due to increased INR values that required vitamin K administration (a ninth subject received vitamin K following completion of the dosing phase of the trial). Although these 8 subjects, who were removed on treatment, were equally divided between the two treatment arms (at the time of discontinuation), an increased INR value would be the signal one would expect if there was an interaction. Based on the removal of subjects due to increased INR values, and the reports of adverse events (hemorrhage) from the clinical database in subjects receiving warfarin concomitantly, b(4)

Exposure-Response (Reviewed by Atul Bhattaram, Ph.D.)

Sponsor has conducted extensive studies in healthy subjects and patients aimed at examining the 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 febuxostat dose groups respectively. The response rate was 22% for the 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 arms 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, the response rate of a lower febuxostat dose (40 mg) 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 are 80 mg QD

. Testing for the target serum uric acid level of <6.0 mg/dL may be performed as early as 2 weeks after initiating febuxostat therapy. (

b(4)

As noted earlier, there are concerns regarding the cardiovascular safety of febuxostat. At the present time the cardiovascular AE for the 40 mg or any dose lower than 80 mg is unknown. Long-term efficacy and safety study at 40 mg (or 60 mg) dose will be needed before a dose recommendation for a dose lower than 80 mg could be made.

Dosage Form Bioequivalence:

The pivotal clinical trials used the to-be-marketed formulation, Abbott Formulation B1. In the NDA database, combinations of lower strength tablets were used to achieve the 80 and 120 mg to-be-marketed dosage strengths. The 20 mg and 40 mg tablets of Formulation B1 used in some of the clinical trials

b(4)

Because of the dose-proportional PK in the range of 10-120 mg for febuxostat, it is expected that these tablets would be bioequivalent. Results from Study C03-044 demonstrated that one febuxostat 120 mg Formulation B1 tablet was bioequivalent to 1 febuxostat 80 mg Formulation B1 tablet plus 1 febuxostat 40 mg Formulation B1 tablet.

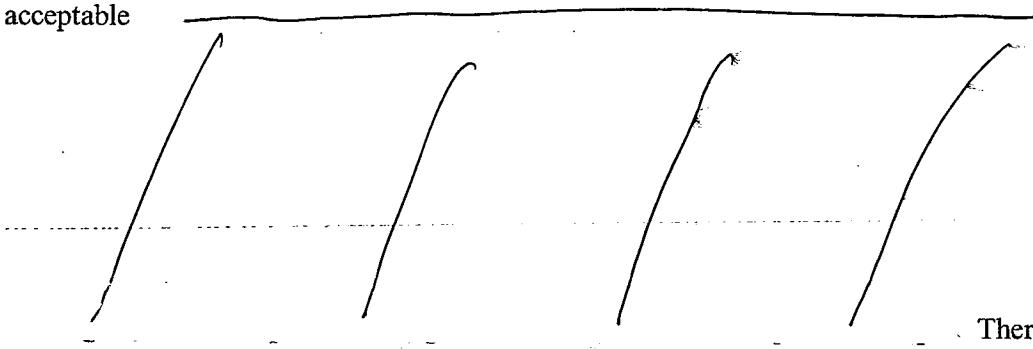
Teijin's formulation, Formulation A3, was used in many PK studies. Results from the bioequivalence study (Study TMX-02-018) demonstrated that 20 mg tablet of Formulation B1 was bioequivalent to 20 mg tablet of Teijin Formulation A3. In addition, the Abbott B1 80 mg tablet was bioequivalent to four Abbott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

Dissolution

The specification was proposed for dissolution testing of febuxostat 80 mg and 120 mg tablets

b(4)

The proposed dissolution method and acceptance criterion for febuxostat tablets are not acceptable



b(4)

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:

Dissolution testing of febuxostat 80 mg and 120 mg tablets using Apparatus 2 (paddle) at 75 rpm with 900 mL of 0.05 *M* potassium phosphate buffer, pH 6.8, maintained at 37°C:

Time Point	**Specification**
15 minutes	Q = — b(4)

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.

Lei Zhang, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

E. Dennis Bashaw, Pharm.D.
Clinical Pharmacology Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

OCPB briefing (Requried Office-Level) Date: July 28, 2005.

2 QUESTION BASED REVIEW

(Reviewer's Note: Febuxostat and TMX-67 are used inter-changeably in the review.)

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1.1. Physical-Chemical Properties of Febuxostat.

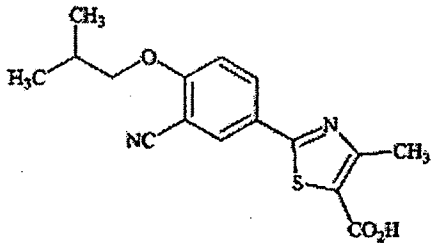
Drug Name	Febuxostat (TMX-67)
Chemical Name	2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid
Structure and Molecular Formula	 $C_{16}H_{16}N_2O_3S$
Molecular Weight	316.38
pKa	The aqueous pKa is calculated to be 3.3, corresponding to that of a carboxylic acid
Appearance	Non-hygroscopic, white crystalline powder
Melting Range	205°C to 208°C.
Solubility	Freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water.

Table 2.1.1.2. Saturated Solubility of Febuxostat in Various Buffer Solutions.

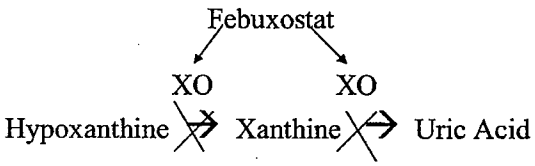
Buffer/pH	Solubility at 37°C (mg/mL)
0.1*N* hydrochloric acid, pH 1.0	
0.05*M* acetate buffer, pH 4.5	
0.05*M* citrate buffer, pH 5.5	
0.05*M* phosphate buffer, pH 6.0	
0.05*M* phosphate buffer, pH 6.8	
0.05*M* phosphate buffer, pH 7.4	

b(4)

Febuxostat tablets are available in two dosage strengths, 80 and 120 mg. Inactive ingredients in the tablets include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. The tablets are coated with Opadry II, green. b(4)
(See Section 2.5.1).

2.1.2 What is the proposed mechanism of drug action and therapeutic indications?

Febuxostat (TMX-67) is a 2-arylthiazole derivative that selectively inhibits the synthesis of uric acid by inhibiting xanthine oxidase (XO), the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans (see the diagram below). The *in vitro* K_i value for the inhibition of human liver XO was 10 nM.



Febuxostat has been shown to inhibit both the oxidized and reduced forms of XO. Unlike allopurinol, febuxostat is not a purine analog. At therapeutic concentrations, febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Gout is a metabolic disorder in which tissue deposition of monosodium urate crystals from supersaturated body fluids results in acute attacks of inflammatory arthritis and the development of palpable crystalline aggregates (tophi), primarily in connective tissue, but potentially in virtually any organ. The underlying metabolic disorder in gout is hyperuricemia, which is best defined as an elevation in serum uric acid level 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 such as temperature, pH, sodium ion and protein concentrations. As serum urate values increase beyond the level of urate solubility, extracellular fluids are increasingly saturated, increasing urate crystals within the joint, resulting in gout flares. Treatment of hyperuricemia in patients with gout is aimed at decreasing serum uric acid below 6.0 mg/dL.

The proposed indication of febuxostat is for the management of hyperuricemia in patients with gout.

2.1.3 What are the proposed dosage recommendations by the Sponsor and route of administration of febuxostat for the proposed indication?

The proposed oral dose of febuxostat is 80 mg QD. b(4)
Testing for the target serum uric acid level of <6.0 mg/dL may be performed as early as 2 weeks after initiating febuxostat therapy.

Concomitant flare prophylaxis [redacted] with an NSAID or colchicine is recommended. Patients may be more prone to developing gout flares during initiation of treatment [redacted]. b(4)

Febuxostat can be administered without regard to food. No dose adjustment is necessary when administering febuxostat to patients with renal impairment or mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment; therefore, caution should be exercised in such patients.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support Clinical Pharmacology and Biopharmaceutics aspects of febuxostat, a total of 27 *in vivo* pharmacokinetic and pharmacodynamic trials have been submitted. In addition, there are more than 30 *in vitro* study reports included to characterize *in vitro* metabolism, transport, protein binding and dissolution profiles of febuxostat.

To support clinical efficacy and safety for febuxostat, the sponsor collected the important efficacy and safety information in the following clinical trials (see Table 2.2.1.1).

APPEARS THIS WAY
ON ORIGINAL

Table 2.2.1.1. Febuxostat Efficacy Studies.

Study	Treatment Groups	Design	N[a]	Duration of Treatment/ Duration of Gout Flare Prophylaxis During Treatment	Study Population	Primary Efficacy Endpoint
Phase 3 Pivotal Studies						
C02-009	Placebo Febuxostat: 80 mg QD 120 mg QD 240 mg QD Allopurinol: 300/100 mg QD[b]	Randomized, double-blind, parallel-group, active- and placebo-controlled	1072	28 weeks/ 8 weeks (naproxen or colchicine)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[109]	The proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.
C02-010	Febuxostat: 80 mg QD 120 mg QD Allopurinol: 300 mg QD	Randomized, double-blind, parallel-group, active-controlled	760	52 weeks/ 8 weeks (naproxen or colchicine)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[109]	The proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.
Supportive Phase 2 Controlled Study						
TMX-00-004	Placebo Febuxostat: 40 mg QD 80 mg QD 120 mg QD	Randomized, double-blind, parallel-group, placebo-controlled	153	4 weeks/ 2 weeks (colchicine)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[109]	The proportion of subjects whose serum urate level decreased to <6.0 mg/dL after treatment with study drug (Day 28).
Supportive Phase 3 Controlled Study						
C02-021[d]	Febuxostat: 80 mg QD 120 mg QD Allopurinol: 300/100 mg QD[c]	Randomized, open-label, active-controlled, safety extension	1074	Up to 24 months/ 8 weeks (naproxen or colchicine)	Subjects who completed Studies C02-009 or C02-010.	The proportion of subjects whose serum urate level decreased to <6.0 mg/dL.
Supportive Phase 2 Uncontrolled Study						
TMX-01-005[d]	Febuxostat: 40 mg QD 80 mg QD 120 mg QD	Open-label, safety extension	116	Up to 260 weeks/ 4 weeks (colchicine)	Subjects who completed Study TMX-00-004.	The proportion of subjects whose serum urate level decreased to or was maintained at <6.0 mg/dL.

