Clinical Trial Simulations

Methods

The main motivation for performing clinical trial simulations was to address the question which was of interest to the clinical division: "What would be benefit at 40 mg dose level?". The benefit as mentioned before is defined in terms of "Proportion of patients whose last three visit serum urate levels are below 6 mg/dL". The PK-PD model developed by the reviewer was used as input model and response rates were calculated in SAS for placebo, 40, 80, 120 and 240 mg dose levels. The idea was if the simulations predicted the response rates satisfactorily then there would be no need to study the 40 mg dose group in a new clinical trial in terms of effectiveness. If the risk at 80 and 120 mg dose groups is acceptable then the risk at 40 mg would probably be similar or lower.

To perform simulations, the PK/PD model was setup in Clinical Trial Simulator (Pharsight Corp). The parameters obtained from PK/PD analysis of the patient data were used for simulation purposes. The trial design used for simulations is shown below in Figure 17 and the PK/PD model is shown in Figure 18. It is very similar to the design used in the pivotal trials. The lead-in phase was included so that only patients whose pre-treatment baseline levels are greater than 8 mg/dL are randomized to one of the treatment groups. The total number of subjects enrolled in the trial was 5000 and the compliance was set to 95% based on observed compliance data in the pivotal trials.

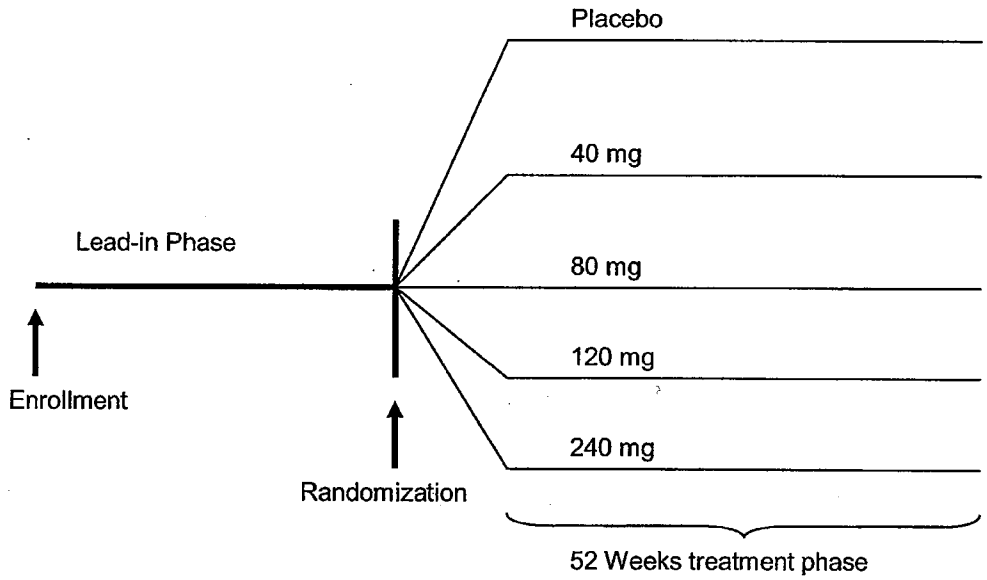


Figure 17. Clinical trial design used for simulations

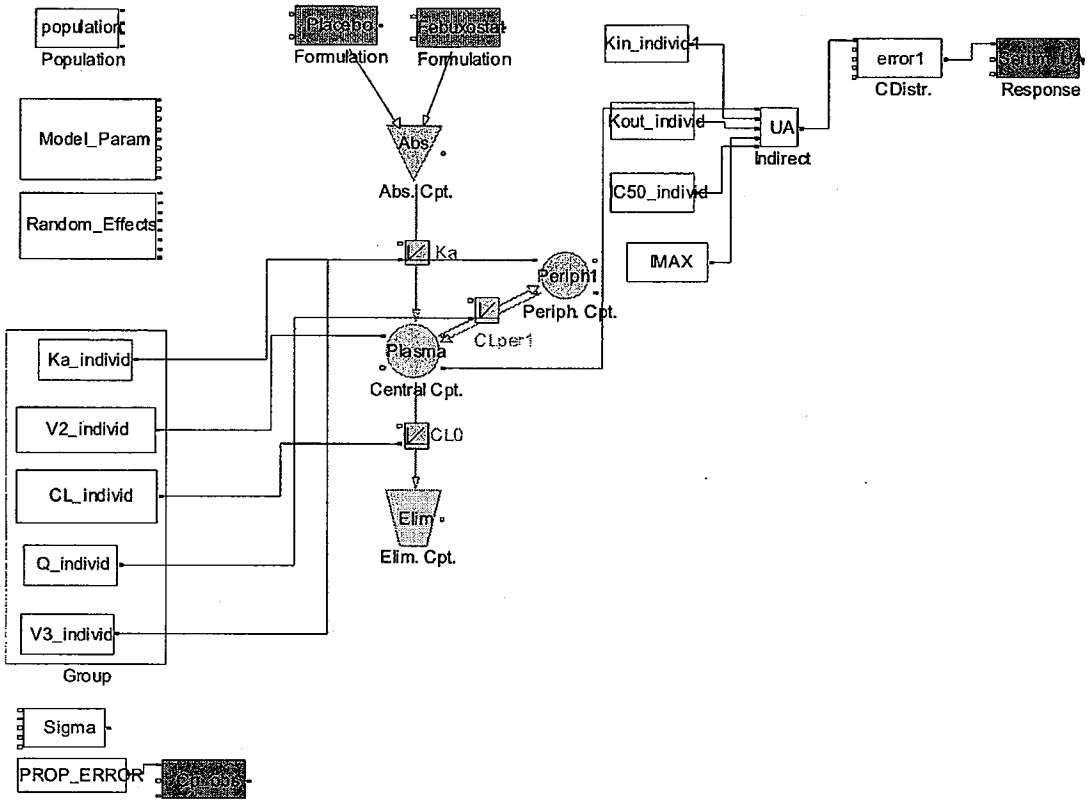


Figure 18. Indirect response PK/PD in Trial Simulator

Findings

The distribution of the model predicted baseline serum urate concentrations is similar to that observed in the clinical trials (Figure 19, 20). Also the distribution of serum trough levels of febuxostat is similar to that observed (Figure 21, 22). The time course of observed and predicted serum urate levels at various dose levels is shown in Figure 23, 24. The model predicts the time course of effects reasonably well. The comparison of observed and predicted response rates using parameters from PK/PD analysis of patient data is shown in Figure 25.