ARA = American Rheumatism Association

a Indicates the number of subjects who received at least 1 dose of study drug.

b Allopurinol 300 mg QD for subjects with serum creatinine ≤1.5 mg/dL at Day -2 or 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at Day -2.

c Allopurinol 300 mg QD (for subjects who had a serum creatinine ≤1.5 mg/dL at the study visit prior to the last visit of the previous study) or 100 mg QD (for subjects who had serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at the study visit prior to the last visit of the previous study).

d Ongoing study.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoints used in the clinical trials are pre-dose serum urate levels at steady-state. The primary efficacy endpoint is the proportion of subjects whose last three serum urate levels were below 6.0 mg/dL (measured every 4 weeks after Week 8). Serum urate level is a reliable predictor of gout. There is strong evidence of a correlation between reducing serum urate levels, and reduction in size of tophi, and decreasing frequency of gout flares over time. In a recent Arthritis Advisory Committee meeting (June 2, 2004), it was generally agreed that targeting

SUA levels to < 6 mg/dL should be sought if SUA is used as a surrogate endpoint for chronic gout treatment (where the endpoint is quality of life and decreased incidence of gout flares).

The pharmacodynamic endpoint used in the Phase 1 clinical studies was the percent decrease in serum urate mean 24-hour concentration from baseline. For the population pharmacodynamic analyses in the Phase 2/3 studies, the change in serum urate concentration from baseline was used.

2.2.3 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure-response relationships?

Yes, the Sponsor measured the appropriate moieties in clinical pharmacology studies.

For pharmacokinetics:
They measured febuxostat and its oxidative metabolites (67M-1, 67M-2, and 67M-4) levels in plasma and urine in most clinical pharmacology studies. They measured the concentrations of other moieties, as appropriate, in drug interaction studies. The metabolite, 67M-3, although seen *in vitro*, was not detected *in vivo*.

For pharmacodynamics:
They measured serum and urinary levels of uric acid, xanthine and hypoxanthine.

Please refer to Section 2.6 Analysis for analytical details.

2.2.4 Is the dose/dosing regimen proposed by the sponsor acceptable?

Dosing regimen: Yes, the dosing regimen proposed by the sponsor is reasonable. In terms of dosing frequency, the sponsor proposed a once-a-day dosing schedule for febuxostat. It is well reflected in the time course of serum urate levels as shown in Figure 2.2.4.1 below:

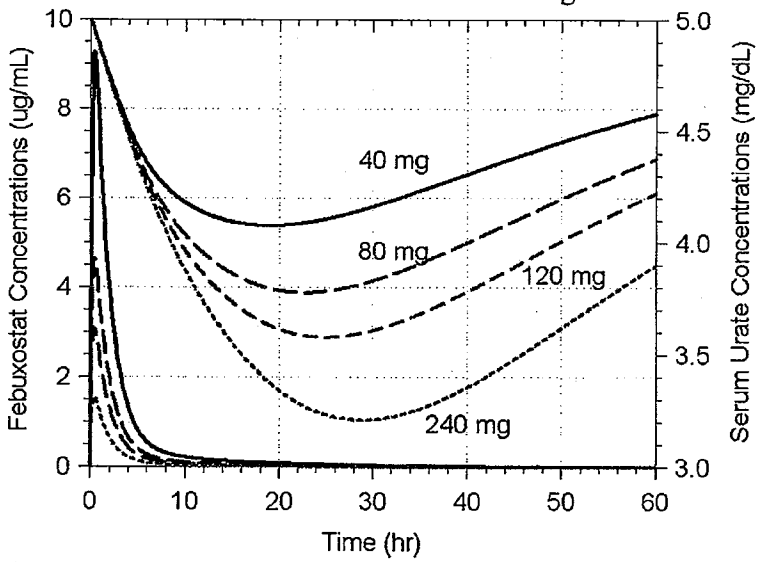


Figure 2.2.4.1. Time Course of Serum Febuxostat and Urate Concentrations after Single Oral Doses of 40, 80, 120 and 240 mg.

Dose: The sponsor conducted extensive studies to characterize dose-response relationship (Figure 2.2.4.2).

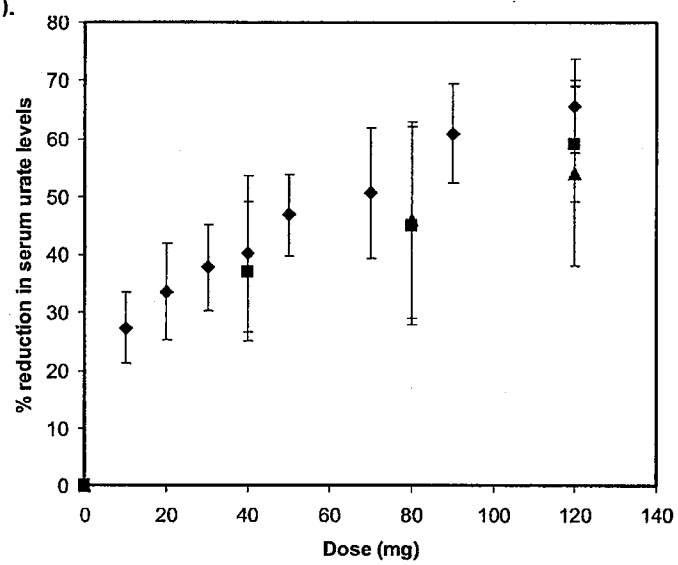


Figure 2.2.4.2. % Reduction (Mean±SD) in Serum Urate Levels (pre-dose) in Healthy Subjects (♦) patients (Phase II-■; Phase III-▲).

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 significantly higher in the febuxostat treatment groups than that observed in the allopurinol (active-control) group (51%, 63%, 69% in febuxostat groups vs. 22% in the allopurinol group). The time course of serum uric acid as observed in pivotal trials is shown in Figure 2.2.4.3 below.

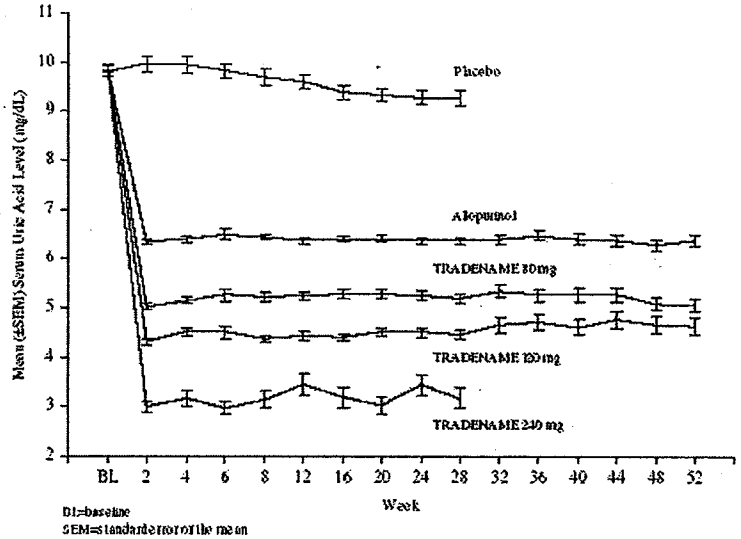


Figure 2.2.4.3. Time Course of Serum Uric Acid (Mean±SEM) in the Pivotal Trials (Shown are Placebo, Allopurinol, Febuxostat).

If there were no cardiovascular safety events (Please refer to the review by the 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 2.2.4.4 below. However, it is not possible to characterize risk at this dose as there is no clear dose-response (risk) relationship. If the rate of cardiovascular events that were observed in the trial are not acceptable, in view of overall utility of the drug, then a 40 mg dose would be a useful alternative

b(4

b(4)

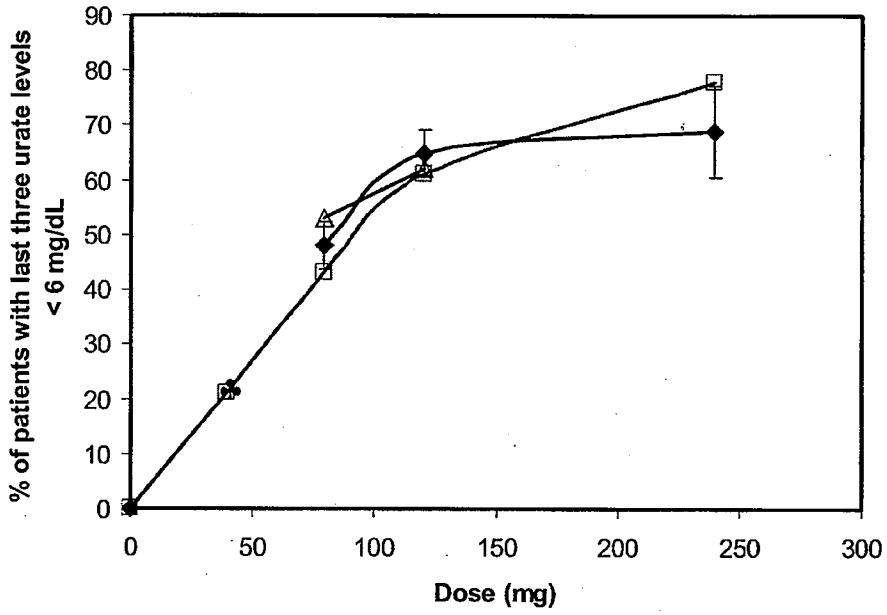


Figure 2.2.4.4. Relationship between primary endpoint vs dose of febuxostat (♦- observed in C02-009; Δ- Observed in C02-010; □- Predicted; ♣- Observed for Allopurinol) (Shown are Mean±2S.E for Observed and Mean for Predicted).

2.2.4.3 Does febuxostat prolong QT or QTc interval?

No, febuxostat does not appear to prolong QT or QTc interval.

QT prolongation potential of febuxostat (80 and 300 mg QD for 4 days) was evaluated in Study C02-023. ___ (moxifloxacin 400 mg) and placebo were included in the study. b(4)

Maximal and Time-Averaged QT_{Fc} Intervals

The mean of the maximum post-dose QT_{Fc} interval values and the time-averaged values for [redacted] 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 (80 and 300 mg) and placebo (Tables 2.2.4.3.1 and 2.2.4.3.2).

Table 2.2.4.3.1. Comparison of Maximum QTFc Intervals.

	Mean of Maximum QT_{Fc} (msec)				Difference from Placebo (msec)			b(4)
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 400 mg	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 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.

Table 2.2.4.3.2. Comparison of Time-Averaged QT_{Fc} Intervals.

	Mean of Time-Averaged QT_{Fc} (msec)				Difference from Placebo (msec)			b(4)
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 400 mg	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 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.

Analyses of Uncorrected QT Intervals

Uncorrected QT interval was analyzed using maximum and time-averaged post-dose values on Days 1 and 4. The results from the analyses are presented in Tables 2.2.4.3.3 and 2.2.4.3.4, respectively.

Table 2.2.4.3.3. Maximum Uncorrected QT Intervals.