The predicted response rate is reasonably close to the observed response rates at 80, 120 and 240 mg dose groups. The predicted response rate at 40 mg dose is 22%.

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

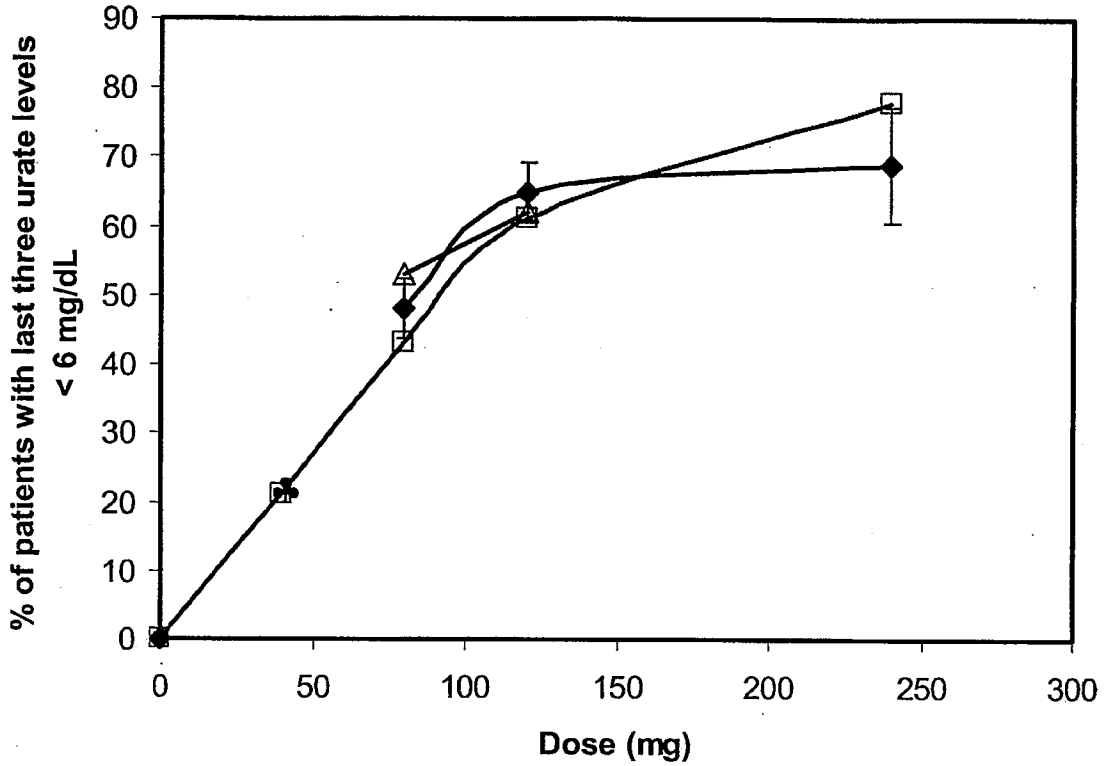


Figure 25. Relationship between primary endpoint vs dose of febuxostat (♦- observed in C02-009; Δ- Observed; in C02-010; □- Predicted; ♣- Observed for Allopurinol) (Shown are Mean±2S.E for Observed and Mean for Predicted)

Simulations based on PK/PD estimates from healthy subjects

Mixed effects analysis of patient data showed a huge variability in Q (intercompartment clearance) and Vp (Peripheral Volume of Distribution). One of the reasons for this is the sparse information for all the parameters to be estimated. Since there are no significant differences between healthy subjects and patients in PK and PD (Figure 26), simulations were performed using the parameters obtained from healthy subjects. In healthy subjects, adequate data was collected to define the various parameters in the PK/PD model. The comparison of observed and predicted response rates in patients based on healthy subjects PK/PD parameters is shown in Figure 27. The predictions are very similar to those observed in patients. The predicted response rate at 40 mg is 27%.

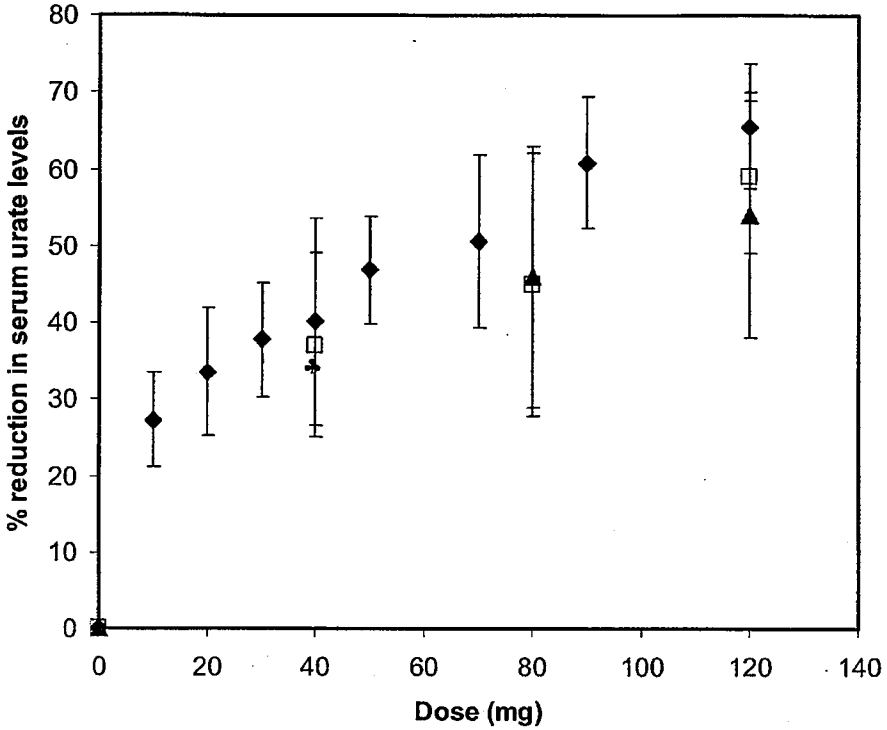


Figure 26. % reduction (Mean±SD) in serum urate levels (pre-dose) in healthy subjects (♦) patients (Phase II-□; Phase III-▲; Allopurinol (300 mg)-♣)

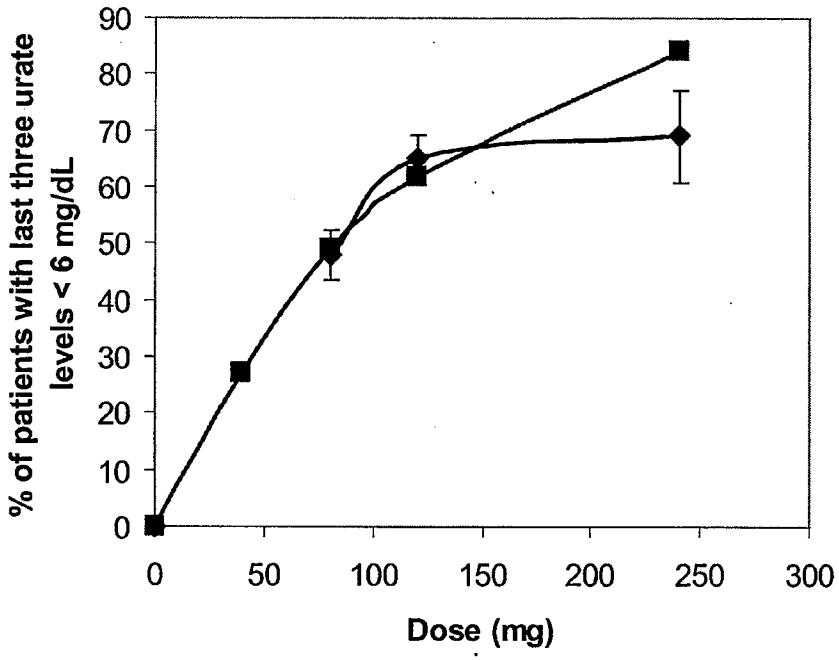


Figure 27. Response rates calculated based on PK/PD parameters from healthy subjects (Shown are Mean±2S.E for Observed -♦ and Mean for Predicted-■)

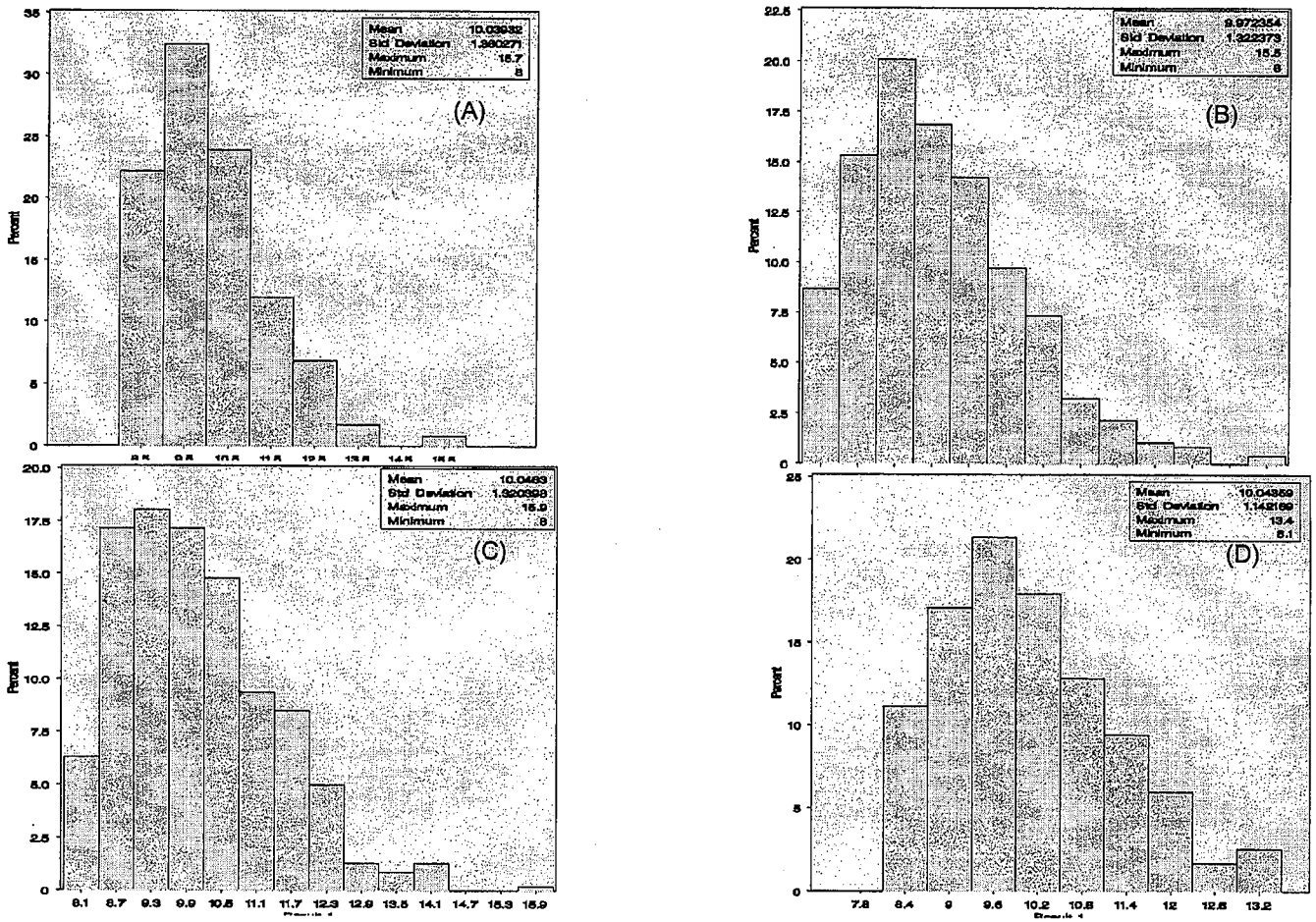


Figure 19. Comparison of observed (A-Placebo, B-80 mg, C-120 mg, D-240 mg) baseline serum urate levels