	Mean of Maximum Values				Difference from Placebo		
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 400 mg	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 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

The mean of the maximum post-dose uncorrected QT values for [redacted] 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 (Table 2.2.4.3.3). b(4)

Table 2.2.4.3.4. Time-Averaged Uncorrected QT Intervals.

	Mean of Time-Averaged Values				Difference from Placebo			b(4)
	Placebo	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 400 mg	Febuxostat 80 mg	Febuxostat 300 mg	[redacted] 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	

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 (Table 2.2.4.3.4). b(4)

In summary, 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 or QT_{Fc} (corrected using the Fridericia's formula) interval prolongations for the febuxostat regimens (80 and 300 mg QD), whereas — (moxifloxacin) 400 mg QD significantly prolonged QT and QT_{Fc} intervals. b(4)

2.2.5 What are the PK characteristics of febuxostat?

2.2.5.1 What are single dose and multiple dose PK parameters of febuxostat?

Single Dose

Single-dose PK parameter estimates pooled from 15 TAP Phase 1 studies including an assessment of inter-subject variability were listed in Table 2.2.5.1.1 for 80 mg dose (N=183) and Table 2.2.5.1.2 for 120 mg dose (N=64).

Table 2.2.5.1.1. Mean Febuxostat Pharmacokinetic Parameters for Healthy Subjects in Phase 1 Studies[a] Following a Single 80 mg Oral Dose of Febuxostat.

	t_{max} (h)	C_{max} (μg/mL)	AUC_∞ (μg·h/mL)	$t_{1/2z}$[b] (h)	V_{ss}/F (L)	CL/F (L/h)
N	183	183	179	179	24	179
Mean	**1.53**	**3.22**	**9.60**	**6.01 [5.29]**	**43.2**	**9.04**
SD	1.04	1.26	2.86	2.17	20.6	2.57
Min	0.50	0.985	4.46	0.892	18.8	3.26
Median	1.00	3.12	9.03	5.74	37.0	8.86
Max	4.00	7.24	24.5	19.3	98.1	17.9
CV%	**68**	**39**	**30**	**36**	**48**	**28**

a Pooled pharmacokinetic parameters from Studies C02-013, C02-033, C02-034, C02-036, C03-059, C03-044, C03-054, TMX-99-001,TMX-01-008, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, and TMX-02-018 where applicable.
b Harmonic mean in brackets.

Table 2.2.5.1.2. Mean Febuxostat Pharmacokinetic Parameters for Healthy Subjects in Phase 1 Studies[a] Following a Single 120 mg Oral Dose of Febuxostat.

	t_{max} (h)	C_{max} (μg/mL)	AUC_∞ (μg·h/mL)	$t_{1/2z}$[b] (h)	V_{ss}/F (L)	CL/F (L/h)	f_e (%)	Cl_r (L/h)
N	64	64	64	64	10	64	10	10
Mean	**1.47**	**5.04**	**16.0**	**6.01 [5.25]**	**54.4**	**8.19**	**1.29**	**0.131**
SD	0.937	1.66	4.50	3.19	19.7	2.57	0.59	0.054
Min	0.25	1.72	7.47	2.84	24.4	4.73	0.69	0.067
Median	1.00	4.85	16.3	5.20	61.3	7.38	1.09	0.130
Max	4.00	8.61	25.4	22.1	79.2	16.1	2.54	0.222
CV%	**64**	**33**	**28**	**53**	**36**	**31**	**46**	**41**

a Pooled pharmacokinetic parameters from Studies C02-013, C02-033, C02-034, C02-036, C03-059, C03-044, C03-054, TMX-99-001, TMX-01-008, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, and TMX-02-018 where applicable.
b Harmonic mean in brackets.

Multiple Doses

Multiple-dose PK parameter estimates pooled from 15 TAP Phase 1 studies including an assessment of inter-subject variability were listed in Table 2.2.5.1.3 for 80 mg dose (N=121) and Table 2.2.5.1.4 for 120 mg dose (N=9).

Table 2.2.5.1.3. Mean Febuxostat Pharmacokinetic Parameters for Healthy Subjects in Phase 1 Studies[a] Following Multiple 80 mg Oral Doses of Febuxostat.

	t_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg·h/mL)	$t_{1/2z}$[b] (h)	V_{ss}/F (L)	CL/F (L/h)	f_e (%)	Cl_r (L/h)
N	121	121	121	120	120	121	46	46
Mean	**1.32**	**2.76**	**7.75**	**6.07 [5.35]**	**52.5**	**11.4**	**1.86**	**0.222**
SD	0.775	1.34	2.63	2.28	19.9	3.67	2.06	0.274
Min	0.50	0.936	3.34	2.26	16.8	3.78	0.34	0.031
Median	1.00	2.40	7.46	5.60	49.9	10.7	1.12	0.126
Max	4.00	7.32	21.2	15.7	114	23.9	11.7	1.22
CV%	**59**	**48**	**34**	**38**	**38**	**32**	**111**	**123**

a Pooled pharmacokinetic parameters from Studies C02-013, C02-033, C02-034, C02-036, C03-059, C03-044, C03-054, TMX-99-001, TMX-01-008, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, and TMX-02-018 where applicable.
b Harmonic mean in brackets.

Table 2.2.5.1.4. Mean Febuxostat Pharmacokinetic Parameters for Healthy Subjects in Phase 1 Studies[a] Following Multiple 120 mg Oral Doses of Febuxostat.

	t_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg·h/mL)	$t_{1/2z}$[b] (h)	V_{ss}/F (L)	CL/F (L/h)	f_e (%)	Cl_r (L/h)
Multiple 120 mg QD Doses - All								
N	9	9	9	9	9	9	9	9
Mean	**1.11**	**5.31**	**12.0**	**18.2 [11.9]**	**55.1**	**10.5**	**6.13**	**0.641**
SD	0.821	1.68	2.42	13.9	15.8	2.48	1.61	0.199
Min	0.50	2.50	7.68	6.74	35.3	8.24	3.74	0.320
Median	1.00	5.87	12.9	12.0	51.8	9.33	5.63	0.714
Max	3.00	7.09	14.6	44.2	79.6	15.6	8.58	0.865
CV%	**74**	**32**	**20**	**76**	**29**	**24**	**26**	**31**

a Pooled pharmacokinetic parameters from Studies C02-013, C02-033, C02-034, C02-036, C03-059, C03-044, C03-054, TMX-99-001, TMX-01-008, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, and TMX-02-018 where applicable.
b Harmonic mean in brackets.

2.2.5.2 What are single dose and multiple dose PK parameters of febuxostat metabolites?

In vitro and *in vivo* metabolism studies performed by Teijin Limited (Teijin) indicated that febuxostat metabolites 67M-1, 67M-2 and 67M-4 are prominent human metabolites (also refer to Section 2.2.5.6). Therefore, these metabolites were measured in the plasma and urine of several of the Phase 1 pharmacokinetic studies performed in the U.S..

Single- (Day 1) and multiple-dose (Day 14) PK parameters for 67M-1, 67M-2, and 67M-4 at a dose of 120 mg QD obtained from Study TMX-99-001 were listed in Table 2.2.5.2.1.

Table 2.2.5.2.1. Summary of Metabolite 67M-1, 67M-2 amd 67M-4 Pharmacokinetic Results (Study TMX-99-001).

Day	Mean Pharmacokinetic Parameters (%CV)							
	t_{max} (h)	C_{max} (µg/mL)	AUC[a] (µg·h/mL)	$t_{1/2}$[b] (h)	C_{max}/Dose (1/L)	AUC[a]/Dose (h/L)	AUC[a]/ febuxostat AUC[a]	Cl_r (L/h)
67M-1								
1	1.33 (50)	0.106 (28)	0.351 (34)	11.7 [9.4] (34)	0.000881 (28)	0.00293 (34)	0.031 (34)	12.5 (27)
14	1.22 (62)	0.126 (41)	0.357 (35)	15.3 [10.9] (60)	0.00105 (41)	0.00297 (35)	0.030 (29)	15.0 (36)
67M-2								
1	1.50 (44)	0.0811 (22)	0.377 (28)	15.9 [12.1] (55)	0.000676 (22)	0.00314 (28)	0.035 (42)	11.5 (28)
14	1.44 (68)	0.0964 (25)	0.392 (30)	22.2 [15.0] (69)	0.000803 (25)	0.00326 (30)	0.034 (36)	12.3 (34)
67M-4								
	t_{max} (h)	C_{max} (µg/mL)	AUC[a] (µg·h/mL)	$t_{1/2}$[b] (h)	C_{max}/Dose (1/L)	AUC[a]/Dose (h/L)	67M-4 AUC[a]/ 67M-1 AUC[a]	Cl_r (L/h)
1	1.94 (35)	0.0508 (24)	0.285 (56)	15.8 [9.4] (96)	0.000423 (24)	0.00238 (56)	0.78 (27)	7.66 (25)
14	1.83 (64)	0.0606 (33)	0.286 (49)	23.3 [15.8] (78)	0.000505 (33)	0.00238 (49)	0.79 (25)	8.32 (31)

a AUC_∞ for Day 1 and AUC_{24} for Day 14 for QD dosing regimen.
b Harmonic mean in brackets.

Although 67M-1, 67M-2 and 67M-4 have been shown to be inhibitors of purified bovine milk XO, and their potency was the same as or less than that of febuxostat and they are present to a much lesser extent than febuxostat in the plasma. AUC ratio of these metabolites to febuxostat at steady state was about 0.03 (<0.1) making febuxostat the major circulating component in plasma responsible for the pharmacodynamic effect.

2.2.5.3 How does the PK of febuxostat in healthy volunteers compare to that in gout patients?

Population PK analysis suggests that PK of febuxostat is similar in healthy subjects and gout patients. The mean apparent clearance is 8.4 L/hr for gout patients and 10.3 L/hr for healthy subjects. The estimated half-life ($t_{1/2,\beta}$) is 7.7 h in healthy subjects and 7.5 h in patients.

2.2.5.4 What are the characteristics of drug absorption?

In a radiolabeled study the absorption of febuxostat was estimated to be 49% (based on total radioactivity recovered in the urine). As unchanged febuxostat accounted for less than 16% of the dose in the feces, absorption could be as high as 84%. (See Tables in Section 2.2.5.6). The absolute bioavailability of febuxostat has not been determined. Mean T_{max} of febuxostat was 1.5

hours post-dose following single or multiple daily oral dose administration (Refer to tables in Section 2.2.5.1).

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

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

Consistent with the *in vitro* finding that absorption of febuxostat is pH-dependent, the *in vivo* drug interaction study with antacid showed that coadministration of febuxostat with an antacid resulted in a delay in achieving peak levels by 1 hour and a 31% decrease in peak levels (see Section 2.4.2.7.1.1). AUC decreased by 15%. As a note, higher pH would increase solubility of febuxostat but would decrease its permeability.