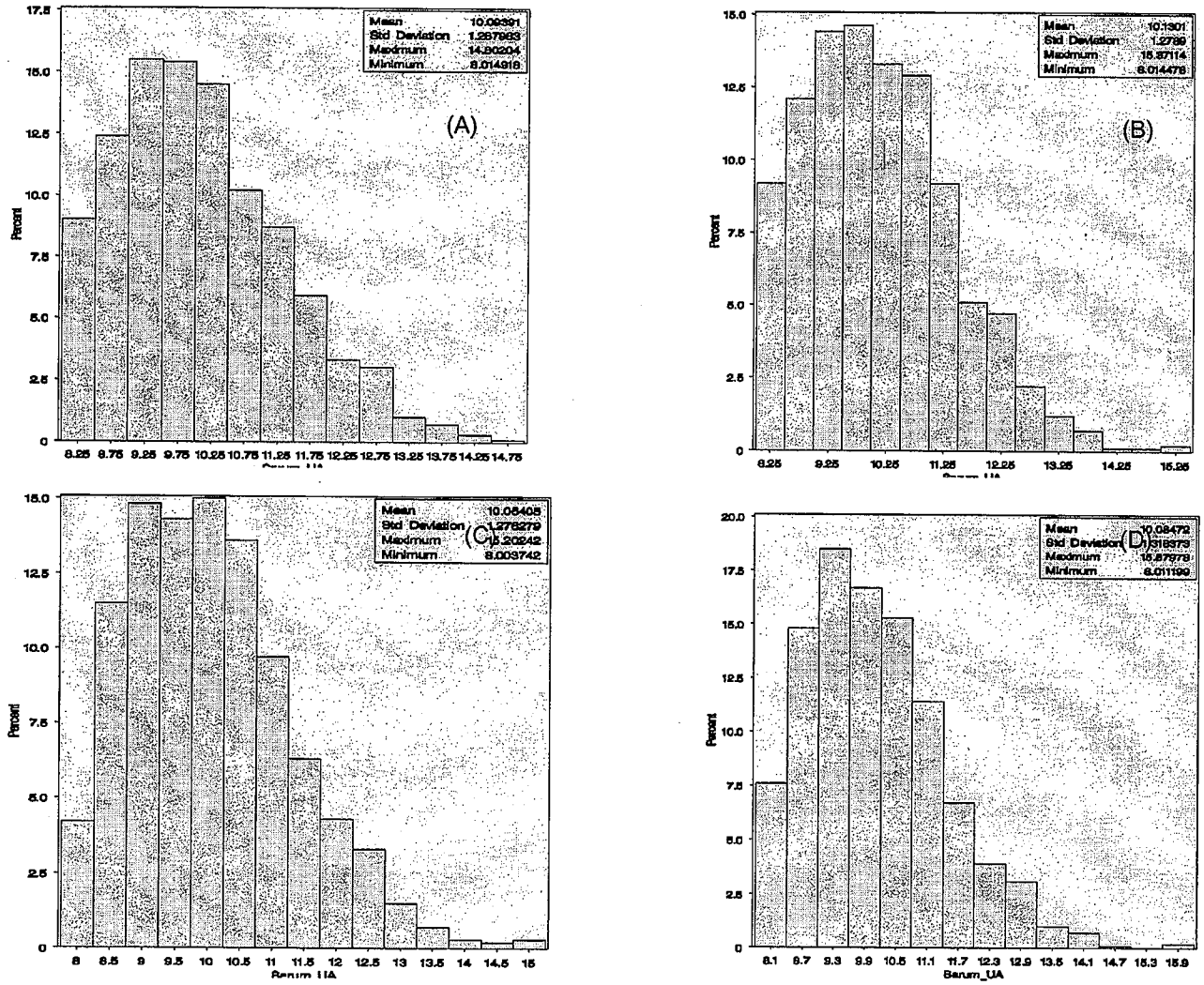


Figure 20. Comparison of simulated (A-Placebo, B-80 mg, C-120 mg, D-240 mg) baseline serum urate levels

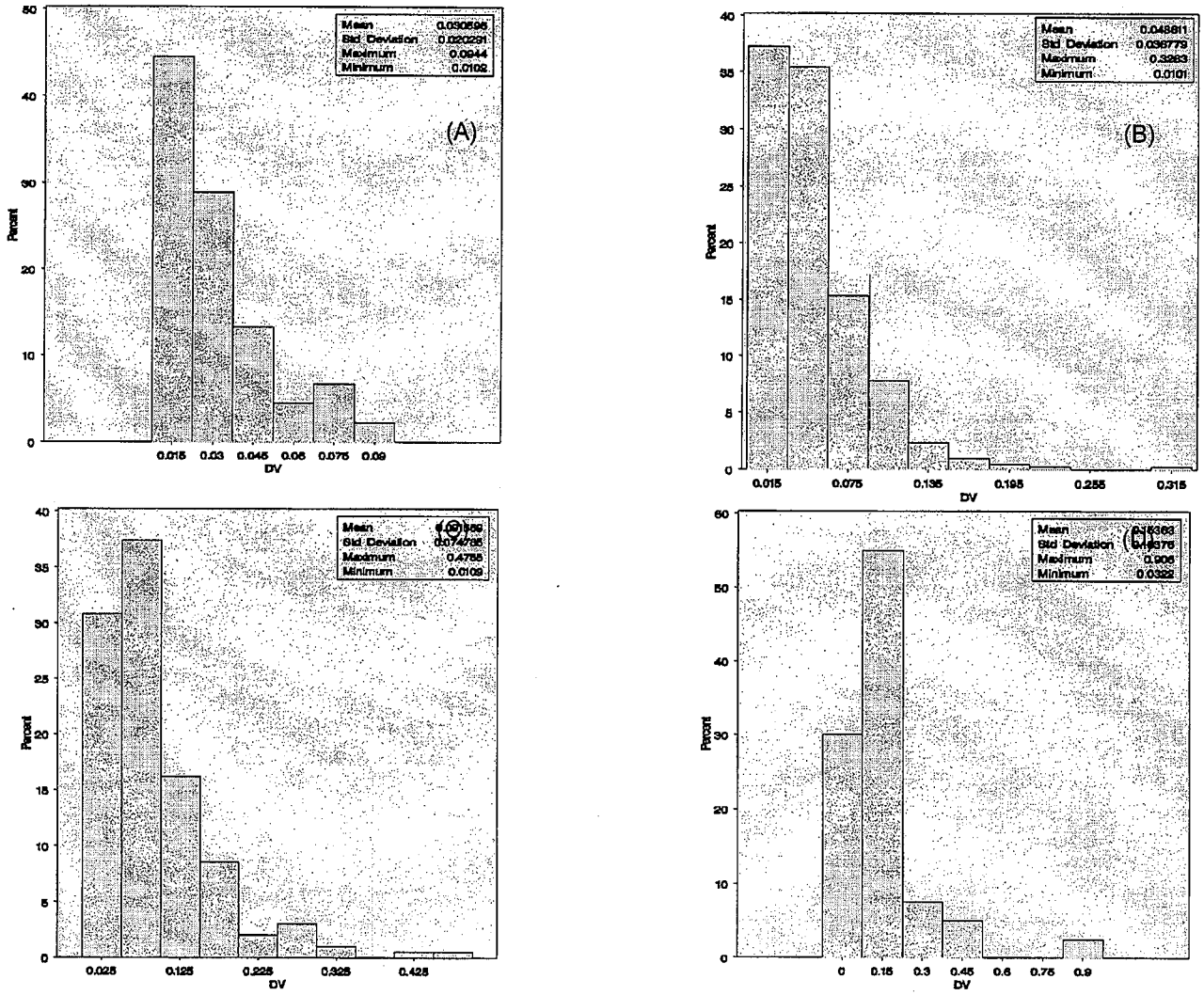


Figure 21. Comparison of observed (A-Placebo, B-80 mg, C-120 mg, D-240 mg) febuxostat serum trough concentrations

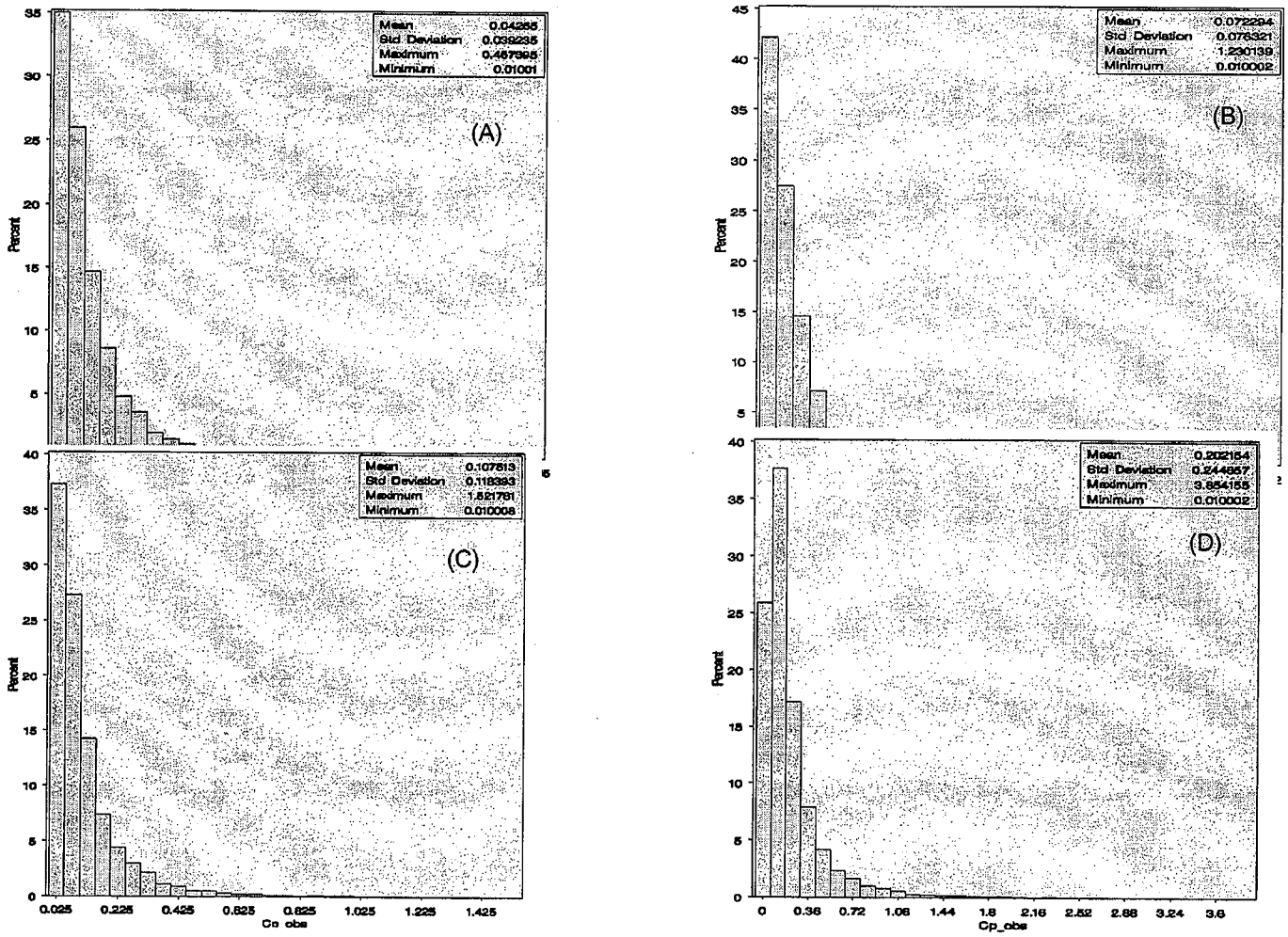
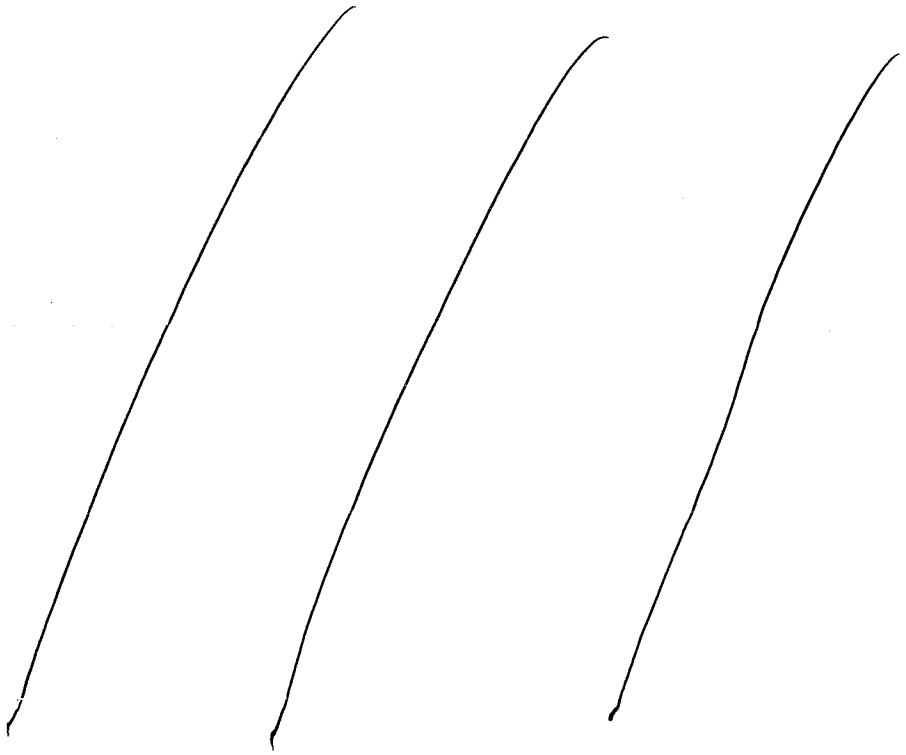