2.2.5.5 What are the characteristics of drug distribution?

Febuxostat is highly bound to plasma proteins, primarily to albumin. The binding of [^{14}C]-febuxostat in human plasma averaged 98%-99% and was independent of the concentration between 0.4 and 10 μg/mL (Table 2.2.5.5.1).

Table 2.2.5.5.1. *In Vitro* Protein Binding of [^{14}C]Febuxostat in Plasma from Healthy Subjects

[$_{14}$C]Febuxostat Conc. (μg/mL)	Protein Binding (%)			
	Study 18-K-96012[a,b]		Study 18-A-94016[a]	Study C02-023[c]
0.4	97.9 ±0.2	97.8 ±0.2	98.9 ±0.1	nd
1	nd	nd	nd	99.3 ±0.1
2	98.1 ±0.2	98.0 ±0.1	99.0 ±0.0	nd
10	98.3 ±0.2	98.2 ±0.1	99.0 ±0.0	nd

nd: Not determined.
a Mean ± standard deviation. N=3 replicates.
b Control samples from 2 separate sets of incubations performed in this study.
c Mean ± standard deviation. N=12 subjects.

In subjects with renal impairment, a slight decrease in protein binding of febuxostat with increasing renal impairment was observed (98.8% in severe renally-impaired subjects vs 99.1% in subjects with normal renal function)(Study TMX-01-008).

Febuxostat metabolites, 67M-1, 67M-2, and 67M-4 are less bound to plasma proteins than the parent drug (Table 2.2.5.5.2).

Table 2.2.5.5.2. *In Vitro* Protein Binding of Metabolites 67M-1, 67M-2 and 67M-4 in Plasma from Healthy Subjects.

	Protein Binding (%)[a]		
	67M-1	67M-2	67M-4
Metabolite alone (200 ng/mL)	90.9 ±0.6	81.8 ±1.2	91.2 ±0.5
Metabolite (200 ng/mL)+ febuxostat (10 µg/mL)	89.9 ±0.4	81.6 ±0.9	92.1 ±0.5

a Mean ± standard deviation. N=5.

The whole blood radioactivity comparison with plasma radioactivity showed that there was no preferential binding of febuxostat with red blood cells (Study C03-040).

Mean apparent steady state volume of distribution (V_{ss}/F) in healthy subjects was approximately 50 L (CV ~40%) (Refer to tables in Section 2.2.5.1). It appeared that febuxostat V_{ss}/F increased slightly for subjects with moderate or severe renal impairment (mean 60-80 L, Study TMX-01-008).

2.2.5.6 Dose the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance study suggests that the elimination of febuxostat is through both renal and biliary excretion routes. Febuxostat is extensively metabolized.

Results from a ^{14}C-ADME study (Study C03-040) in healthy subjects demonstrated that the mean cumulative recovery of radioactivity in excreta was 94% at 216 hours (9 days) post-dose. An average of 49% of radioactivity was recovered in urine and 45% in feces (Table 2.2.5.6.1).

Table 2.2.5.6.1. Cumulative Recovery of Radioactivity

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

b(4)

Intact febuxostat represented a combined total of 10%-18% (1%-4% urine and 8%-16% feces) of the dose, indicating that febuxostat is extensively metabolized in humans (Table 2.2.5.6.2). The minimum absorption of febuxostat was 49% based on radioactivity recovered in the urine. Urinary excretion of unchanged febuxostat was typically accounted for less than 4% of the

administered dose (Table 2.2.5.6.2). The low recovery of febuxostat in the feces (8-16%) indicated that the absorption of febuxostat could be > 84% if assuming all the feces were collected and no degradation of febuxostat occurred in the gastrointestinal tract or feces.

Table 2.2.5.6.2. Distribution of the Prominent Radioactive Components in Human Excreta Samples Following a Single 80 mg Oral Dose of [^{14}C]Febuxostat.

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

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

2.2.5.7 What are the characteristics of drug metabolism?

In vitro metabolism and *in vivo* ADME studies indicated that febuxostat is metabolized both by conjugation and oxidative pathways.

In urine, the major metabolites were the acyl-glucuronides of febuxostat isomers (26.7%-37.5%), the hydroxylated febuxostat 67M-2 (3.9%-7.3%), the hydroxylated febuxostat 67M-1 (2.5%-7.1%), febuxostat (1-4%), the dicarboxylic acid 67M-4 (0.1%-3.1%), and the glucuronide of reduced febuxostat (0.3%-0.6%).

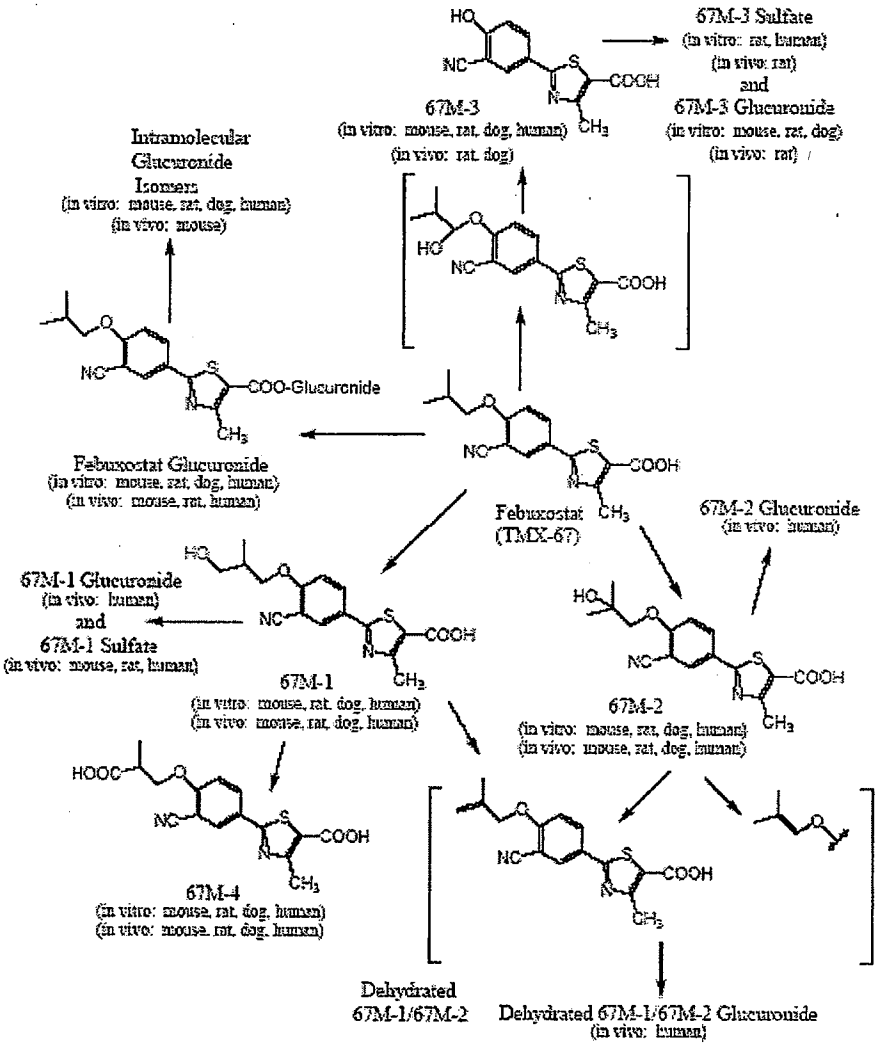
In feces, febuxostat and metabolite 67M-4 were the most prominent components, accounting for 7.8% to 16% and 7.8% to 15% of the dose, respectively. Other major metabolites were 67M-1 (3.6%-7.1%), 67M-2 (3.7%-6.7%), and the sulfate conjugate of 67M-1 (Table 2.2.5.6.2).

Therefore, acyl glucuronide metabolites of febuxostat (~35% of the dose) recovered in the urine, and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4 (a secondary metabolite from 67M-1, ~14% of the dose) recovered in the urine and feces appeared to be the major metabolites of febuxostat *in vivo* (See Section 2.2.5.6).

Based on the collective results of the *in vitro* and *in vivo* studies, the metabolic pathways shown in Figure 2.2.5.7.1 was proposed by the Sponsor.

The relative contribution of P450 isoforms in the oxidative metabolism of febuxostat is not clear. It is likely that 67M-1 was mainly metabolized by non-P450 enzymes and the same maybe true for its metabolite, 67M-4. 67M-2 was mainly formed by CYP1A2, CYP2C8 and CYP2C9 in the liver. 67M-3, a major metabolite formed *in vitro*, was not detected in significant amount *in vivo*. 67M-3 was mainly metabolized by CYP1A1, whose level is low in healthy non-smoking

subjects. Febuxostat is metabolized to its acyl glucuronide by several uridine diphosphate glucuronosyltransferase (UGT) isoforms (mainly UGT1A1, UGT1A3, UGT1A9, and UGT2B7).



Note: This metabolic pathway illustrates febuxostat metabolites that have been tentatively identified in in vitro and in vivo metabolism studies. However, metabolites not identified in some species may actually be present, but in concentrations too low to allow identification.

Figure 2.2.5.7.1. Proposed Metabolic Pathways for Febuxostat (TMX-67).

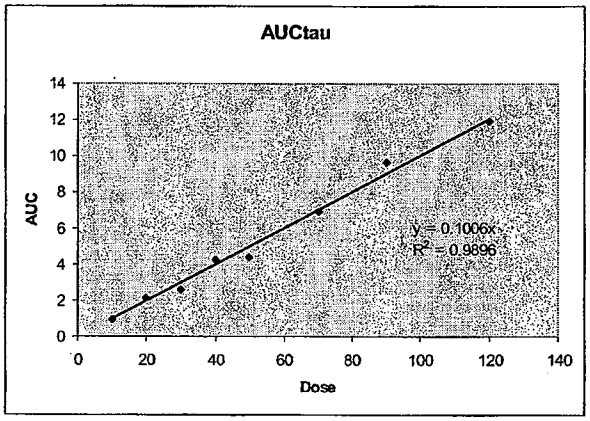
2.2.5.8 What are the characteristics of drug excretion?

See Section 2.2.5.6.

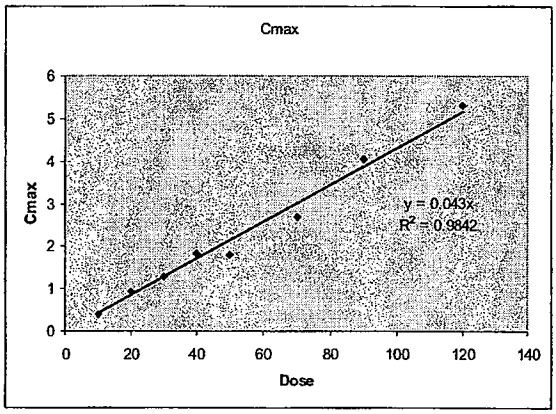
The mean steady-state plasma elimination half-lives of febuxostat was approximately 5-10 hours.

2.2.5.9 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Both AUC_τ and C_{max} of febuxostat in plasma were dose-proportional at the proposed clinical dose range (80 and 120 mg) at steady state (Figure 2.2.5.9.1) as evidenced by the linear relationship between AUC_τ and dose, and C_{max} and dose (10-120 mg). AUC_τ increased more than dose proportionally at doses above 120 mg while C_{max} appeared to be dose proportional up to 300 mg (Figures not shown, Table 2.2.5.9.1).



a. AUC_τ



b. Cmax

Figure 2.2.5.9.1. Relationship between TMX-67 AUC_τ (a) and dose, and Cmax (b) and dose.

Table 2.2.5.9.1. Mean Febuxostat Pharmacokinetic Parameters from Ascending Dose and High Dose Pharmacokinetic Studies.

Study No.	Dose	Day	t_{max} (h)	C_{max} (µg/mL)	C_{max}/Dose (1/L)	AUC_a (µg·h/mL)	AUC_a/Dose (h/L)	$t_{1/2\,b}$ (h)
TMX-99-001	10 mg QD	1	0.99	0.336	0.0336	0.727	0.073	1.5 [1.3]
		14	0.70	0.399	0.0399	0.951	0.095	3.0 [2.0]
	20 mg QD	1	1.06	1.11	0.0556	2.18	0.109	3.2 [2.6]
		14	0.89	0.934	0.0467	2.11	0.106	4.7 [3.8]
	30 mg QD	1	0.72	1.12	0.0373	2.55	0.085	9.2 [4.6]
		14	0.89	1.28	0.0428	2.57	0.086	6.7 [5.7]
	40 mg QD	1	1.44	1.53	0.0382	3.98	0.099	4.2 [3.8]
		14	1.19	1.82	0.0456	4.30	0.108	10.3 [6.3]
	50 mg QD	1	0.78	1.97	0.0394	4.41	0.088	5.0 [4.5]
		14	1.14	1.79	0.0358	4.38	0.088	10.1 [6.7]
	70 mg QD	1	1.00	3.08	0.0440	6.93	0.099	5.0 [4.7]
		14	1.10	2.69	0.0384	6.95	0.099	12.5 [8.5]
	90 mg QD	1	0.95	3.48	0.0387	9.09	0.101	9.3 [6.8]
		14	0.95	4.06	0.0451	9.65	0.107	14.6 [10.0]
	120 mg QD	1	1.00	4.47	0.0373	11.3	0.094	11.4 [9.1]
		14	1.11	5.31	0.0442	12.0	0.100	18.2 [11.9]
	160 mg QD	1	0.75	7.30	0.0456	20.7	0.130	10.7 [9.8]
		14	0.80	8.77	0.0548	22.3	0.139	11.8 [9.5]
	180 mg QD	1	1.07	8.40	0.0467	25.6	0.142	23.6 [11.0]
		14	1.00	8.05	0.0447	24.0	0.133	20.8 [15.8]

	240 mg QD	1 14	1.06 0.94	8.39 11.3	0.0349 0.0469	28.3 35.0	0.118 0.146	12.7 [10.2] 9.9 [8.1]
C02-023	300 mg QD	7	1.00	14.3	0.0475	48.4	0.161	6.3 [5.9]

a AUC refers to AUC_∞ for Day 1, and AUC_{24} for Day 14.
b Harmonic mean in brackets.

From Study TMX-99-001, mean dose-normalized febuxostat C_{max} values did not show any statistically significant trend with increasing doses ($p > 0.05$). On both Day 1 and Day 14, even though the mean dose-normalized AUC (AUC/D) for the doses from 10 to 120 mg appeared to be similar to each other, a statistically significant increase in AUC/D was detected with increasing doses ($p \leq 0.05$), which was most likely due to the increase in AUC/D for doses above 120 mg. Because febuxostat dose-normalized C_{max} values remained relatively unchanged, the greater than dose-proportional increase in febuxostat AUC for doses above 120 mg was most likely the result of a decrease in the renal elimination.

2.2.5.10 How do the PK parameters change with time following chronic dosing?

Steady-state of PK was in general reached by Day 4. Steady-state for PD (SUA reduction) was reached by Day 6.

The accumulation index was quantified by the following formula:

Accumulation Index = AUC(0-24hr) (multiple dose)/ AUC(0-24hr) (single dose)

The results presented in Table 2.2.5.10.1 indicate that accumulation index of febuxostat (~1.08) is consistent with what is estimated from its apparent half-life of 5-10 hrs (1.04-1.23) assuming one-compartment model.

Table 2.2.5.10.1. Accumulation Index Following Febuxostat Dosing (Study TMX-99-001).

	Febuxostat
70 mg	1.02
90 mg	1.09
120 mg	1.08

2.2.5.11 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients, and what are the major cause of variability?

Please refer to the Pharmacometrics Review (See Appendix 4.3).

2.2.6 What is comparison of PK for febuxostat after AM and PM dosing (Is there a diurnal effect)?

In Study TMX-99-001, PK of febuxostat after AM and PM dosing were compared with a 30 mg BID dosing regimen. As shown in Table 2.2.6.1 and Figure 2.2.6.1, there was a one hour delay in T_{max} and a 40% decrease in C_{max} when comparing the PM dosing to the AM dosing. The AUC_{12} appeared to remain the same for the PM dosing as compared to the AM dosing.

Table 2.2.6.1. Summary of Pharmacokinetic Parameters of Febuxostat (30 mg BID).

Dose	Day		t_{max} (h)	C_{max} (µg/mL)	AUC_{12} (µg·h/mL)	$t_{1/2z}$ [a] (h)	V_{ss}/F (L)	Cl/F (L/h)	C_{max}/D	AUC_{12}/D
30 mg BID	14 AM	Mean	0.70	1.4882	2.9146	4.9 (4.8)	41.1	10.81	0.0496	0.0972
		SD	0.35	0.3208	0.7564	1.0	6.7	2.28	0.0107	0.0252
	14 PM	Mean	1.75	0.8986	3.3083	11.1 (5.8)	61.0	9.88	0.0300	0.1103
		SD	0.68	0.2994	1.1573	11.8	17.9	2.73	0.0100	0.0386

a Arithmetic Mean (Harmonic Mean)

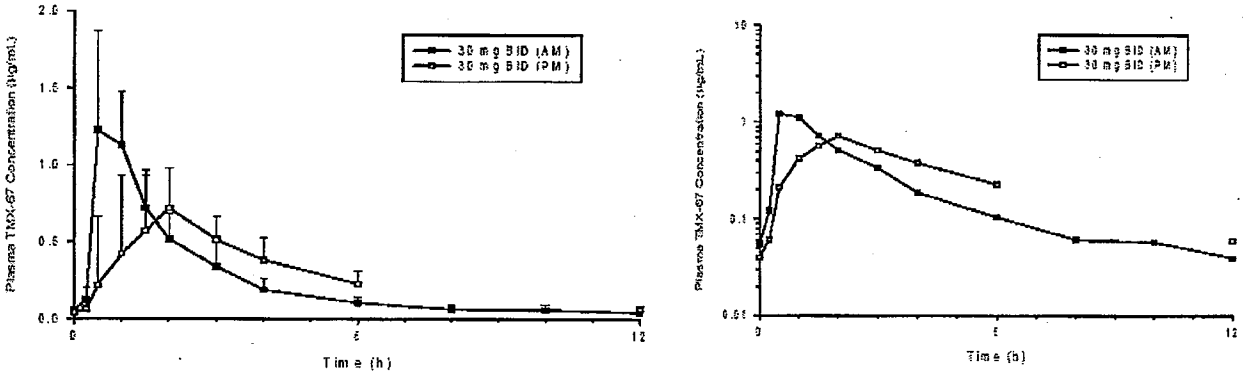


Figure 2.2.6.1. Mean (± SD) Plasma Febuxostat Concentration versus Time Profiles Following AM and PM Oral Administration of Febuxostat (30 mg BID Regimen) on Day 14. (Left, linear scale and Right, semi-log scale)

2.2.7 What are the PD characteristics of febuxostat and PK/PD relationship in healthy subjects?

Serum and urinary uric acid, xanthine and hypoxanthine were measured as pharmacodynamic measures. The percent decrease in serum urate mean 24-hour concentration from baseline was used as the primary indicator for PD effect.

Serum Uric Acid:

In Study TMX-99-001, mean 24-hour serum urate concentrations decreased from baseline as doses increased (10-240 mg) on Day 1, 8, 14 and 15. In addition, % changes increased from Day 1 to Day 8 (following multiple doses) but the maximum effect appeared to be achieved by Day 8 because no difference was noted between Day 8 and Day 14. On Day 15 (1 day after drug administration was stopped), it appeared there were slightly increase in 24-hr serum urate concentrations.

The relationship between the serum urate $C_{mean,24}$ on Day 14 and AUC_{24} on Day 14 could be described with a baseline E_{max} model, assuming Day 14 AUC_{24} of 0 for all placebo-treated subjects. The baseline E_{max} model fit the data well with an R^2 of 0.88 (Figure 2.2.7.1). Based on the results of the modeling, taking placebo would result in a percent decrease in serum urate

$C_{mean,24}$ on Day 14 (E_0) of 2.64±1.78% (mean±SE). The maximum percent decrease in serum urate on Day 14 caused by taking multiple doses of TMX-67 (E_{max}-E_0) was predicted to be approximately 78.76% (E_{max} was estimated as 81.40±2.42%). The EAUC50 value estimation was 3.3059±0.3886 µg.h/mL, achieved at the approximate 30-40 mg QD TMX-67 dosage range.