Figure 22. Comparison of simulated (A-Placebo, B-80 mg, C-120 mg, D-240 mg) febuxostat serum trough concentrations.



b(4)

Conclusions

The time course of serum urate and febuxostat levels were well characterized using appropriate structural models. The predicted response rates based on model derived parameters for healthy and patient data are also similar indicating that the results observed at 40 mg dose group are acceptable. Simulations show that 40 mg dose group would be similar to allopurinol in terms of benefit. There is some evidence that the response rate at 40 mg dose group is about 29-38% based on open label phase data from TMX-01-005 study in patients. However, caution should be used in interpreting this data as there were only about 10 patients at this dose level. It is not known however, if the risk of cardiovascular events (not reviewed by this reviewer) would be similar or lower at 40 mg dose in comparison to higher dose groups.

b(4)

4.4 Evaluation of Allopurinol Encapsulated Tablets

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3869

Date: August 12, 2005

To: Capt. E. Dennis Bashaw, Pharm. D., Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III, HFD-880

From: B.J. Westenberger, Deputy Director, Division of Pharmaceutical Analysis, HFD-920

Subject: Evaluation of allopurinol encapsulated tablets

Background: Febuxostat is a new treatment for hyperuricemia related to gout. During the clinical studies, the test product performed much better than the standard therapy, allopruinol. This increase in performance caused concern that the allopurinol tablets were either sub-potent or stored incorrectly which may have affected the drug release rate. Division of Pharmaceutical Analysis (DPA) was requested to perform quality assessment of four lots collected from [redacted] and to compare the results to the innovator's product, Zyloprim®. b(4)

Conclusion: Analyses of allopurinol encapsulated tablets collected from [redacted] indicate that all products passed USP quality assessment tests thereby eliminating sub-potency or incorrect storage as possible reasons for differences observed during clinical studies.

Experimental: Color, shape, dimensions, and average tablet/capsule weight were recorded, as well as a digital photograph of each capsule and its contents. Uniformity of dosage, using the USP 28 assay method, was conducted on all samples. Chromatographic purity was assessed by using a technique known as High/Low chromatography based on the assay method. Dissolution profiles were determined using the USP 28 method with additional sampling times at 15, 30 and 60 minutes.

Drug Product: Zyloprim® (allopurinol) 300 mg Tablet, Lot 3G1974, EXP 10/07 (purchased by DPA)
Allopurinol 300 mg Encapsulated Tablet, Lot 020145
Allopurinol 300 mg Encapsulated Tablet, Lot 020138
Allopurinol 300 mg Encapsulated Tablet, Lot 020065
Allopurinol 100 mg Encapsulated Tablet, Lot 020137

Results: All samples met USP specifications for weight variation, uniformity of dosage, and % Dissolved in 45 minutes (See Tables 1 – 3). Chromatographic purity and dissolution profile data are in Tables 4 and 5. Dissolution profiles for all samples are presented in Figure 1. A representative photo of the broken tablet and contents of the 100mg capsule is presented in Figure 2. A representative photo of the broken tablet and contents of the 300mg capsule is presented in Figure 3. Microscopic examination of the powder in each capsule was identified as [redacted] Comparative evaluations of the four samples collected at [redacted] showed no difference between each other nor was any difference between these products and the purchased innovator product observed. b(4)

Table 1. Weight Variation - USP 28 Specification % RSD NMT 6.0

Lot Number	Sample	Average tablet or capsule weight (mg)	%RSD	Disposition
Zyloprim	300 mg Tablet	0.47729	1.3	pass
020145	300 mg Encapsulated Tablet	0.74850	4.0	pass
020138	300 mg Encapsulated Tablet	0.74211	2.7	pass
020065	300 mg Encapsulated Tablet	0.74749	4.0	pass
020137	100 mg Encapsulated Tablet	0.62785	3.2	pass

Table 2. Uniformity of Dosage - USP 28 Specification 93.0 to 107.0 % of declared

Lot Number	Assay (10) Tablets or Capsules	%RSD (10)	Disposition
Zyloprim	99.7	1.2	pass
020145	99.8	1.2	pass
020138	100.4	1.1	pass
020065	99.7	1.8	pass
020137	99.7	4.1	pass

Table 3. % Dissolve in 45 minutes – USP 28 Specification NLT 75% dissolved in 45 minutes

Lot Number	% Dissolved Avg (6)	% RSD	Disposition
Zyloprim	99.9	0.8	pass
020145	97.8	1.4	pass
020138	97.3	1.8	pass
020065	99.7	1.3	pass
020137	99.6	1.1	pass