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

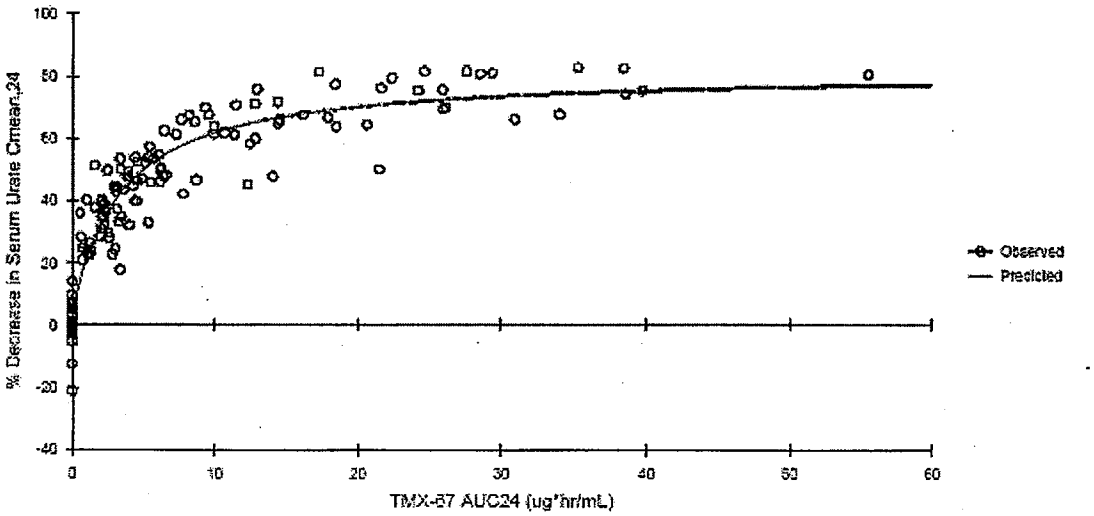


Figure 2.2.7.1. The Correlation Between the Percent Decrease in Serum Urate $C_{mean,24}$ from Baseline and Febuxostat Area Under the Curve (AUC_{24}) Following Multiple Dosing with Febuxostat.

The exposure from the proposed 80 and 120 mg doses (8-12 µg·hr/mL) appears to be towards the plateau of the exposure/PD response curve (Figure 2.2.7.1).

Serum Xanthine:
In Study TMX-99-001, following administration of febuxostat, serum xanthine concentrations were increased, with peak concentrations occurring at approximately 6 to 12 h post-dose. Mean 24-hour serum xanthine concentrations increased from baseline as doses increased on Day 1, 8, 14 and 15 (Figure 4, Day 14). In addition, larger changes were observed on Days 8 and 14 compared to Day 1 but the maximum effect appeared to be achieved by Day 8 because no difference was noted between Day 8 and Day 14. Following multiple dosing with febuxostat, on Day 14, the mean estimates for the 24-hour mean serum xanthine concentrations increased to approximately 5 times those of the baseline at doses 70-120 mg (the proposed clinical dose), but the levels (0.14-0.19 mg/dL) were significantly below the solubility of xanthine in serum at pH 7.4 (10 mg/dL), thus the risk of xanthine stone formation is low.

Serum Hypoxanthine:
Following administration of febuxostat, the concentrations of hypoxanthine in serum did not change substantially.

The following table summarized the serum and urinary concentration changes of uric acid, xanthine and hypoxathine following febuxostat administration.

Table 2.2.7.1. Summary of Change from Baseline (Day -1) in PD Parameters with 14 days of Febuxostat Administration (10-240 mg QD) on Day 14.

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

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The Sponsor evaluated the effect of the following intrinsic factors on exposure and PD response to febuxostat at 80 mg dose in healthy subjects: age, gender, renal impairment, and hepatic impairment. As described below, gender, renal impairment, and hepatic impairment affected febuxostat exposure. In renal impairment patients, exposure increased 60% compared to healthy subjects. Because the exposure at 80 mg is towards the plateau of the exposure/PD response curve (see Section 2.2.7) observed in healthy subjects, change in AUC did not result in big change in serum uric acid reduction. However, due to the cardiovascular safety concern coupled with little increased effect in uric acid reduction

b(4)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly (Study TMX-01-016)

No dose adjustment would be recommended based on differences in age. In Study TMX-01-016, the plasma exposure to febuxostat was similar between subjects 18-40 years and subjects ≥ 65 years following the administration of daily 80 mg oral doses of febuxostat for 7 days (Table 2.3.2.1.1). In addition, the percent decrease in serum urate was also similar between different age groups 18-40 years and ≥ 65 years (55% vs. 56%) (Table 2.3.2.1.2). Therefore, the pharmacokinetics and pharmacodynamics of febuxostat did not appear to be substantially affected by age. As a result, no dose adjustment would be recommended based on differences in age.

Table 2.3.2.1.1. Comparison of Geometric Mean Ratios and Confidence Intervals for Febuxostat Total and Unbound C_{max} and AUC_{24} Following Administration of Febuxostat (80 mg) for 7 days. (Reviewer's Analysis)

Parameter	Group	Geometric Mean	Ratio	90%CI
C_{max} (μg/mL)	18-40 yrs ≥ 65 yrs	3.772 3.85	102.1	(85.03, 122.54)
AUC_{24} (μg·h/mL)	18-40 yrs ≥ 65 yrs	7.788 8.783	112.8	(97.82, 130.01)
$C_{max,u}$ (ng/mL)	18-40 yrs ≥ 65 yrs	25.54 25.43	99.57	(81.33, 121.9)
$AUC_{24,u}$ (ng·h/mL)	18-40 yrs ≥ 65 yrs	52.74 58.01	110	(93.81, 128.99)

Table 2.3.2.1.2. Mean Serum Urate, Xanthine and Hypoxanthine $C_{mean,24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of Daily 80 mg Oral Doses of Febuxostat for 7 Days.

	Urate			Xanthine		Hypoxanthine	
	$C_{mean,24}$ (mg/dL)		% Change	$C_{mean,24}$(mg/dL)		$C_{mean,24}$(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

2.3.2.2 Pediatric Patients

The pharmacokinetic profile of febuxostat in pediatric patients has not been established.

The Sponsor requests a full waiver from the pediatric assessment requirements stated in 21 CFR 314.55(a), on the basis that necessary studies are impossible or highly impractical because the number of patients is very small.

2.3.2.3 Gender (Study TMX-01-016)

No dose adjustment would be recommended based on gender differences. In Study TMX-01-016, the plasma exposure to febuxostat was greater in female subjects compared to male subjects following the administration of daily 80 mg oral doses of febuxostat for 7 days (Table 2.3.2.3.1). An average of 35% and 15% increase was observed for C_{max} and AUC_{24}, respectively, in female subjects. Part of the difference could be accounted for by the average 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 (Table 2.3.2.3.2). As of note, the baseline uric acid levels were lower in female subjects. Although higher % reduction was observed in female subjects, the magnitude of uric acid reduction did not differ much between female and male subjects (Table 2.3.2.3.2). Therefore, the difference in % reduction was not considered significant as it appears to be related not to a differential effect, but due to the different baselines used in the calculation. Coupled with PK data, no dose adjustment would be recommended based on gender differences.

Table 2.3.2.3.1. Comparison of Geometric Mean Ratios and Confidence Intervals for Febuxostat Total and Unbound C_{max} and AUC_{24} Following Administration of Febuxostat (80 mg) for 7 days. (Reviewer's Analysis)

Parameter	Group	Geometric Mean	Ratio	90%CI
C_{max} (µg/mL)	All Male All Female	3.346 4.34	129.7	(109.3, 153.9)
AUC_{24} (µg·h/mL)	All Male All Female	7.749 8.828	113.9	(98.87, 131.26)
$C_{max,u}$ (ng/mL)	All Male All Female	21.71 29.91	137.75	(114.35, 165.93)
$AUC_{24,u}$ (ng·h/mL)	All Male All Female	50.29 60.84	120.99	(103.7, 141.12)

Table 2.3.2.3.2. Mean Serum Urate, Xanthine and Hypoxanthine $C_{mean,24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of Daily 80 mg Oral Doses of Febuxostat for 7 Days.

	Urate			Xanthine		Hypoxanthine	
	$C_{mean,24}$ (mg/dL)		% Change	$C_{mean,24}$(mg/dL)		$C_{mean,24}$(mg/dL)	
	Day -1	Day 7	Day 7	Day -1	Day 7	Day -1	Day 7
	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

2.3.2.4 Race

In the literature, there is a racial difference in terms of gout incidence. The incidence of gout is higher in African Americans compared to Caucasians in the U.S. (3.11 per 1,000 person-years vs. 1.82 per 1,000 person-years). No specific pharmacokinetic study was conducted to investigate the effects of race on PK of febuxostat.

Subgroup analysis (via a multivariate logistic regression model) of the pivotal Phase 3 efficacy data indicated that race was one of the significant factors associated with achieving the primary efficacy endpoint. The results suggested that Caucasian subjects had a higher chance of achieving the primary efficacy endpoint compared to non-Caucasian subjects (estimated adjusted odd ratio 1.605 (95%CI (1.192, 2.162)).

2.3.2.5 Renal impairment (Study TMX-01-008) b(4)

From Study TMX-01-008, following the administration of daily 80 mg oral doses of febuxostat for 7 days, AUC and $T_{1/2}$ of febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. $AUC_{24,u}$ of febuxostat increased about 60% from normal to mild, moderate and severe renal impairment (Table 2.3.2.5.1).

Table 2.3.2.5.1. Mean (SD) Febuxostat Plasma Pharmacokinetic Parameters on Day 7 Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days.

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

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

a $t_{1/2z}$ arithmetic mean [harmonic mean in brackets]

Linear regression analysis was performed to determine the correlation between measured creatinine clearance and $AUC_{24,u}$ of febuxostat. As shown in Figure 2.3.2.5.1, $AUC_{24,u}$ is somewhat decreased with increasing Clcr. With every 20 mL/min increase in Clcr, $AUC_{24,u}$ would decrease 10 ng*h/mL).

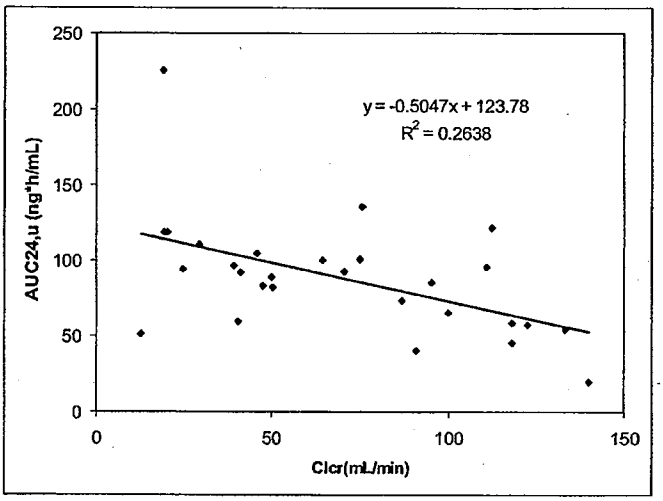


Figure 2.3.2.5.1. Simple Linear Regression Plot of $AUC_{24,u}$ of Febuxostat versus Creatinine Clearance.

Based on results from the regression models for $AUC_{24,u}$, $AUC_{24,u}$ predictions and the 95% prediction intervals for a hypothetical subject with Cl_{cr} at about the midpoint of each renal function category were calculated, and are presented in Table 2.3.2.5.2. The 95% prediction intervals for $AUC_{24,u}$ were wide and had substantial overlap between groups.

Table 2.3.2.5.2. Individual Predictions (Ind. Pred.) and 95% Prediction Intervals (95% P.I.) for Febuxostat $AUC_{24,u}$ in Study TMX-01-008.

	Predictions for Hypothetical Subjects with Indicated Clcrin each Renal Function Group							
	Normal (Clcr=100 mL/min) N=11		Mild Impairment (Clcr=65 mL/min) N=6		Moderate Impairment (Clcr=40 mL/min) N=7		Severe Impairment (Clcr=20 mL/min) N=6	
Parameter	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.	Ind. Pred.	95% P.I.
$AUC_{24,u}$	73.3	(2.2, 144.4)	91.0	(20.6, 161.3)	103.6	(32.5, 174.6)	113.7	(41.3, 186.0)

Units for $AUC_{24,u}$ are ng·h/mL.

The percent decrease in serum urate on Day 7 appeared to be similar regardless of the renal function (Table 2.3.2.5.3).

Table 2.3.2.5.3. Mean (SD) Serum Urate, Xanthine, and Hypoxanthine $C_{mean,24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of a Daily 80 mg Oral Dose of Febuxostat for 7 Days.

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

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

Serum xanthine concentrations on Day 7 for subjects with severe renal impairment were about 3-fold higher than those for subjects with normal renal function (Table 2.3.2.5.3). However, the 24-hour mean serum xanthine concentrations (0.55 ± 0.24 mg/dL) in patients with severe renal impairment were substantially lower than the solubility limit of xanthine in pH 7.4 serum (10 mg/dL), indicating the less likelihood of xanthine stone formation.

Based on the results of this study (60% increase in AUC in renal impairment patients), ——— b(4)

PK or PD of febuxostat in end-stage renal impairment patients who are on dialysis has not been studied. However, febuxostat is not expected to be routinely used in end-stage renal impairment patients who are on dialysis because dialysis would effectively remove uric acid.

2.3.2.6 Hepatic Impairment (Study TMX-01-012)

No dose adjustments would be recommended for febuxostat in subjects with mild or moderate hepatic impairment.

In Study TMX-01-012, the plasma exposure to febuxostat was greater in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function following the administration of daily 80 mg oral doses of febuxostat for 7 days. An average of 20-30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatically impaired groups (Table 2.3.2.6.1).

Table 2.3.2.6.1. Comparison of Geometric Mean Ratios and Confidence Intervals for Febuxostat Total and Unbound C_{max} and AUC_{24} Following Administration of Febuxostat (80 mg) for 7 days in Healthy Subjects and Subjects with Hepatic Impairment. (Reviewer's Analysis)

Parameter	Group	Geometric Mean	Ratio	90%CI
$C_{max,u}$ (ng/mL)	I	18		
	II	22.89	127.2	(86.43, 187.19)
	III	19.76	109.8	(74.61, 161.58)
	II + III	21.27	118.18	(85.73, 162.91)
$AUC_{24,u}$ (ng·h/mL)	I	47.92		
	II	64.06	133.65	(92.85, 192.38)
	III	53.34	111.3	(77.32, 160.21)
	II + III	58.46	121.97	(89.97, 165.35)
C_{max} (ug/mL)	I	2.70		
	II	3.44	127.38	(87.23, 186.01)
	III	3.59	133.10	(91.14, 194.36)
AUC_{24} (ug·h/mL)	I	7.19		
	II	9.62	133.85	(92.52, 193.63)
	III	9.70	134.92	(93.26, 195.18)

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

Greater exposure of febuxostat in hepatically-impaired groups did not translate to greater reduction in serum uric acid levels on Day 7. Percent reduction in both mild (49%) and moderate (48%) hepatic impairment groups were 13 and 14% less than the reduction observed in healthy group (62%) (Table 2.3.2.6.2). The mean percent decrease in serum urate for healthy subjects in other special population studies ranged from 52% to 58% (Study TMX-01-008 and Study 01-016). Therefore, 48-49% reduction of uric acid level observed in this study appeared to be comparable to healthy groups.

Table 2.3.2.6.2. Mean (SD) Serum Urate, Xanthine, and Hypoxanthine $C_{mean,24}$ Values on Days -1 and 7 and Urate Percent Change Values Following Administration of a Daily 80 mg Oral Dose of TMX-67 for 7 Days

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

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

Dose adjustments for febuxostat in subjects with mild or moderate hepatic impairment are not necessary based on the moderate change in febuxostat systemic exposure and % reduction in serum urate on Day 7 observed in this study.

PK or PD of febuxostat in subjects with severe hepatic impairment has not been studied. A dose recommendation could not be made for severe hepatic impairment patients.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The Sponsor evaluated the effects of drug-drug interactions and food on febuxostat exposure. Food effect is described in Section 2.5.2. The drug-drug interactions are described in Section 2.4.2.

2.4.2 Drug-drug interaction

2.4.2.1 Is there an in vitro basis to suspect drug-drug interaction?

Febuxostat is a moderate CYP2D6 inhibitor with a Ki of 40 μM (12.6 μg/mL). An *in vivo* study was conducted to evaluate the effect of febuxostat on the pharmacokinetics of desipramine (a known 2D6 substrate) (See section 2.2.2.7.1.6).

Febuxostat is a potent xanthine oxidase inhibitor (with a K_i of 10 nM), so it may significantly increase the exposure of drugs that are metabolized by XO (e.g., theophylline, mercaptopurine, and azathioprine) *in vivo*. However, drug interaction studies were not performed to determine the interaction potential of febuxostat and drugs that are metabolized by XO.

From the theophylline label, allopurinol (a weaker XO inhibitor than febuxostat with a Ki of 300-700 nM) at a dose of 600 mg increased theophylline exposure by 25%. Based on the mercaptopurine and azathioprine labeling, it is recommended to reduce mercaptopurine or azathioprine dose to 1/3 to ¼ of the normal dose when co-administered with allopurinol. Because febuxostat is a more potent XO inhibitor than allopurinol, larger increase in the exposure of these drugs is anticipated at comparable doses.

There were only 7 febuxostat-treated patients in the clinical trials who took concurrent theophylline. There is no safety information for co-use of febuxostat with azathioprine because azathioprine was an excluded medication per the protocols.

Because theophylline is a narrow therapeutic index drug, and cardiac arrhythmias is one of the adverse events associated with theophylline, it is important to understand the effect of febuxostat on theophylline to safely co-administer these two drugs. An *in vivo* drug-drug interaction study should be conducted as a Phase IV study if the application is approved. Because of the potential for increased levels of theophylline to induce tachycardia, sub-therapeutic doses of theophylline could be used to assess the degree of interaction between the drug products.

An *in vivo* drug-drug interaction study between febuxostat and mercaptopurine or azathioprine needs to be conducted.

b(4)

2.4.2.2 Is febuxostat a substrate of CYP enzymes? Is metabolism influenced by genetics?

Febuxostat is metabolized by both Phase 1 and Phase 2 enzymes (see Section 2.2.5.7) The relative contribution of P450 isoforms in the oxidative metabolism of febuxostat to form metabolites, 67M-1, 67M-2, 67M-3, and 67M-4 (from 67M-1), is not clear. It is likely that 67M-1 was mainly metabolized by non-P450 enzymes and the same maybe true for its metabolite, 67M-4. 67M-2 was mainly formed by CYP1A2, CYP2C8 and CYP2C9 in the liver. 67M-3, a major metabolite formed *in vitro*, was not detected in significant amount *in vivo*. 67M-3 was mainly metabolized by CYP1A1.

Because of multiple metabolism pathways for febuxostat, its metabolism is not likely to be influenced by the inhibition or induction of one particular pathway nor by genetics.

2.4.2.3 Is febuxostat an inhibitor and/or inducer of CYP enzymes?

Febuxostat was found to be an *in vitro* competitive inhibitor of CYP2D6 with a Ki of 40 μM (12.6 μg/mL) (see Study C-02-005, section 2.4.2.7.1.6-In vivo drug-drug interaction study of febuxostat and desipramine).

Febuxostat showed little inhibitory activity against the other CYP isoform activities evaluated (i.e., CYP1A2, CYP2C9, CYP2C19, and CYP3A4), with Ki values greater than 100 μM (Table 2.4.2.3.1).

The induction potential of febuxostat on human CYP enzymes has not been studied either *in vitro* (hepatocytes) or *in vivo*.

Table 2.4.2.3.1. Inhibition of CYP Isoform Activities by Febuxostat in Human Hepatic Microsomes.

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

2.4.2.4 Is febuxostat a substrate or an inhibitor of P-glycoprotein transport process?

Whether febuxostat is a P-gp substrate is not clear due to lack of positive control in the assay.

Inhibition potential of febuxostat on P-gp has not been studied.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Febuxostat is metabolized to its acyl glucuronide by several uridine diphosphate glucuronosyltransferase (UGT) isoforms (mainly UGT1A1, UGT1A3, UGT1A9, and UGT2B7).

Febuxostat is likely to be a substrate for pH-dependent transporter(s) in the apical side of the intestine.

Non-CYP enzymes may be responsible for the metabolism of 67M-1 and subsequently 67M-4 (that totally accounted for ~25% of the dose).

2.4.2.6 What other co-medications are likely to be administered to the target patient population?

From a therapeutic point of view, DDI studies were conducted to evaluate the effect of febuxostat coadministration with agents commonly used in the treatment of acute gouty attacks; colchicine, indomethacin, and naproxen.

2.4.2.7 What are the in vivo drug-drug interaction studies for febuxostat?

The potential for drug interactions was evaluated in eight *in vivo* clinical pharmacology studies in the United States which incorporated an evaluation of the effect of antacid, the relevant *in vitro* DDI results, drugs that can be expected to be coadministered with febuxostat, and warfarin.

Potential for febuxostat to affect other drugs	**Potential for other drugs to affect febuxostat**
Desipramine, Colchicine, Indomethacin, Naproxen, and Warfarin	Antacid, Colchicine, Indomethacin, Naproxen, and Hydrochlorothiazide

While the *in vitro* metabolism studies did not suggest a high likelihood of a CYP-P450 mediated DDI, a study was done to evaluate the effect of febuxostat on the pharmacokinetics of desipramine (a known 2D6 substrate) as a "possible" effect was seen *in vitro*.

From a therapeutic point of view, additional DDI studies were conducted to evaluate the effect of febuxostat coadministration with agents commonly used in the treatment of acute gouty attacks; colchicine, indomethacin, and naproxen. As hydrochlorothiazide is known to inhibit the renal secretion of uric acid (thus exacerbating serum uric acid levels), a DDI study incorporating both PK and PD measurements (serum uric acid) was also completed.

2.4.2.7.1 Individual DDI Study Result

2.4.2.7.1.1 What is the effect of concomitant antacid administration on the pharmacokinetics of Febuxostat?

The results of this study confirmed the previous finding that absorption of febuxostat is pH-dependent. Administration of an antacid both prolongs the Tmax and lowers the Cmax of febuxostat with no change in the overall AUC.