Table 4. Chromatographic Purity – No USP monograph specification

Lot Number	% Impurity found
Zyloprim	0.07
020145	0.07
020138	0.07
020065	0.06
020137	0.09

Table 5. Dissolution Profile Data - No USP monograph specification

Lot Number	Zyloprim	020065	020138	020145	020137
Time (min)	% Dissolved average (6) tablets				
0	0	0	0	0	0
15	97.2	92.2	89.8	88.5	93.3
30	100.5	99.0	96.2	95.1	98.2
45	99.9	99.7	97.3	97.8	99.6
60	100.5	100.0	97.5	98.1	100.2
90	101.0	100.9	98.9	99.1	100.7

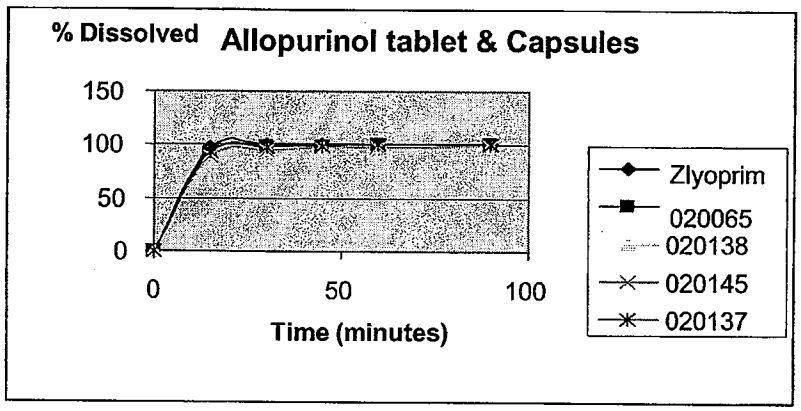


Figure 1. Dissolution Profile

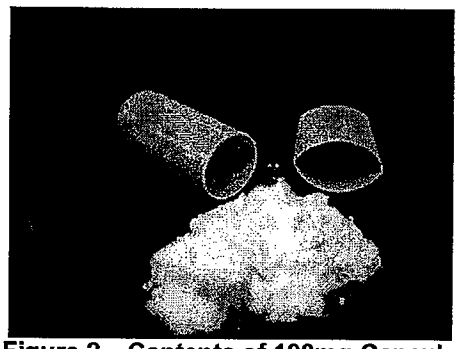


Figure 2. Contents of 100mg Capsule

Figure 3. Contents of 300mg Capsule

4.5 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Number	**21-856**	**Brand Name (Proposed)**	Urolic
OCPB Division (I, II, III)	**DPE III (HFD-880)**	**Generic Name**	**Febuxostat**
Medical Division	**DAAODP (HFD-550)**	**Drug Class**	**Serum urate lowering agent**
OCPB Reviewer **PM Reviewer**	**Lei Zhang, Ph.D.** **Atul Bhattaram, Ph.D.**	**Indication(s)**	**Hyperuricemia in patients with gout**
OCPB Team Leader	**Dennis Bashaw, Pharm. D.**	**Dosage Form**	**80 and 120 mg tablets**
		Dosing Regimen	**80 mg QD or** **120 mg QD for patients** b(4)
Date of Submission	**12/14/2004**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**8/15/2005**	**Sponsor**	**TAP Pharmaceuticals**
PDUFA Due Date	10/15/2005	**Priority Classification**	New Molecular Entity (1-S)
Division Due Date			IND 58,229

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
Human PK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance: (14C ADME study)	**X**	**1**	**1**	**C03-040 (SN 164)** **(PK-03-013 (radiation dose prediction))**
Isozyme characterization:	**X**	**19**	**11**	
Blood/plasma ratio:				
Plasma protein binding:	**X**	**6**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	**TMX-99-001 (Phase 1 PK/PD, 13 dose days) (SN 171)**
multiple dose:	**X**	**(1)**		**TMX-99-001 (Phase 1 PK/PD, 13 dose days) (SN 171)**
Patients-				
single dose:				
multiple dose:	**X**	**3**	**2**	**TMX-00-003 (PK/PD, 14 dose days)** **Pop PK/PD:** **TMX-01-005 (SN 167)** **C-02-009 (SN 170)**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**(1)**		**TMX-99-001 (SN 171)**
fasting / non-fasting multiple dose:	**X**	**(1)**		**TMX-99-001**
Drug-drug interaction studies -				

In-vivo effects on primary drug:	X	5	5	TMX-0-01-014: antacid (single dose) (SN 126) TMX 00-006: colchicines (7 dose days) (SN 85) TMX-02-017: indomethacin (5 dose days) (SN 124) C-02-013: naproxen (7 dose days) (SN 129) C03-059: hydrochlorothiazide (single dose) (SN 165)
In-vivo effects of primary drug:	X	3 (5)	3	C02-006: colchicines (14 dose days) TMX-02-017: indomethacin (SN 124) C-02-013: naproxen (7 dose days) (SN 129) C02-005: desipramine (9 dose days) (SN 129) C03-057: warfarin (13 dose days)
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	TMX-01-016 (7 dose days, PK/PD) (SN 129)
pediatrics:				
geriatrics:	X	(1)		TMX-01-016 (7 dose days, PK/PD) (SN 129)
renal impairment:	X	1	1	TMX-01-008 (7 dose days, PK/PD)
hepatic impairment:	X	1	1	TMX-01-012 (7 dose days, PK/PD) (SN 126)
PD:				
Phase 2:	X	(1)		TMX-01-005 (SN 167)
Phase 3:	X	(1)		C02-009 (SN 170)
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	(6)		TMX-99-001 (Phase 1, 13 dose days) (SN 171) TMX-00-003 (14 dose days, in hyperuricemic patients) TMX-01-005 (SN 167) TMX-01-008 (renal impairment) TMX-01-012 (hepatic impairment) TMX-01-016 (gender and age)
Phase 3 clinical trial:	X	(1)		C02-009 (SN 170)
Population Analyses -				
Data rich:				
Data sparse:	X	(2)		TMX-01-005 (SN 167) C02-009 (SN 170)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	6	3	TMX-01-009 (single dose) TMX-01-010 (single dose) (SN 162) TMX-02-018 (single dose) C02-033 (single dose) (SN 134, return to DOC) C02-034 (single dose) (SN 139) C03-044 (single dose) (SN 164)

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/s/

Lei Zhang
8/29/2005 02:18:40 PM
BIOPHARMACEUTICS

Atul Bhattaram
8/29/2005 02:24:37 PM
BIOPHARMACEUTICS

Jogarao Gobburu
8/29/2005 04:36:02 PM
BIOPHARMACEUTICS

Dennis Bashaw
8/29/2005 05:59:04 PM
BIOPHARMACEUTICS

2/10/05

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-856	Brand Name (Proposed)	Urolic
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Febuxostat
Medical Division	DAAODP (HFD-550)	Drug Class	Serum urate lowering agent
OCPB Reviewer PM Reviewer	Lei Zhang, Ph.D. Atul Bhattaram, Ph.D.	Indication(s)	Hyperuricemia in patients with gout
OCPB Team Leader	Dennis Bashaw, Pharm. D.	Dosage Form	80 and 120 mg tablets
		Dosing Regimen	80 mg QD or 120 mg QD b(4)
Date of Submission	12/14/2004	Route of Administration	Oral
Estimated Due Date of OCPB Review	8/15/2005	Sponsor	TAP Pharmaceuticals
PDUFA Due Date	10/15/2005 *see "other comments" section on P.3	Priority Classification	New Molecular Entity (1-S)
Division Due Date			IND 58,229

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance: (14C ADME study)	X	1		C03-040 (SN 164) (PK-03-013 (radiation dose prediction))
Isozyme characterization:	X	19		
Blood/plasma ratio:				
Plasma protein binding:	X	6		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		TMX-99-001 (Phase 1 PK/PD, 13 dose days) (SN 171)
multiple dose:	X	(1)		TMX-99-001 (Phase 1 PK/PD, 13 dose days) (SN 171)
Patients-				
single dose:				
multiple dose:	X	3		TMX-00-003 (PK/PD, 14 dose days) Pop PK/PD TMX-01-005 (SN 167) C-02-009 (SN 170)
Dose proportionality -				
fasting / non-fasting single dose:	X	(1)		TMX-99-001 (SN 171)
fasting / non-fasting multiple dose:	X	(1)		TMX-99-001
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	5		TMX-0-01-014: antacid (single dose) (SN 126) TMX 00-006: colchicines (7 dose days) (SN 85) TMX-02-017: indomethacin (5 dose days) (SN 124) C-02-013: naproxen (7 dose days) (SN 129) C03-059: hydrochlorothiazide (single dose) (SN 165)

In-vivo effects of primary drug:	X	3 (5)		C02-006: colchicines (14 dose days) TMX-02-017: indomethacin (SN 124) C-02-013: naproxen (7 dose days) (SN 129) C02-005: desipramine (9 dose days) (SN 129) C03-057: warfarin (13 dose days)
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1		TMX-01-016 (7 dose days, PK/PD) (SN 129)
pediatrics:				
geriatrics:	X	(1)		TMX-01-016 (7 dose days, PK/PD) (SN 129)
renal impairment:	X	1		TMX-01-008 (7 dose days, PK/PD)
hepatic impairment:	X	1		TMX-01-012 (7 dose days, PK/PD) (SN 126)
PD:				
Phase 2:	X	(1)		TMX-01-005 (SN 167)
Phase 3:	X	(1)		C02-009 (SN 170)
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	(6)		TMX-99-001 (Phase 1, 13 dose days) (SN 171) TMX-00-003 (14 dose days, in hyperuricemic patients) TMX-01-005 (SN 167) TMX-01-008 (renal impairment) TMX-01-012 (hepatic impairment) TMX-01-016 (gender and age)
Phase 3 clinical trial:	X	(1)		C02-009 (SN 170)
Population Analyses -				
Data rich:				
Data sparse:	X	(2)		TMX-01-005 (SN 167) C02-009 (SN 170)
I. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	6		TMX-01-009 (single dose) TMX-01-010 (single dose) (SN 162) TMX-02-018 (single dose) C02-033 (single dose) (SN 134, return to DOC) C02-034 (single dose) (SN 139) C03-044 (single dose) (SN 164)
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3		TMX-00-002 (single dose, 40 mg) C02-036 (6 dose days, 80 mg) (SN 142) C03-054 (single dose, 120 mg) (SN 165)
Dissolution:	X	11		3.2.P.5.6.7 and 3.2.P.5.4.1
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				

QTc study	X	1		C02-023 (4 dose days) (SN 132)
Phase 1 multiple dose PK/PD study of oral allopurinol	X	1		TMX-01-007 (SN 161)
Caco-2 permeability	X	1		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		64 (27 in vivo)		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?		•
QBR questions (key issues to be considered)	• What is single and multiple dose PK of TMX-67? Is PK linear? • Is there a food effect on TMX-67 at 120 mg? • What is PK of TMX-67 in patients and how it is compared with that in healthy subjects? • What is the exposure-response (PK/PD) relationship of TMX-67? • How clinical doses were selected? What are the criteria for patients to be dosed with 80 mg or 120 mg? Is the dose selection appropriate? • What are the major safety concerns? • What are the potential drug interactions with TMX-67 (effect on TMX-67 and effect on others)? • What is PK of TMX-67 in special populations (e.g., renal and liver impairment, age and gender effect)?	
Other comments or information not included above	This is an eCTD submission. At the filing meeting, this NDA was classified as 1S. The Sponsor sent us a letter asking us to reconsider this decision. They requested for priority review. The PDUFA date may get changed to June 15, 2005 if 1P is granted.	
Primary reviewer Signature and Date	Lei Zhang, 1/27/2005	
Secondary reviewer Signature and Date	Dennis Bashaw, 1/27/2005	

CC: NDA 21-856, HFD-850 (P. Lee), HFD-550 (Dean), HFD-880 (L. Zhang, Bashaw, Lazor, Selen), CDR

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/s/

Lei Zhang
2/10/05 05:12:25 PM
BIOPHARMACEUTICS

Dennis Bashaw
2/10/05 06:23:28 PM
BIOPHARMACEUTICS