Antacid Study TMX-01-014 (U.S.)

This was a Phase 1, open-label, randomized, single-center, single dose, two-period complete crossover study performed in the U.S. evaluated the effect of an antacid on the pharmacokinetics of febuxostat in 24 healthy subjects. Subjects were randomly assigned to receive either an 80 mg oral dose of febuxostat (administered as four 20 mg tablets) with concurrent oral administration of 20 mL of an antacid liquid (800 mg magnesium hydroxide and 900 mg aluminum hydroxide), or an 80 mg oral dose of febuxostat alone in each study period.

Relative to administration of febuxostat alone, co-administration of the antacid with febuxostat delayed the mean Tmax by approximately 1 hour with a 31% decrease in mean Cmax. A 15% decrease in AUCt and AUC∞, was also seen along with an attendant decease in MRT (see table below).

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_z/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

From a confidence interval point of view, the 90% CI's for AUC were within the acceptance limits of 80-125%, but the CI for Cmax was well below the lower bound:

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.

The data from this study does suggest that there is a significant decrease in the febuxostat absorption rate (as evidenced by the increased Tmax, and reduced Cmax and MRT) following coadministration with an antacid. The results are consistent with the *in vitro* finding that absorption of febuxostat is pH-dependent (absorption is lower at higher pH). Examination of the timecourse of the serum urate lowering effect of febuxostat indicates that AUC more than Cmax is related to drug effect. As such, the changes seen here in the presence of antacid would not require a dose adjustment to be made.

2.4.2.7.1.2 Is there an interaction between colchicine and febuxostat?

In the evaluation of the interaction between colchicine and febuxostat, the sponsor conducted two trials:

TMX-00-006 Colchicine's effect on Febuxostat (CxF)
C02-006 Febuxostat's effect on Colchicine (FxC)

The sponsor has not provided a reason as to why two studies were conducted. The studies do differ in the dose of febuxostat used (40 mg qd in TMX-00-006, and 120 mg qd in C02-006) and the duration of therapy.

In general, based on the results from the two studies, there does not appear to be a significant interaction between colchicine and febuxostat in terms of their effects on the pharmacokinetics of either drug.

TMX-00-006

This was a Phase 1, open-label, randomized, single-center, two-period complete crossover study to evaluate the effect of colchicine on the pharmacokinetics of febuxostat in 22 healthy subjects after multiple-doses of both compounds. Subjects were randomly assigned to receive either once daily 40 mg oral doses of febuxostat (administered as two 20 mg tablets) alone for 7 days, or once daily 40 mg oral doses of febuxostat with concurrent administration of 0.6 mg colchicine BID on the last four days of febuxostat dosing in each study period.

The co-administration of colchicine with febuxostat increased mean febuxostat Cmax, AUCt and AUC24 central values by 12%, 6%, and 7%, respectively, in comparison to the febuxostat alone regimen. Tmax was essentially unchanged, although the statistical analysis provided by the sponsor found it to be statistically significant (a mean increase of 18min). This difference in Tmax is not likely to be clinically relevant.

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).

Of more interest is the observation that the 90%CI for Cmax was outside of the 90%CI, but only barely.

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

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

As noted above in the antacid study, as the effect of febuxostat is thought to be due to exposure and not peak level this difference is not likely to be clinically relevant, especially given the way

in which colchicine is used in an acute manner in treating gout attacks as prophylaxis for relatively short time. No dose adjustment in colchicine is needed in the presence of febuxostat.

C02-006

The second colchicine study was an open-label, randomized, single-center, three-period crossover study designed to evaluate the effect of febuxostat on the pharmacokinetics of colchicine. 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 febuxostat ***placebo*** for14 days

Trt C-120 mg febuxostat alone for 14 days in each study period.
(Note:The febuxostat 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 febuxostat pre-dose at Day 1, 7, 13, and 14. No complete profiles were obtained for febuxostat in this study.

Following multiple doses of colchicine with febuxostat for 14 days, the colchicine pharmacokinetic parameters for both AM and PM Cmax, AUC12, t1/2, and AUC24, the means for the coadministered colchicine and febuxostat 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_{24} (pg·h/mL)	$t_{1/2}$[a] (h)	CL/F (L/h)	V_z/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.

Examination of the data from this trial did not reveal a significant impact of 120 mg doses of febuxostat on colchicine pharmacokinetics. There is, however, a slight difference in the Tmax values for colchicine (between 30-45min) between the AM and PM levels for colchicine for both Trt A & B, suggesting that either the timing of daily activities or some other diurnal factor may be in play. While interesting, it is a secondary finding and of no pharmacokinetic importance.

2.4.2.7.1.3 Is there a drug-drug interaction between indomethacin and febuxostat?

Following administration of indomethacin with febuxostat, no drug-drug interaction was found at steady-state.

Indomethacin Interaction Study-Study TMX-02-017

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

Following administration of febuxostat with indomethacin for 5 days, the changes in mean febuxostat pharmacokinetic parameters, including tmax, Cmax, AUCt, AUC24, t1/2, and Vss/F for the febuxostat with indomethacin regimen were all within 11% of the respective parameters in the febuxostat alone regimen. Both Cmax 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} (µg/mL)	AUC_t (µg·h/mL)	AUC_{24} (µg·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	1.0	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 Cmax and AUC24 were within the 0.80-1.25 range, although the Cmax 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 TMX-67, the changes in the mean indomethacin pharmacokinetic parameters, including tmax, Cmax, AUC12, and AUC24, 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} (ng/mL)	AUC_{12} (ng·h/mL)	AUC_{24} (ng·h/mL)	$t_{1/2z}$[a] (h)	MRT (h)	V_z/F (L)
Indomethacin	N	26	26	26	-	26	26	26
Alone	Mean	1.37	2757.6	8709.0	-	7.2 (5.2)	7.6	22.54
(AM Dose)	SD	0.61	536.2	2062.3	-	4.1	2.8	9.04
Indomethacin	N	26	26	26	26	26	26	26
Alone	Mean	2.56	1916.4	9094.1	17803.1	4.9 (4.2)	7.7	22.10
(PM Dose)	SD	1.47	646.8	1964.0	3797.6	2.4	2.0	7.03
TMX-67 &	N	26	26	26	-	26	26	26
Indomethacin	Mean	1.52	2743.8	9261.9	-	5.7 (5.2)	6.2	17.18
(AM Dose)	SD	0.66	680.9	1798.4	-	1.7	1.3	4.69
TMX-67 &	N	26	26	26	26	26	26	26
Indomethacin	Mean	2.27	1770.2	8430.0	17692.0	5.7 (4.4)	8.6	32.12
(PM Dose)	SD	1.19	627.2	1912.4	3359.7	3.4	2.9	40.27

a Arithmetic mean (harmonic mean)

A statistically significant ($p<0.05$) change was detected in the mean AM AUC12 values between the two regimens (8709 vs. 9261 ng*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, 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 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}, AUC_{12} and AUC_{24}.

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

2.4.2.7.1.4 Is there a drug-drug interaction between naproxen and febuxostat?

Yes, following administration of febuxostat with naproxen for 7 days, febuxostat Cmax, AUCt and AUC24 mean values were increased over the febuxostat alone arm. Unlike the changes seen in febuxostat pharmacokinetics, the plasma levels of naproxen are relatively unchanged following concomitant administration with febuxostat.

Naproxen Interaction Study-Study C02-013

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: A total of 27 healthy subjects were enrolled in the trial and 25 completed both phases and were available for analysis. 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.[3]

Following administration of febuxostat with naproxen for 7 days, febuxostat Cmax, AUCt and AUC24 mean values were approximately 28%, 40%, and 40% higher, respectively, than the febuxostat alone regimen.

[3] It should be noted that this is an anti-rheumatic dose of naproxen. The phase III clinical trials used a dose of 250mg BID of naproxen as a prophylaxis for gout flares during the initial phases of the trial.

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} (µg/mL)	AUC_τ (µg·h/mL)	AUC_{24} (µg·h/mL)	$t_{1/2z}$[a] (h)	Cl/F (L/h)	MRT (h)	V_z/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

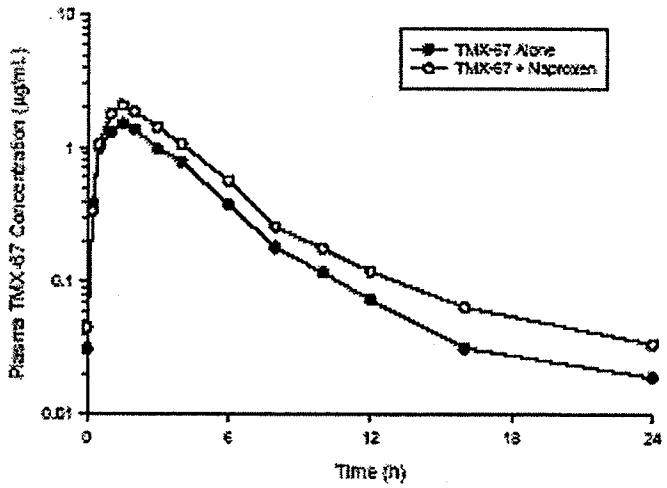
a Arithmetic mean (harmonic mean)

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 - 1.3874)
AUC_τ	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:



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 increased. The data clearly indicates that patients receiving the 80 mg dose will in fact be exposed to levels more akin to 120 mg, and patients receiving 120 mg will be exposed to levels approaching 180 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_τ (ng·h/mL)	AUC_{12} (ng·h/mL)	AUC_{24} (ng·h/mL)	$t_{1/2a}$* (h)	CL/F (L/h)	MRT (h)	V_{ss}/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 with the acceptance interval for naproxen.

2.4.2.7.1.5 Is there a drug interaction between hydrochlorothiazide and febuxostat?

There is no significant drug-drug interaction between the two agents.

Hydrochlorothiazide Interaction Study-Study Study C03-059

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. Subjects were randomly assigned to receive either an 80 mg oral dose of febuxostat (administered as a single 80 mg tablet) with co-administration of 50 mg hydrochlorothiazide or an 80 mg oral dose of febuxostat in each study period. Hydrochlorothiazide levels were not determined in this trial.

Following administration of febuxostat with or without co-administration of hydrochlorothiazide, mean febuxostat Cmax, AUCt, 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)	Vss/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	44.9
	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.

With regards to pharmacodynamic measures the mean 24 and 48 hour serum urate concentration (Cmean,24; Cmean,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 Clr 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

		Serum		Urine	
Regimen		$C_{mean,24}$ (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 Cmean,24, Cmean,48, and Clr 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 is necessary when administered with hydrochlorothiazide at these doses.